The Economics of Pharmaceutical Research and Development: Investment Models, Capital Market Imperfections, and Policy Considerations

by

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A dissertation submitted for consideration for the qualification of Doctor of Philosophy at City University, London.

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January 2001

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Acknowledgements

I would like to thank the staff at the Pfizer Inc. corporate library for their assistance in helping me collect the vast amount of pharmaceutical financial data used in this thesis. Similarly, I am grateful to several of my colleagues at Pfizer Inc. who, over the course of this research, provided me with countless suggestions and insights. In particular, I would like to thank Drs. Jack McMillan, Avanish Mishra, and Larry Gorkin.

I owe my largest debt of gratitude to my advisors, Professor Alistair McGuire and Professor Michael Grossman. Their help, advice, and patience throughout this research were considerable. I am very grateful to have had the opportunity to work with both of these distinguished economists.

I would also like to thank my father, Professor John M. Vernon, for his invaluable suggestions and advice.

I am extremely grateful to my wife Karyn. Her patience and willingness to put up with me during all those late nights and weekends still astounds me. Without her support, finishing this thesis would have been impossible.

Finally, I would like to dedicate this thesis to my mother, Jerry Vernon; her encouragement throughout my life has been truly inspiring.

Abstract

Pharmaceutical research and development (R&D) is the scientific process by which new medicines are discovered, developed, and brought to market. The social benefits of innovative new medicines are, and have been, enormous. In fact, few other health care technologies have improved the social welfare of the world's population as much, and as profoundly, as pharmaceuticals have. For example, breakthrough medicines and vaccines have played a vital role in the treatment of fatal diseases. As a result, most of this century's leading causes of death have been eliminated, and people of all ages enjoy increased life expectancy and vastly improved qualities of life (PhRMA, 2000).

Pharmaceutical R&D is also, not surprisingly, a very long and costly process. The average drug spends 14.9 years in development and costs approximately 320 million dollars to bring to market (Tuft's Center for the Study of Drug Development 1998, DiMasi, 1991). Consequently, the pharmaceutical industry has, in recent years, consistently ranked first in R&D investment intensity (the ratio of R&D to sales) among U.S. industries. Interestingly though, once the technology—and, more specifically, the vast safety and efficacy information accumulated through the R&D process—is fully established, the manufacturing costs of the pharmaceuticals are quite small compared to other manufacturing industries.

These unique characteristics of pharmaceuticals, and pharmaceutical R&D in particular, have resulted in the pharmaceutical industry being the focus of a great deal of political attention in recent years. This has been especially true given the perceived high cost of prescription medications —especially in the United States. Indeed, real pharmaceutical prices have been growing steadily over the past decade (U.S. Statistical Reports 1990-1999). As a result, there has been a pressing need, both political and academic, to better understand the economics of pharmaceutical R&D—the benefits, the risks, and the costs.

Consequently, the aim of this thesis will be to investigate, both theoretically and empirically, the economics of pharmaceutical R&D investment. As such, the main body of our research will focus on the firm R&D investment decision—with a particular focus paid to the role played by internal cash flows. Specifically, it will be hypothesized that, because of the unique characteristics associated with pharmaceutical R&D, capital market imperfections exist in the markets for external R&D finance. This, in turn, it will be argued, results in firm cash flows having a lower cost of capital relative to external debt and equity. Hence, a positive relationship is expected to exist between firm cash flows and firm R&D investment levels. This hypothesis, which runs contrary to classical investment theory—where internal and external capital are considered perfect substitutes (Miller and Modigliani 1958)—will be shown to have important policy implications.

The thesis is separated into a background section, a theoretical section, and several empirical sections. The background section will review the clinical and economic

characteristics of the pharmaceutical R&D process, and discuss the major research findings in this area.

Next, the theoretical section will review the literature on capital market imperfections and develop, from sound microeconomic principles, a framework from which the pharmaceutical R&D decision may be analyzed. This section will demonstrate why, theoretically, cash flows are expected to exert a positive influence on pharmaceutical R&D investment.

Lastly, the empirical sections will estimate several models of R&D investment using recent data from 60 of the world's leading pharmaceutical firms. These models, which employ several variables designed to measure a firm's internal cash flow, will be used to test our hypothesis that cash flows are an important determinant of pharmaceutical R&D investment. Models will be estimated over multiple samples of firms and time periods.

Our general findings from this research will reveal that cash flows are a very significant determinant of pharmaceutical R&D investment. This is the case independent of the sample of firms considered or the time period studied. We found that the coefficient estimates for the cash flow variable ranged from 0.08 to 0.27, depending on the sample and model specification. This indicates, based upon our general model specification, that a $1 decrease (increase) in cash flows will result in an approximate $0.08-$0.27 decrease (increase) in firm R&D investment.

In addition to testing the capital markets imperfections hypothesis, investment models were also developed to address the important public policy of issue prescription drug price controls in the U.S. This has been a particularly controversial political topic in recent years. This section will use a modified version of our investment model and estimate the impact of a new U.S. prescription drug price control policy. We will demonstrate that such a policy can be expected to result in an approximate 10% to 30% decline in R&D investment.

Throughout the course of the aforementioned research, we will also investigate several other related issues. For example, in the context of our general R&D investment model, we will consider the issues of structural change, simultaneity, and causality.

Chapter One

Introduction

Pharmaceutical Research and Development: A General Introduction

Pharmaceutical research and development (R&D) is the scientific process by which new medicines are discovered, developed, and brought to market. The social benefits of innovative new medicines are, and have been, enormous. In fact, few other health care technologies have improved the social welfare of the world's population as much, and as profoundly, as pharmaceuticals have. Breakthrough medicines and vaccines have played a vital role in the treatment of fatal diseases. As a result, most of this century's leading causes of death have been eliminated, and people of all ages enjoy increased life expectancy and vastly improved qualities of life (PhRMA, 2000). For example, breakthrough antibiotics and vaccines led the way in the near eradication of syphilis, polio, diphtheria, whooping cough, and measles. Additionally, cardiovascular drugs, ulcer therapies, and anti-inflammatories have dramatically improved the treatment of heart disease, ulcers, emphysema, and asthma.

Pharmaceutical R&D is also, not surprisingly, a very long and costly process. The average drug spends 14.9 years in development and costs approximately 320 million dollars to bring to market (DiMasi, 1991). Consequently, the pharmaceutical industry has, in recent years, consistently ranked first in R&D intensity (the ratio of R&D to sales) among U.S. industries. Interestingly though, once the technology—and, more specifically, the vast safety and efficacy information accumulated through the R&D process—is fully established, the manufacturing costs of the pharmaceuticals are quite small compared to other manufacturing industries.

These unique characteristics of pharmaceuticals, and pharmaceutical R&D in particular, have resulted in the pharmaceutical industry being the focus of a great deal of political attention in recent years. This has been especially true given the perceived high

cost of prescription medications —especially in the United States. Indeed, real pharmaceutical prices have been growing steadily over the past decade (Danzon, 2000). The pharmaceutical industry was also ranked first in return on equity among all U.S. industries in 1999 (Forbes Annual Report, 1999). Consequently, there has been a pressing need, both political and academic, to better understand the economics of pharmaceutical R&D—the benefits, the risks, and the costs. The aim of this thesis will be to investigate, both theoretically and empirically, a very particular issue: pharmaceutical R&D investment.

Research Focus: The Firm R&D Investment Decision

The main body of research in this thesis will focus on the firm R&D investment decision—with a particular focus paid to the role played by internal cash flows. Specifically, it will be hypothesized that, because of the unique characteristics associated with pharmaceutical R&D, capital market imperfections exist in the markets for external R&D finance. This, it will be shown, results in firm cash flows having a lower cost of capital relative to external debt and equity, which, in turn, results in a positive relationship between firm cash flows and firm R&D investment levels. This hypothesis, which runs contrary to classical investment theory—where internal and external capital are considered perfect substitutes (Miller and Modigliani 1958)—will be shown to have important policy implications.

Outline of the Dissertation

Before considering the specifics of the pharmaceutical R&D investment decision, it will be useful to review both the clinical and economic characteristics of the R&D process. As will become apparent later in the thesis, it is the highly unique nature of *pharmaceutical* R&D—both scientifically and economically—that forms the foundation for the hypothesis that capital market imperfections exist for pharmaceutical R&D finance. For this reason, Chapter Two will review the major clinical and economic characteristics and trends of pharmaceutical R&D. In addition to providing a detailed

background from which we will initiate our research, this chapter will also review the seminal works of other authors whose research is relevant to the central issues addressed in this thesis. Chapter Two will be different from subsequent chapters in this thesis due to its generality—its main purpose is to describe the pharmaceutical R&D process.

Chapter Three will investigate the theoretical rationale for pharmaceutical R&D financing constraints. This chapter will begin by developing a simple analytical framework from which both the classical investment model, and, a new, alternative model—one based on capital market imperfections—can be considered and compared. After demonstrating the implications of such an alternative-type model specification, the model's theoretical underpinnings will be thoroughly explored and developed. Specifically, the rest of Chapter Three will be devoted to demonstrating that, from a theoretical standpoint, there are several reasons to hypothesize that capital market imperfections may be present in the markets for pharmaceutical R&D finance. These reasons are based on transaction costs, tax advantages, asymmetric information, costs of financial distress, and agency problems.

Chapter Four will mark the first of three empirical chapters (and one appendix) devoted to estimating models of the determinants of pharmaceutical R&D. These models, which will employ various variables designed to measure a firm's internal cash flows, will be used to test the hypothesis that cash flows—because of their relative cost advantage to external debt and equity—are an important determinant of pharmaceutical R&D investment. Specifically, Chapter Four will begin by critically reviewing the empirical work of other authors. Following this, model specifications will be developed, discussed, and estimated using data from 11 U.S. pharmaceutical firms from 1976 to 1996. Given the pooled nature of the data set (i.e., the use of both time series and cross-sectional data), various panel data estimation techniques will be reviewed and applied.

Chapter Five will expand on the analyses in Chapter Four by estimating models using a larger, and international, sample of 60 firms over the period from 1983 to 1997. The work in this chapter is the first empirical study of pharmaceutical R&D investment with an international focus. Specifically, several samples of firms from Europe, the U.S., and Japan will be employed to further—and more completely—test the hypothesis that firm cash flows are an important determinant of pharmaceutical R&D investment. In

addition to testing this primary hypothesis, several other hypotheses related to the firm R&D investment decision will be examined. In particular, given the dynamic nature of the pharmaceutical industry over time, and the vastly different regulatory environments for U.S- and non-U.S.-based firms, tests of structural change (and differences)—both over time and across firms groups—will be conducted.

Chapter Six will deviate somewhat from the focus on capital market imperfections and will use the models estimated in Chapters Four and Five to address the issue of pharmaceutical price controls in the United States. This has been a particularly controversial political topic in recent years. In fact, it is one the most debated policy issues in politics today. For this reason, and because the models estimated in the previous chapters are especially well suited for addressing (from an economic perspective) the impact of such a policy, Chapter Six will endeavor to answer the question: "What impact, if any, will pharmaceutical price controls in the U.S. have on future investment in pharmaceutical R&D?" This is an especially important question given the widespread benefits attributable to pharmaceutical innovation—which, of course, is a direct result of investment in pharmaceutical R&D. Answering this question, to one degree or another, will provide a very useful quantitative estimate of the economic consequences—in terms of the effect on R&D investment—such a policy can be expected to have.

Lastly, it should be mentioned that Appendix Two is, in essence, an additional empirical chapter—one that investigates the issue of model specification. More specifically, because the majority of models estimated in this thesis use reduced form specifications, the appropriateness of this specification had to be tested statistically. In fact, this constituted one of the first phases of the thesis research. Issues of model simultaneity and variable causality were considered in detail. The findings, which are discussed in detail in this appendix, support the use of a reduced form model specification. Therefore, this specification was deemed appropriate for testing our primary hypothesis that firm cash flows—because of capital market imperfections—are an important determinant of pharmaceutical R&D investment.

Finally, Chapter Seven will summarize the main findings from this research, draw conclusions, and discuss possible directions for future research.

Chapter Two

Pharmaceutical Research and Development: The Costs, Risks, and Returns

Section 1: Introduction

Pharmaceutical research and development (R&D) has received a considerable amount of attention in recent years. In particular, the risks, the costs, and the returns of pharmaceutical R&D have come under much scrutiny. This attention has primarily arisen from the general perception that the pharmaceutical industry is excessively profitable, which—in light of the increased movement towards greater cost-containment in healthcare—has been particularly accentuated. As an illustration of this view, consider the following quote from Senator Pryor during a 1992 congressional debate on pharmaceutical price controls:

> *Fortune* Magazine, July 29, 1991, said the manufacture of pharmaceuticals is America's most profitable business. In 1990 the average rate of profit for the Fortune 500 companies was 4.6 percent. What about the pharmaceutical companies? Let us see how they are getting along—15.5 percent, that was their average profit in the year 1990. Now how do they make these enormous profits? By outright price gouging of our American citizens . . .

Consequently, a tremendous amount of research activity has been undertaken in recent years to estimate the costs and returns of pharmaceutical R&D. Therefore, the first objective of this chapter will be to provide an overview of the key factors that affect such R&D costs and returns. To this end, recent studies that have estimated these costs and returns will be summarized along with brief descriptions of each study's methodology. The second objective of this chapter will be to examine, within the same context, recent trends in the pharmaceutical R&D process. This will "lay the ground work" for future discussions and provide the reader with a broad overview of the pharmaceutical R&D landscape and how this landscape has changed over the years.

In the context of a comprehensive overview of the pharmaceutical R&D process, it will be advantageous to examine it from two separate but related perspectives—the scientific perspective and the economic perspective. However, the principal focus of this chapter will be on the economic perspective. Specifically, as already stated, this chapter will be concerned with R&D in the context of its inherent costs, risks, and returns. The scientific perspective on pharmaceutical R&D, while not the main focus of this chapter, will be explored first—in particular, the R&D process, scientific developments, recent technological developments, and research trends. The scientific perspective will establish a framework in which the economic considerations relating to R&D may be couched.

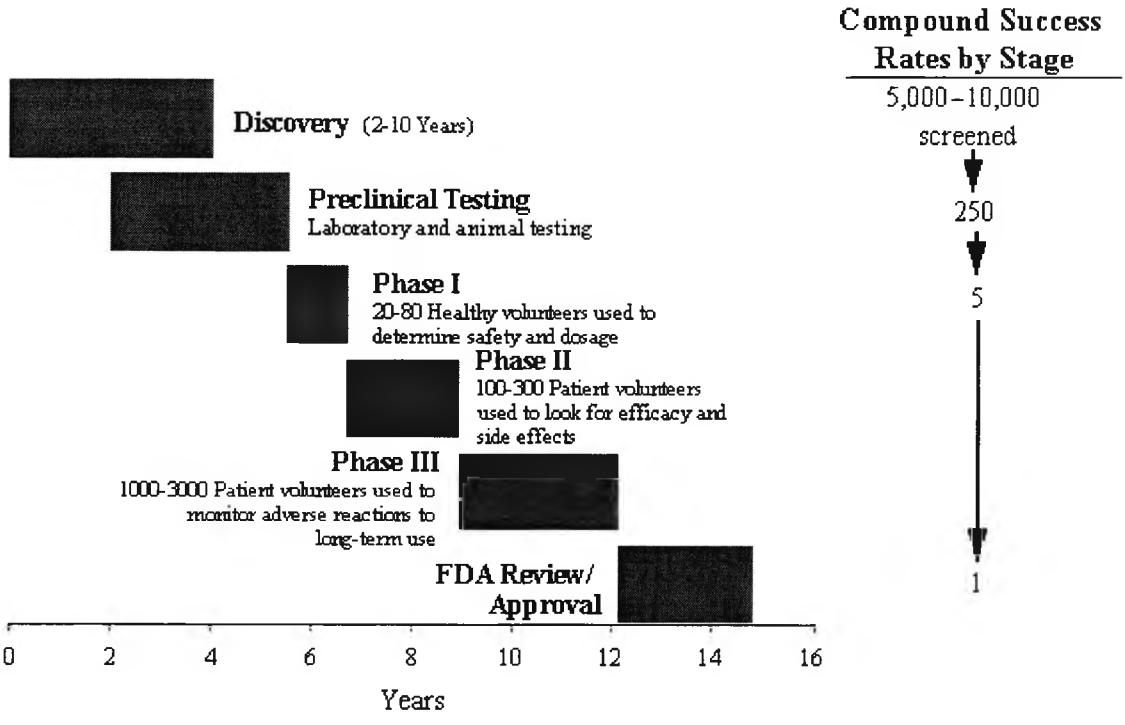
Section 2.1: Scientific Perspectives on Pharmaceutical R & D

Section 2.2.1: The R&D Process

The Pharmaceutical Research & Development process is one of discovering, developing, and bringing to market new ethical drug products. This process has long been the main means of competition among firms in the pharmaceutical industry. As such, understanding this process and its inherent risks, costs, and potential rewards will be of paramount importance to understanding how firms make strategic R&D decisions —the subject of this thesis.

The pharmaceutical R&D process for a new drug candidate is comprised of many phases. For the successful drug candidate (the one that eventually makes it to market) this process takes an average of 14.9 years (PhRMA, 1998). Indeed, pharmaceutical R&D is a very long, risky, and costly process, in which only one out of five drugs in clinical development reaches the market (PhRMA, 1998). The pharmaceutical R&D process is illustrated below in figure 2.1 along with the average length of time a successful drug candidate spends in each stage of development. Following this figure is a brief description of each stage.

Figure 2.1



Source: PhRMA, based on data from Center for the Study of Drug Development Tufts University, 1995

Section 2.2.2: *Synthesis and Extraction*

The first step in the R&D process begins with synthesis and extraction. This initial process involves the identification of new molecules. New molecules may be produced through artificial synthesis or extracted from various natural resources such as plants, animals, or minerals. Specifically, new molecules are sought that have the potential to alter certain biological systems. For example, a molecule may be extracted or synthesized and found to be capable of stimulating or inhibiting an important enzyme within the aforementioned biological system. Alternatively, a new molecule may be found to have certain properties that allow it to alter metabolic pathways or change various cellular structures within the biological system.

Synthesis and extraction may involve many different activities directed towards the identification of new molecules. Initially, the disease-state may be studied and examined in detail to uncover or better understand the key mechanisms or biological

processes of the disease. Additionally, the pharmacokenetics, metabolic properties, or other actions of known and available therapeutic agents may be researched in order to identify potential new molecules. Finally, the random selection and broad-based biological screening of extracted or synthesized molecules may lead to new molecules with favorable properties.

Section 2.2.3: *Biological Screening and Pharmacological Testing*

The second major step in the early drug discovery process involves the biological screening and pharmacological testing of the new molecules produced during synthesis and extraction. These studies are aimed at identifying the therapeutic potential and pharmacological properties of new compounds. This highly sophisticated process has evolved dramatically over the past few decades. The end result has been the transformation of the drug discovery process from one of random screening and serendipitous drug discovery to one of rational drug design. More will be said on this evolution in drug discovery and rational drug design later in this chapter.

The various tests and/or techniques used during the screening phase of discovery typically involve the use of isolated tissues and cell cultures, animals, cloned drug receptor sites (usually proteins), enzymes, and more recently sophisticated computer models. Once the above tests have identified compounds with beneficial activity and therapeutic potential, an iterative process of structural modification is undertaken. This iterative process is continued until the structure of the molecule with the highest potential therapeutic benefit is found.

Section 2.2.4: *Pharmaceutical Dosage Formulation and Stability Testing*

Following the determination of a molecule's structural form, the active compound will have to be turned into a strength and dosage appropriate for use in humans. In addition to the different possible dosage strengths (e.g., 50, 100, 250, 500 mg), there are several dosage forms that may be used in administration. For example, an active

compound may be administered in liquid form, tablet form, capsule form, or in sprays, ointments, and patches. Moreover, because the final formulation of any pharmaceutical product necessarily contains substances other than the active ingredient, the impact of these substances on the human body must be tested. These additional substances, also called excipients, are used for various reasons. For example, excipients may be needed to improve the taste of an oral product, to delay the absorption of the drug into the body's blood stream, to prevent bacterial growth in liquid or cream preparations, or to allow the active ingredient to be compounded into stable tablets. Thus, the dosage formulation and stability testing phase of the R&D process is concerned primarily with turning an active compound into a strength and formulation suitable for use in human beings.

Section 2.2.5: *Toxicology and Safety Testing*

The next phase in the R&D process is toxicology and safety testing. Toxicity and safety tests are conducted to determine the risks and or dangers that a compound may pose to both human beings and the environment. Specifically, these tests are conducted to provide vital information on the relationships between dosage, frequency of drug administration, the duration of exposure, and the short- and long-term survival of living organisms (i.e., animals and tissue cultures). Furthermore, in addition to providing information on the toxicity of a compound, toxicology and safety testing also provide key information on dose-response patterns.

Section 2.2.6: *Investigational New Drug Application (IND)*

After completion of toxicity and safety testing, if a compound still seems viable, the company may file an Investigational New Drug Application (IND) with the United States Food and Drug Administration (FDA) to begin testing in human beings. The IND contains the findings from the pharmacological testing, stability testing, toxicity and safety testing, and all other known information about the compound. Moreover, a full

and detailed clinical research plan for the compound must accompany the application. Unless the FDA rejects the IND, the IND is automatically approved 30 days after submission.

Section 2.2.7: *Phase I Clinical Studies*

After the IND application has been approved, phase I clinical studies may begin. Phase I studies are conducted primarily to evaluate the compound's absorption, distribution, metabolism, and excretion patterns in healthy human beings. Furthermore, it is during this phase that compound tolerance is assessed and pharmacological properties are determined.

Section 2.2.8: *Phase II Clinical Studies*

Subsequent to phase I clinical evaluations, and assuming there were no unforeseen negative clinical findings, phase II clinical studies begin. In phase II controlled clinical trials are conducted. Generally, these trials are double-blinded and randomized and seldom involve more than a few hundred subjects. It is during this phase that the clinical efficacy of a compound is first examined. Typically, Phase II trials evaluate the relative therapeutic efficacy between the new compound and placebo and between the new compound and a known therapeutic agent (i.e., a marketed drug with a similar indication). In addition to assessing therapeutic efficacy, these trials also allow the company to study and evaluate any observed adverse events or side effects. Finally, the phase II clinical trial results play a major role in planning the phase III program for the compound. However, poor phase II results may lead to the termination of the compound's entire development program. This decision of whether or not a compound should advance into a phase III program is often referred to as the Go/No-Go decision.

Section 2.2.9: *Phase III Clinical Studies*

If the determination is made to take a compound into full development (i.e., a Go decision at the end of phase II), phase III clinical trials begin. Phase III programs often involve both a greater number of clinical trials and greater number of subjects per clinical trial. Primarily, phase III trials seek to demonstrate, at a statistically significant level, a compound's therapeutic efficacy and safety. In particular, phase III trials gather precise information on a drug's efficacy for highly specific indications. This is unlike the phase II trials, which examine a much broader base of potential indications. Furthermore, a broader range of potential adverse events are examined and considered in phase III trials. Finally, phase III trials study the best way of administering and using the drug for the purpose it is indicated. In more recent years, phase III programs have also started to include studies on the potential economic impact new drugs. That is, the impact that new drugs may have on health care resource utilization. While the FDA does not presently require these economic data, they are becoming increasingly more relevant in reimbursement and formulary decisions. Consequently, these economic studies—sometimes referred to as pharmacoeconomic studies—are becoming much more integrated into phase III programs.

Section 2.2.10: *Process Development for Manufacturing and Quality Control*

Process development for manufacturing and quality control generally takes place towards the end of the phase III program. This is an engineering process that develops an efficient, large-volume production infrastructure for the new drug should it be approved. This process also involves quality control issues like product or batch-to-batch uniformity and chemical stability. Furthermore, the initial planning for this process is conducted in parallel fashion to the phase III clinical trials. This ensures that the new drug may be launched quickly at the time of FDA approval.

Section 2.2.11: *Bioavailability Studies*

Bioavailability studies take place both at the beginning of human testing and just prior to market launch. They are conducted in healthy volunteers to document the rates of absorption and excretion from the body of the active ingredient used in the formulation of the drug. The bioavailability studies conducted immediately prior to launch are required to demonstrate that the formulation of the active ingredient used in the phase III trials will be equivalent to the formulation distributed to the market.

Section 2.2.12: *New Drug Application (NDA)*

After phase III clinical trials are completed, a New Drug Application is filled with the FDA to market the drug. The NDA contains all the information obtained about the new drug from all phases of discovery and development. Upon receipt of the application, the FDA will review all the data from the discovery and development phases and may request clarifications of the data or additional information--possibly more phase III studies. Finally, the FDA will make a decision on whether or not to approve the drug for market.

Section 2.2.13: *Post-approval Research and Phase IV Clinical Studies*

Post-approval research and phase IV clinical studies frequently involve surveillance activities and new clinical trials. While the FDA sometimes mandates phase IV research as a contingency of drug approval, this type of research often occurs in the absence of such FDA requirements. Phase IV research is important for several reasons. These studies provide important information on yet undetected adverse outcomes. This is particularly true in sub-populations not studied in the phase II and III clinical trials (i.e., the elderly, young children, or pregnant women). Furthermore, phase IV observational studies and a similar type of research may be used to evaluate the drug's long-term morbidity and mortality profile. Finally, phase IV economic studies may be conducted

for marketing purposes to evaluate the potential economic benefit a new drug may provide the health care system.

Section 2.3: *Trends in Science and Technology: Rational Drug Design*

The process of drug discovery has changed dramatically in the past few decades. Drug discovery, once a more or less random process of screening huge volumes of chemicals and looking for a desired chemical or biological response, has now become a highly precise process of a priori drug design. Specifically, the majority of new drug discoveries involve a detailed study and analysis of drug receptors. Drug receptors are molecules that bind with specific agents to cause a change in cellular or biological function. A frequently used analogy for drug action and receptor molecules is that of a lock and key—in which the lock is the receptor molecule and the key is the drug. To carry the analogy a little further, developing a key to fit the lock with knowledge of the lock's precise shape will be a much simpler process than randomly making keys and seeing if they open the lock. In scientific terms, precise information about a receptor molecule's properties and characteristics makes it possible to design a chemical compound that will effectively bind with the receptor molecule. Furthermore, when a substance is capable of binding with a receptor molecule one of the following cellular actions may occur:

1) The receptor molecule may open the cellular "gate," allowing for an influx of charged molecules through the cell membrane.
2) The receptor molecule may open the cellular "gate" for an efflux of charged molecules through the cell membrane.
3) The receptor molecule may catalyze a biochemical reaction.

Examples of some of the above cellular actions would be the secretion of insulin or the synthesis of specific proteins. Clearly, understanding the properties and structure of receptor molecules as well as understanding the biomedical causes of a given disease are the key to discovering new drugs. The technology needed to acquire this detailed

knowledge, specifically regarding the receptor molecules, includes a variety of expensive analytical instruments and techniques (i.e., magnetic resonance spectroscopy and x-ray crystallography) and massive computer power to conduct structure activity analysis. Both the rapid growth in technology and the rapid growth in science have resulted in an exponentially expanding base of knowledge about disease mechanisms. The result has been a virtually endless supply of potential research directions related to the use and discovery of new pharmaceutical products.

In addition to the aforementioned advances in the drug discovery and development processes, there has evolved a new and expanding field of genetic research known as pharmacogenomics. This new field, which involves the study of the relationship between genetics and drug response, will almost certainly have a tremendous impact on pharmaceutical R&D in the future. However, this new field of genetic research is beyond the scope of this thesis and will not be addressed further.

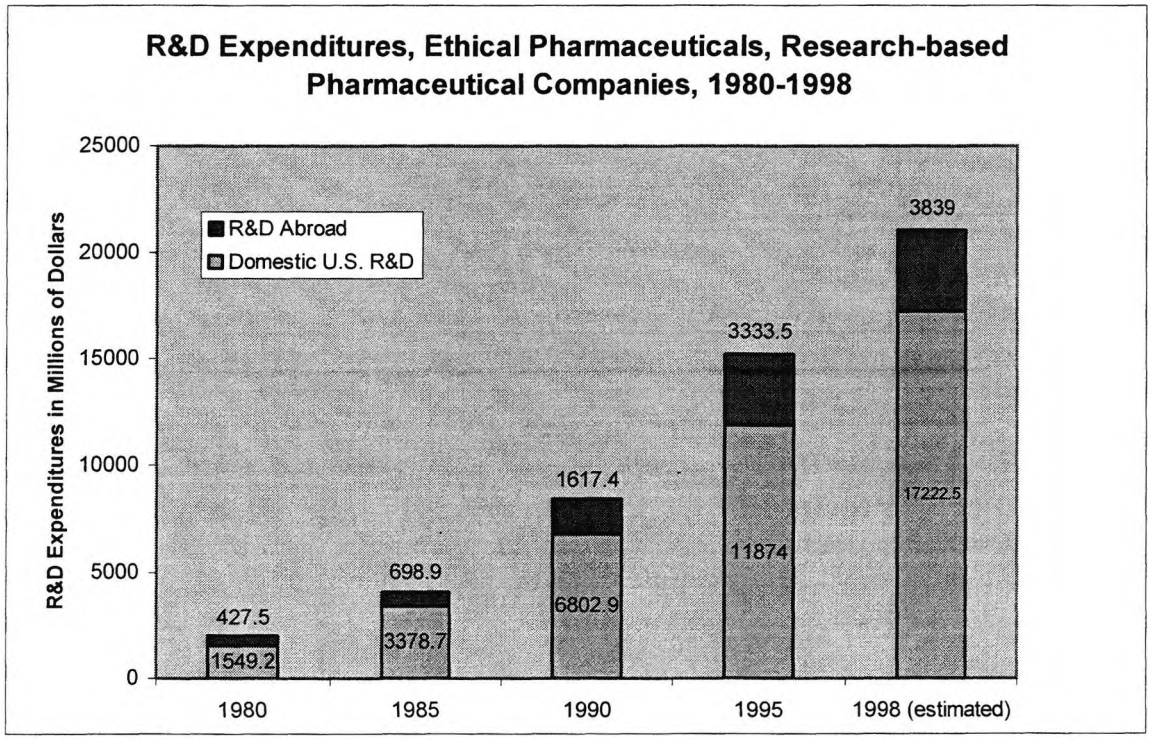
Section 3.1: Economic Perspectives on Pharmaceutical R&D

A number of changes have occurred in the past few decades that have dramatically altered the pharmaceutical R&D landscape. Specifically, drug development times have steadily increased, and FDA regulation has become much more stringent. This has, in part, contributed to the cost of bringing a new drug to market. Despite the more costly drug development programs, both pharmaceutical accounting profits and total R&D expenditures have risen considerably. These and other trends in the R&D economic landscape are explored and examined in more detail in the following sections.

Section 3.2: *Growth in R&D Expenditures*

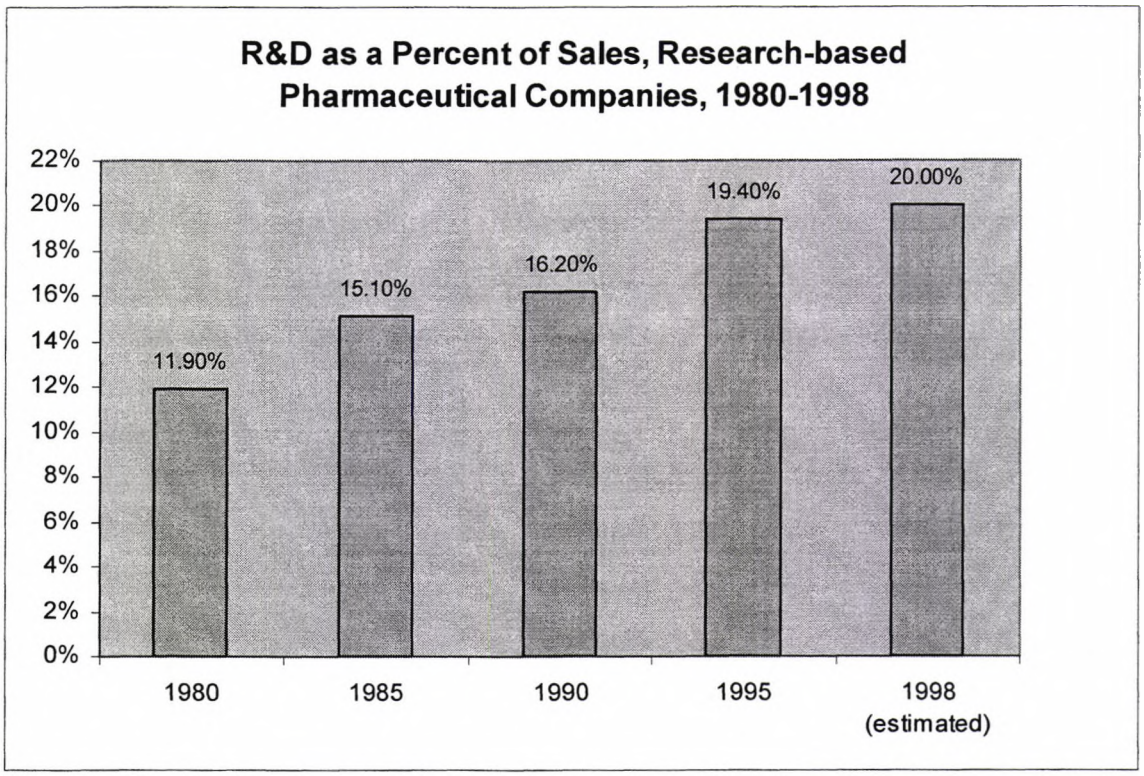
Because one of the central themes of this thesis surrounds the question of how pharmaceutical firms make important R&D spending decisions, trends in aggregate R&D spending are of particular interest. Indeed, in and of its own right pharmaceutical R&D has received much attention due to the dramatic growth in R&D expenditures in recent years. Moreover, these increases in R&D expenditures have been accompanied simultaneously by substantial increases in R&D intensities—the ratio of R&D expenditures to total pharmaceutical sales. Figures 2.2 and 2.3 show these trends in R&D growth below.

Figure 2.2



Source: PhRMA Annual Survey, 1998.

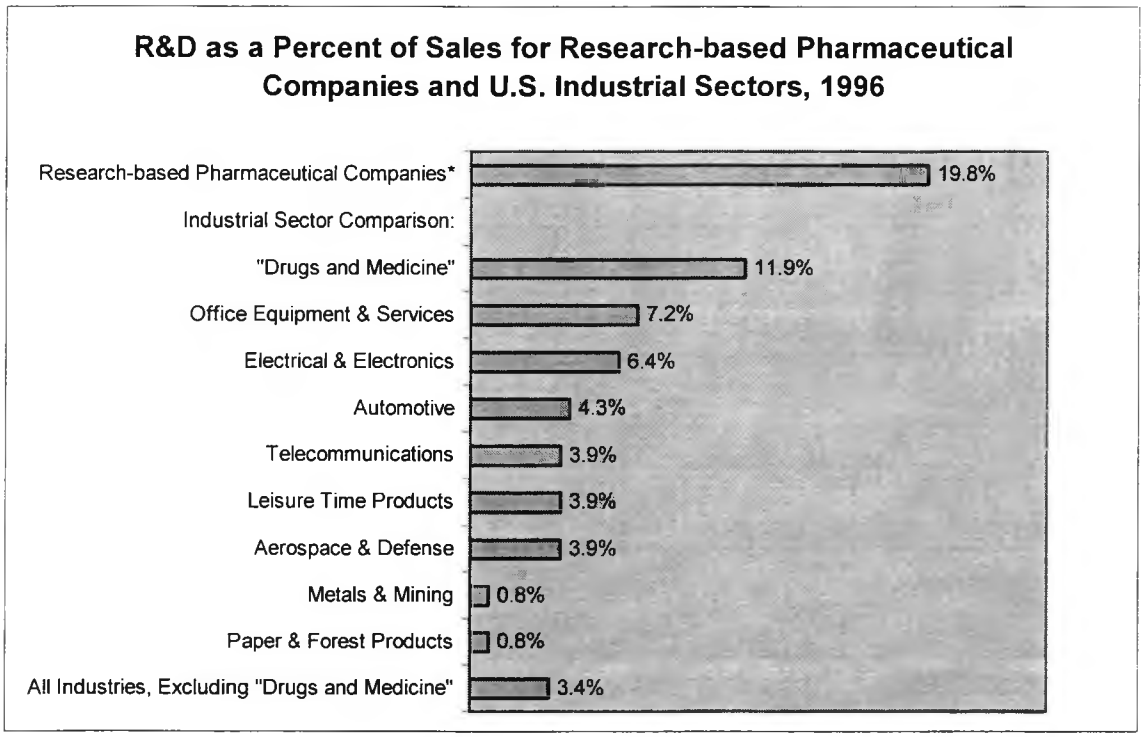
Figure 2.3



Source: PhRMA Annual Survey, 1998.

This steady growth in pharmaceutical R&D spending is especially interesting, because the pharmaceutical industry is one of the most research-intensive and innovative industries in the world. The R&D intensities of several key research-based industrial sectors are shown below in Figure 2.4.

Figure 2.4



Source: PhRMA, 1998, based on data from PhRMA Annual Survey and Standard & Poor's Compustat, a division of McGraw-Hill.

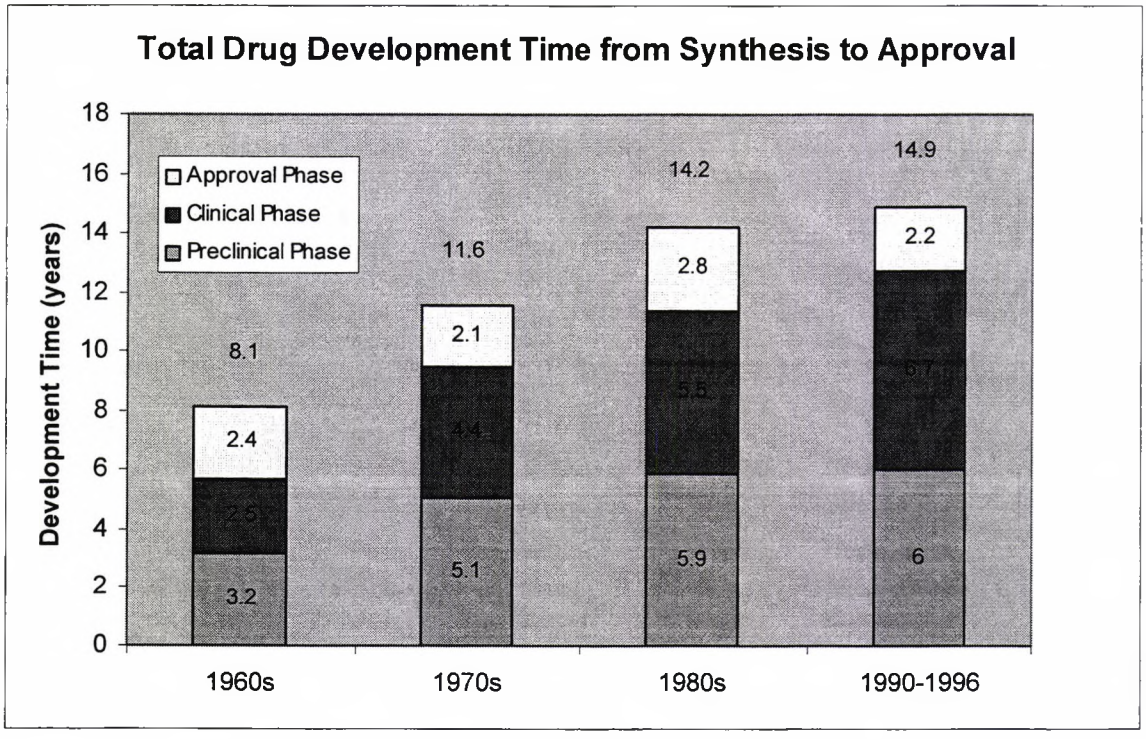
**"Research-based Pharmaceutical Companies," is based on ethical pharmaceuticals and ethical pharmaceuticals R&D only as tabulated by PhRMA. Drugs and categories are based on total R&D and sales for companies classified within the "Drugs and Medicine" sector as tabulated by Standard & Poor's Compustat, a division of McGraw-Hill.*

Section 3.3: *Trends in Drug Development Times*

Investment in pharmaceutical R&D is a very long and risky process. In fact, as scientific knowledge and technology have increased, allowing researchers to target more complex diseases and test more complex drug molecules, so too has the average length of time it takes a pharmaceutical product to advance through the development process. In fact, total drug development times have been increasing steadily since the 1960s. Specifically, the average drug development time has increased from 8.1 years in the 1960's, to 11.6 years in the 1970's, to 14.2 years in the 1980's, and finally to 14.9 years for drugs approved in the 1990's. This change in total drug development time, which is

defined to be the time from molecular synthesis to FDA approval, is show below in Figure 2.5 .

Figure 2.5



Source: Tufts Center for the Study of Drug Development, 1998.

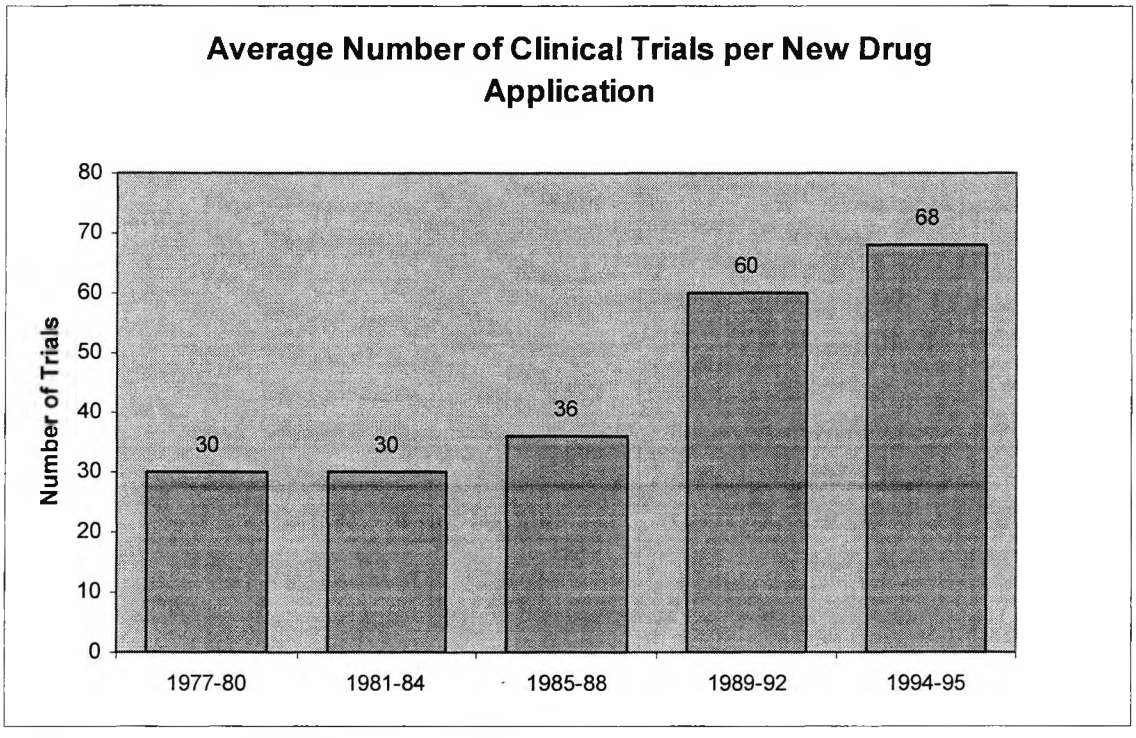
There are several possible reasons for the above trend in drug development times. First, there has been a rapid growth in the scientific complexity of the drug development process. Today, as well as in the recent past, drugs are being developed to target persistent, degenerative, and life-threatening diseases. These new drugs typically take a much longer time to research and fully develop. Another reason for this trend may be the growing number of FDA guidelines and data requirements—possibly the result of a more complex and scientifically advanced drug development process. For example, the FDA now requires that demographic analyses of clinical data be conducted.

Furthermore, now more than ever before clinical studies are designed to satisfy the regulatory requirements of many countries and not just the U.S. FDA. This has been due largely to the expanding global market place—in which most pharmaceutical firms

now operate. These aforementioned scientific and regulatory dynamics have almost certainly been the driving force behind the observed increase in average drug development times[1].

One effect of these new regulatory hurdles has been an increase in the quantity of clinical trials conducted per NDA. Specifically, this number has more than doubled since 1980 (Boston Consulting Group, 1997). This is shown below in Figure 2.6. Similarly, and along the same lines, there has been a three-fold increase in the number of clinical trial subjects enrolled per NDA (Boston Consulting Group, 1997). This trend is shown in Figure 2.7.

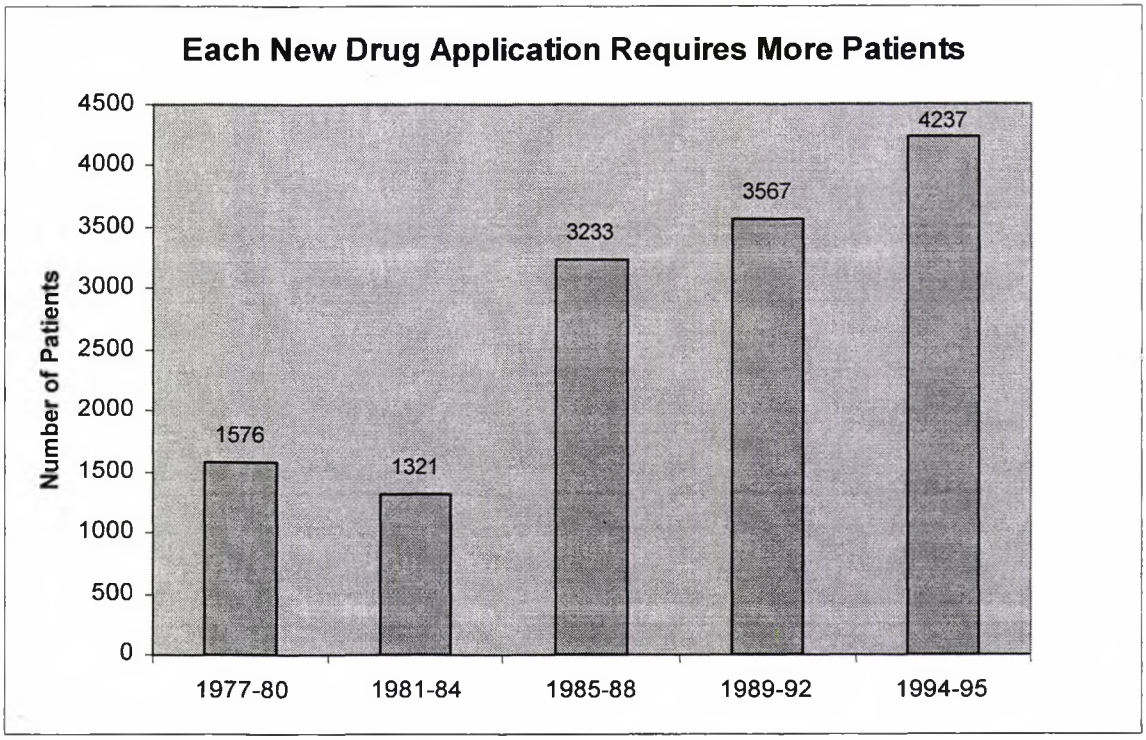
Figure 2.6



Sources: Boston Consulting Group, 1993; C. Peck., "Drug Development: Improving the Process," Food Drug Law Journal, Vol. 52, 1997.

[1] The recent growth in managed care is also likely to be a contributing factor to aforementioned trends. Indeed, pharmaceutical firms must ultimately satisfy the data requirements of their major customers—the managed care plans. One such major data requirement is pharmacoeconomic studies/data. These studies unquestionably add to the cost and time of conducting R&D.

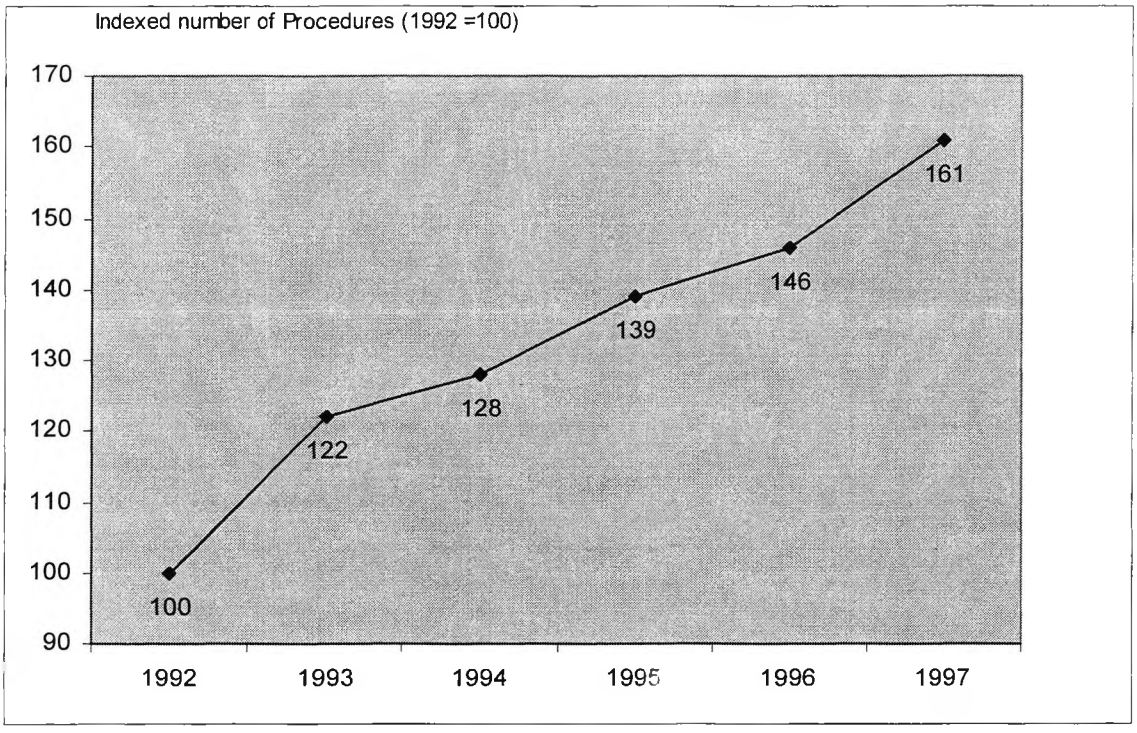
Figure 2.7



Sources: Boston Consulting Group, 1993; C. Peck, "Drug Development: Improving the Process," Food Drug Law Journal, Vol. 52, 1997.

Indeed, the average number of medical procedures performed per clinical subject has also risen considerably in recent years. This too is a direct result of the elevated regulatory requirements facing clinical trials. These data are summarized below in Figure 2.8.

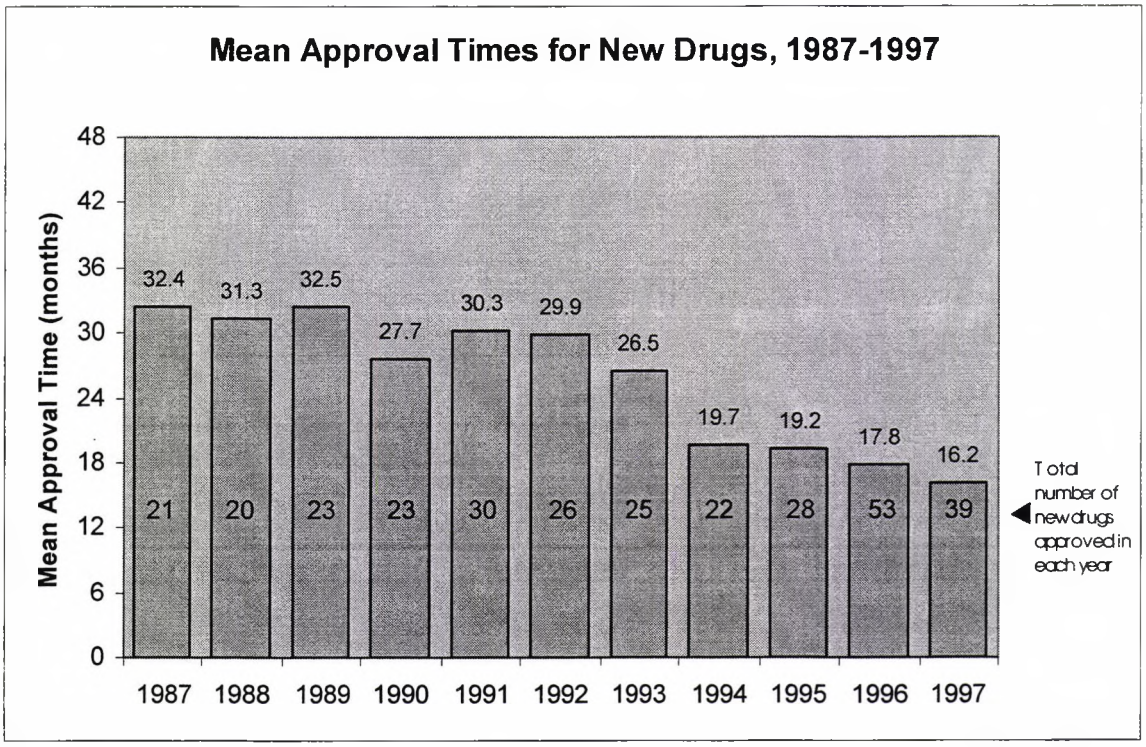
Figure 2.8



Source: DataEdge, 1998.

Furthermore, while clinical development times have increased steadily over the years, the opposite is true for FDA review times. The average FDA review time has decreased from 32.4 months in 1987 to half that, or 16.2 months in 1997 (FDA, 1998). This trend is depicted below in Figure 2.9.

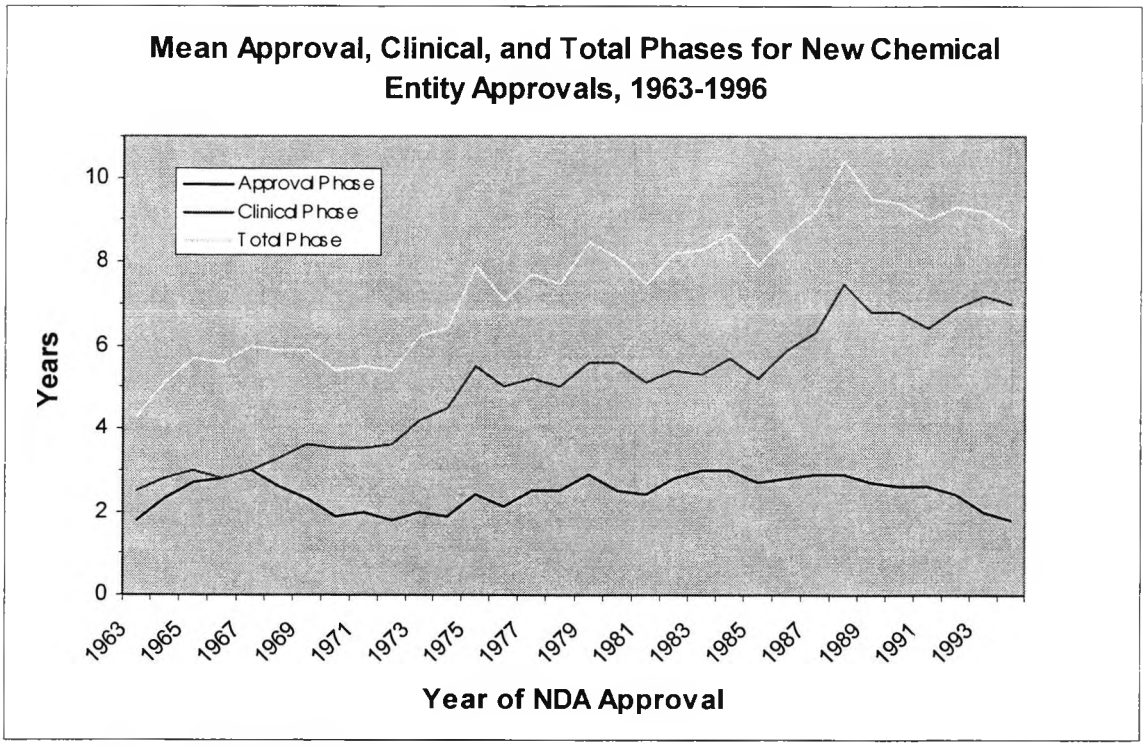
Figure 2.9



Source: U.S. Food and Drug Administration, 1998.

The above trend in regulatory review times for new drugs may be explained largely by the 1992 Prescription Drug User Fee Act. This Act, which was passed in an effort to streamline FDA operations, was an arrangement in which the pharmaceutical industry agreed to supply the FDA with $327 million in funding to hire 600 additional NDA reviewers. More recently, the 1997 FDA Modernization Act extended the 1992 Act and made provisions for an additional $550 million in funds to support the FDA's efforts to improve and modernize its review process. This 1997 Act is likely to shorten review times even more. So while the length of clinical development times have increased substantially, regulatory review times have decreased. The net effect, however, has been a significant increase in the total length of time it takes the average drug to reach the market—from IND submission to FDA approval. These trends are shown together in Figure 2.10.

Figure 2.10



Source: Tufts Center for the Study of Drug Development, 1997.
Note: Clinical phases in Figure 2.10 do not include the pre-phase I discovery times.

Finally, another important, yet relatively new trend, has been the rapid growth of economic, or pharmacoeconomic, studies. Because these studies are conducted alongside most phase II and phase III clinical studies, it is possible that they, too, may add to the duration of a clinical development program. Pharmacoeconomic studies, which are quickly becoming an integral part of the drug development process, seek to establish economic value (or cost-effectiveness) of new therapies. Indeed, many counties and managed care organizations now require this type of data for approval, reimbursement, and or formulary acceptance.

There have been many changes in the pharmaceutical R&D landscape over the past few decades. Indeed, the increased complexity of modern drug development, the growth in FDA requirements, and several other factors have significantly lengthened drug development times. These changes have almost certainly increased the risk and cost of pharmaceutical R&D. In fact, the risk, the time, and the cost of conducting R&D are all very intimately related, as will be discussed in detail in the sections that follow.

Section 3.4: *Drug Research & Development Costs: The Cost of Bringing a New Drug to Market*

The cost of developing a new drug will necessarily be sensitive to a number of variables. For example, trends in science and technology, shifts in the therapeutic classes and types of drugs being developed, and changes in the regulatory environment. In recent years several studies have attempted to estimate this cost. However, these estimates may not reflect the contemporary cost of developing a new drug. This is because they are based on drugs that were recently approved—implying that they started through the development process many years ago. Consequently, these estimates will be, by definition, retrospective in nature and hence not likely to be representative of current development patters and costs. Nonetheless, estimates of these costs should shed light on the pharmaceutical R&D landscape of past decades—the focus of this thesis. That having been said, it is likely that the cost of bringing a new drug to market has increased substantially. This may be due in part to the fact that, as mentioned previously, the average number of clinical trials per NDA has more than doubled, and the average number of clinical subjects per NDA has approximately tripled since 1980. (Refer to Figures 2.6 and 2.7.) Moreover, the average drug development time has increased substantially. (Refer to figure 2.5.) Clearly, these trends towards larger and longer clinical development programs are likely to add to the cost of bringing a new drug to market.

Section 3.5: *Methodologies and Estimates*

Several factors play a key role in determining the cost of bringing a new drug to market. These factors, and the methods used to estimate them, will be discussed in detail below. Before delving into a review of recent study estimates, it will be necessary to first discuss the methodologies of how, theoretically, the cost of bringing a new drug to market should be estimated.

The cost of bringing a new drug to market should, in theory, include expenditures on R&D projects that failed or were abandoned in the search for (and development of) the eventually approved drug. That is, without any a priori knowledge as to which projects will fail and which projects will succeed, it is impossible to avoid these expenditures. Indeed, pharmaceutical R&D has often been compared to drilling for oil, because there are many "dry holes" and relatively few "gushers." Consequently, the cost of bringing a new drug to market is more than the expenditures on the successful drug's R&D program. The true cost must also include the expenditures incurred by the failed and abandoned R&D programs.

However, there is considerably more to estimating this cost than simply aggregating all cash outlays for both the successful and unsuccessful R&D projects. To accurately estimate the cost of bringing a new drug to market it is imperative to consider two other key factors: **time** and **risk.** A fair amount of detail is devoted to these two factors in the following sections due to the importance that both have in the later chapters of this thesis.

In theory, the true cost of bringing a drug to market can be thought of as the smallest payoff required to induce investors to supply the necessary funds at each stage of the R&D process. This includes the funds for projects that will ultimately fail. Then, in order to obtain an estimate of the total cost required to bring the drug to market, each of the R&D cash outlays must be capitalized forward—at an appropriate rate of interest—to the day of NDA approval. From this perspective it is easy to see how the true cost of bringing a new drug to market will necessarily be greater than the sum of the expenditures on the successful and unsuccessful R&D projects.

The above explanation may be re-stated more precisely in the following way. For investors in pharmaceutical R&D to be willing to provide the necessary funds for the R&D, they must:

1) Expect to recoup their initial investment;
2) Be adequately compensated for the risk that they might lose their entire investment;
3) Be compensated for the time they must spend waiting for the returns from their investment.

These three key components highlight the important roles time and risk play in determining the true cost of bringing new drugs to market. Consequently, a detailed explanation of exactly how time and risk affect the cost of bringing a new drug to market will be given. Particular attention will be focused on the component of risk and its influence on the cost of pharmaceutical R&D.

Section 3.6.1: *Time and the Opportunity Cost of Capital*

When considering inter-temporal R&D investment decisions, the timing of the cash flows (i.e., investment expenditures and returns) is crucial. This is particularly true for pharmaceutical R&D investments because of their extremely long time horizons. The following section will briefly explain the fundamental principles that underlie this concept.

A dollar received today is not equivalent to a dollar received one year from today. This is because a dollar received today may be invested and earn interest for one year. For example, assume a per annum interest rate r, where r is the interest rate on a bank deposit. Therefore, a dollar today will be worth, or have a *future value* of, $1+r$ dollars next year—clearly preferable to 1 dollar next year. Alternatively stated, $1+r$ dollars received one year from today has a *present value* of 1 dollar today. Thus, the benefit of receiving a dollar today, versus receiving it one year from today is r dollars. This may be expressed in another way: the opportunity cost of a one-year delay in receiving the dollar is the forgone interest, r.

Therefore, it is clear that in order to make comparisons between R&D investment dollars in different years, one must adjust for the above type of opportunity cost—the opportunity cost of capital. Specifically, when estimating the cost of bringing a new drug to market one must account for these forgone opportunities by capitalizing past R&D expenditures up to the year of the NDA approval. This capitalized value will then represent the true economic cost of bringing the new drug to market.

Mathematically, the capitalization of R&D expenditures for an n-year drug development program—with an NDA approval in year t—is represented below by equation (1):

$$PV_t = \sum_{i=0}^{n} A_{t-i}(1+r)^i \qquad (1)$$

Where PV_t is the present value of all R&D expenditures capitalized to year t (the year of NDA approval) and A_{t-i} is the R&D expenditure in year $t-i$. Recall, however, that A_{t-i} should include R&D expenditures on the projects that failed in the process of developing the successful drug. A theoretically more realistic representation, however, will take into account the fact that R&D expenditures occur in a continuous, rather than discreet, fashion. Hence the following:

$$PV_t = \int_0^n A(t-i)e^{ri}di \qquad (2)$$

It is crucial to note from equations (1) and (2) that this capitalized value will necessarily be highly sensitive to:

1) The length of the R&D project/program;
2) The timing of the cash outlays;
3) The opportunity cost of capital.

A simple hypothetical example will illustrates this point:

Example 1: The Cost of Bringing a New Drug to Market

Assume that a particular R&D program required investments of $1,000,000 once a year, each year, for 10 successive years prior to receiving an NDA approval for a new drug (with the last expenditure occurring a year before NDA approval). In this example,

the capitalized value of the stream of R&D expenditures at the time of FDA approval would be:

$$PV = 1{,}000{,}000\sum_{i=0}^{9}(1+r)^{10-i} \tag{3}$$

Assuming an opportunity cost of capital equal to 10%, this would yield:

$$PV = \$17{,}531{,}167 \tag{4}$$

Which is substantially greater than the sum of all 10 outlays—i.e. $10,000,000[2].

To illustrate within the context of the above example the sensitivity of this cost to various development times and costs of capital, sensitivity analyses were performed—refer to Table 2.1 below. Note, however, that what is not considered in Table 2.1 is the distribution of R&D expenditures over the total development period—this distribution was assumed to be uniform for simplicity. Nonetheless, Table 2.1 illustrates nicely the sensitivity of the cost of bringing a drug to market to both the length of the development program and the opportunity cost of capital.

Table 2.1

10MM cash outlays under different assumptions

Cost Of Capital	Time in Development: 5 Years	10 Years	15 Years
5%	$11,603,826	$13,206,787	$15,104,994
10%	$13,431,220	$19,531,167	$23,299,812
15%	$15,507,477	$23,349,276	$36,478,315

It can be seen from Table 2.1 that the opportunity cost of capital has a dramatic effect on the cost of bringing a new drug to market. For example, a 5% difference in the cost of capital (15% vs. 10%) for a 15-year development program increases the true

[2] Following Hansen (1979) and DiMasi (1991), total drug development costs were evaluated at the time of market launch. For this reason cash outlays were capitalized instead of discounted. If, however, total drug development costs were evaluated at the time of discovery, an inverse relationship would be observed between total development costs and the cost of capital. The later measure is the appropriate type for contemporaneous investment decision-making—when future cash flows are *expected* cash flows.

economic cost of developing the new drug by 57%! Consequently, estimates of the cost of bringing a new drug to market must utilize the appropriate opportunity cost of capital. For this important reason the opportunity cost of capital for pharmaceutical R&D will be the focus of the next section.

Section 3.6.2: *Risk: The Appropriate Opportunity Cost of Capital for Pharmaceutical R&D*

While a rigorous exploration into the theoretical determinants of the cost of capital for pharmaceutical R&D is beyond the scope of this chapter, a thorough explanation and detailed overview of some of the key concepts that underlie these determinants will be presented. Investors in pharmaceutical R&D invest their money because they expect returns that, on average, sufficiently compensate them for the time and risk involved in their investment. Furthermore, the returns that investors in pharmaceutical R&D expect are no different than, say, the interest depositors expect from their bank accounts. That is to say, the interest paid on a bank deposit is a payment in exchange for the depositers' money (or capital). This is analogous to the returns from R&D being a payment in exchange for the capital needed to undertake the R&D. The one major difference is the level of risk involved in these two investments.

As was mentioned earlier, pharmaceutical R&D is a long and risky process with few drugs actually making it to market. Hence, if the expected returns from pharmaceutical R&D were no greater than the interest that could be earned on a bank deposit (which has very little risk), then investors would have no incentive to invest in the riskier R&D. Therefore, the expected returns on R&D must be greater than the interest on the bank deposit for investors to be willing to put up their money. That is, as investors assume more risk, they expect to be compensated with higher returns. This is the risk and return tradeoff. However, in the conventional view of the risk of pharmaceutical R&D it is not the risk per se that matters when estimating the opportunity cost of capital appropriate for pharmaceutical investments. This important fact will be the focus of the following two sections, which will characterize and discuss two types of risk, unique risk

and market risk, and the role each plays in determining the opportunity cost of capital for pharmaceutical R&D.

Section 3.6.3: *The Two Types of Risk: Unique Risk and Market Risk*

Section 3.6.4: *Unique or Diversifiable Risk*

What is the risk of a pharmaceutical R&D investment? This is a question that must be answered in order to determine the cost of capital for any R&D project. If there were no risk at all, the cost of capital would be the same, say, as that of a US Treasury Bill (a risk free investment). Indeed, pharmaceutical R&D is not risk free. In fact, pharmaceutical R&D is one of the riskiest types of R&D. For that matter, it is one of the riskiest types of investments period. However, the conventional notion regarding the risk of pharmaceutical R&D is quite different from the risk that ultimately influences the cost of capital for this type of investment.

Modern finance theory distinguishes between two different types of risk: unique risk, which is diversifiable, and market risk, which is not diversifiable. The first type of risk, unique risk, is the risk that is highly specific to the individual R&D projects. This is the type of risk that has created the conventional notions regarding the investment risks of pharmaceutical R&D. However, this type of risk (which has given pharmaceutical R&D a reputation similar to that of drilling for oil—i.e., many dry holes and few gushers—may be completely diversified away by investors. The term "diversifying away" means that the risk of a specific R&D project (or collection of projects) may be completely eliminated by the investor. This is done, for example, when an investor invests in a large number of such projects (or companies undertaking such projects) and establishes, on average, a cash flow that is very predictable. Consequently, and counter-intuitive to many, this type of risk will not influence a project's opportunity cost of capital and hence the cost of bringing a new drug to market. A simple example nicely illustrates this point:

Example 2: Reducing Unique Risk Through Diversification

Assume a particular R&D project has a 50% chance of being successful and consequently a 50% chance of being unsuccessful. Furthermore, assume that if the project is successful, it will result in a 20% return to the investor. Alternatively, if the project is unsuccessful, it will result in a 0% return to the investor. Therefore, there are two possible outcomes that may result from investing in this project. These outcomes are shown below in Table 2.2.

Table 2.2

Hypothetical Outcomes and Probabilities

Outcome (i)	Return (R_i)	Probability $P(R_i)$
Project is Successful	20%	50%
Project is Unsuccessful	0%	50%

Thus, the investor's expected return on this project may be found by taking mathematical expectations as follows:

$$\text{Expected Return} = E(R) = \sum_{i=1}^{2} P(R_i)(R_i) = 10\% \qquad (5)$$

Hence, the expected return on this R&D project is 10%.

However, the realized return on this project can never be 10%; it must either be 20% or 0%. This motivates the necessity for another means by which this particular R&D investment may be characterized: the distribution or "spread" of possible returns. This distribution of returns is characterized by the variance of the project's returns. The variance of returns for this R&D project is calculated below:

$$\text{Variance of Returns} = Var(R) = \sum_{i=1}^{2} P(R_i)(E(R_i) - R_i)^2 = 1\% \quad (6)$$

From (6) it can be seen that the standard deviation of returns, the square root of the variance, is 10%. The standard deviation and variance are measures of the risk of the project.

To see how diversification enables investors to reduce their investment risk (the variance of investment returns), consider investing equal proportions in two pharmaceutical R&D projects that are identical to the project just discussed. For simplicity, assume that the projects are statistically independent of one another. That is to say, the probability of the occurrence of one event does not depend on whether or not the other event has occurred (this assumption will be relaxed and discussed in detail later). Therefore, if, for example, events A and B are independent, the probability of event A *and* event B occurring ($P(AB)$) is equal to the product of their individual probabilities ($P(A) \times P(B)$). By definition this is statistical independence. This is a very big assumption, and the point will be re-visited shortly. Therefore, in a fashion analogous to the investment in the single R&D project, we have the following four possible outcomes summarized in Table 2.3.

Table 2.3

Hypothetical Outcomes and Probabilities

Outcome (i)	Return (R_i)	Probability $P(R_i)$
Both Successful	20%	25%
Only P1 is Successful	10%	25%
Only P2 is Successful	10%	25%
Neither is Successful	0%	25%

Where the Expected return is,

$$E(R) = \sum_{i=1}^{4} P(R_i)(R_i) = 10\% \tag{7}$$

Hence, the expected return from investing equal proportions in both projects is 10%, the same expected return from investing in the single R&D project.

More interesting, however, is the variance around this expected return:

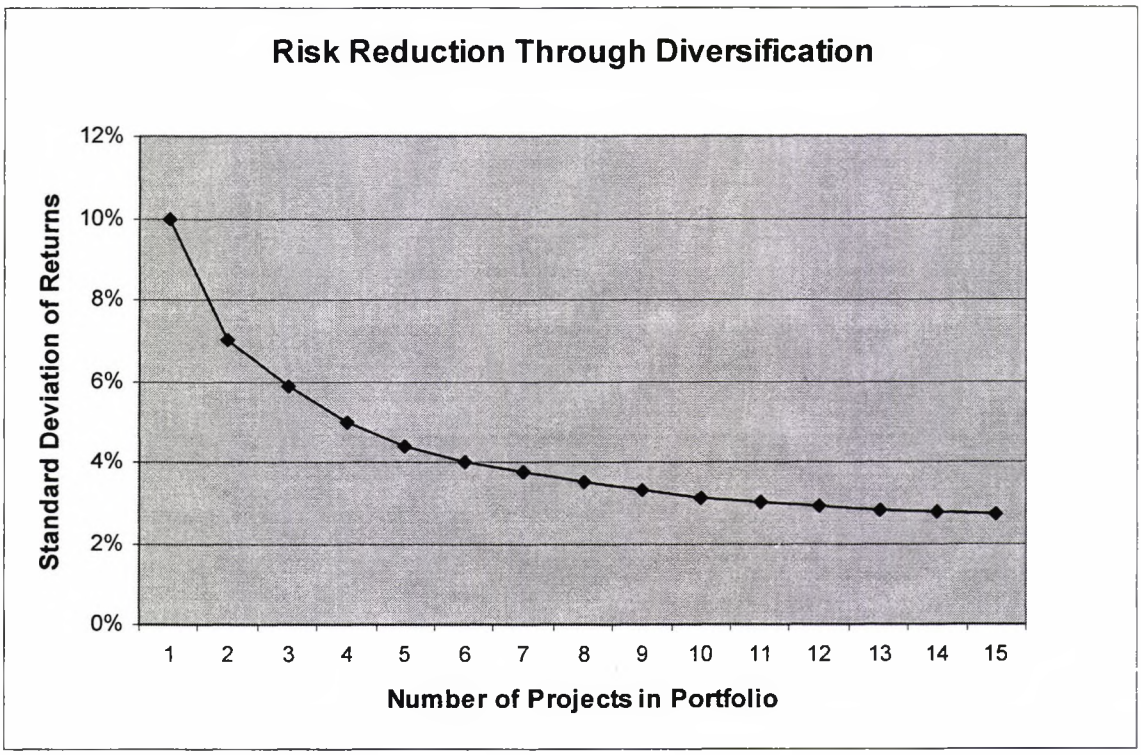
$$Var(R) = \sum_{i=1}^{4} P(R_i)(E(R_i) - R_i)^2 = 0.5\% \tag{8}$$

Which gives a standard deviation of approximately 7.1%.

Thus, by diversifying across the two projects the investment risk is reduced (from a standard deviation of 10% to 7.1%) while the expected return remains the same, or 10%. Clearly, this would be a preferable investment strategy for a risk-averse individual.

In a perfectly analogous fashion, diversification in more of these R&D projects can be shown to further reduce the investment risk while expected returns remain at 10%. This is shown in Figure 2.11.

Figure 2.11



More generally, it can be shown that as an investor diversifies over more and more projects he may eliminate his unique risk completely. This is shown in the context of the above example. First, however, it will be necessary to recall the following properties of statistical expectations:

$$E(R_p) = E(\sum_{i=1}^{n} a_i R_i) = \sum_{i=1}^{n} a_i E(R_i) \qquad (9)$$

Equation (9) states that the expected return on an n-project portfolio (where a_i is the proportion of the portfolio invested in project i) is equal to the weighted-average of the projects' expected returns. Similarly,

$$Var(R_p) = Var\ (\sum_{i=1}^{n} a_i R_i) = \sum_{i=1}^{n} a_i^2\ Var(R_i) \qquad (10)$$

Equation (10) states that the variance of returns from an n-project portfolio (when the project returns are statistically independent) is equal to the sum of the variances of each project's returns—wherein each project's variance is weighted by the square of its proportion to the total portfolio.

Therefore, the variance of returns for an equally weighted n-project portfolio—in which all projects are statistically independent and identical to the projects in the last example—may be expressed as follows:

$$Var(R_p) = \left(\frac{1}{n}\right)^2 \sum_{i=1}^{n} Var(R_i) \tag{11}$$

Where $Var(R_p)$ is the variance of returns from the n-project portfolio.

Furthermore, because all the projects are identical, $Var(R_i) = .01$ for $\forall i$ where $i \in (1,2,3,...n)$. Thus, (11) becomes:

$$Var(R_p) = \left(\frac{1}{n}\right)^2 (.01n) \tag{12}$$

Which obviates the following:

$$\lim_{n \to \infty} Var(R_p) = \left(\frac{1}{n}\right)^2 (.01n) = \frac{.01}{n} = 0 \tag{13}$$

Indeed, even if the n-projects had different variances (or expected returns, for that matter) it is easy to see that the result remains the same. In general, (13) becomes:

$$\lim_{n \to \infty} Var(R_p) = \left(\frac{1}{n}\right)^2 \sum_{i=1}^{n} Var(R_i) = \frac{\overline{Var}}{n} = 0 \tag{14}$$

Where $\overline{Var}$ is the average project variance.

From (14) it is clear that as n grows sufficiently large the distribution of returns around the expected return converges to a spike. This property, in a more general sense, is a direct result of the Law of Large Numbers.

While the above examples are insightful and useful in explaining the concept of diversifiable risk and the benefits thereof, they ignore the possibility that project returns (or returns from investments in firms undertaking pharmaceutical R&D) may not be statistically independent of one another. That is, the above example assumes that the covariance between any two projects i and j is zero. Explicitly, the assumption is:

$$Cov(R_i, R_j) = \sum_{i=1}^{n}\sum_{j=1}^{n}(E(R_i) - R_i)(E(R_j) - R_j) = 0 \quad \text{for } \forall\, i \text{ and } j \text{ where } i \neq j. \tag{15}$$

Indeed, this is a very unrealistic assumption. There are many reasons why the returns from different projects may be correlated, as will be discussed in the next section. Most importantly, when investment returns are not statistically independent, there is a limit to the amount of risk reduction that can be achieved through diversification. In the extreme case, if all projects are perfectly correlated, then no risk may be eliminated through diversification. This nondiversifiable risk, as it will be shown, is the only type of risk that influences the opportunity cost of capital for pharmaceutical R&D projects. This leads naturally into the next section on nondiversifiable, or market, risk.

Section 3.6.5: *Market or Nondiversifiable Risk*

The other type of risk, market risk, is by definition the type of risk that cannot be diversified away. Market risk is determined directly by the co-variations between the various project returns (assumed to be zero in the examples from the last section). When allowing for the possibility of non-zero covariance between projects, the total variance of a portfolio of n pharmaceutical R&D projects becomes:

$$Var(R_p) = \sum_{i=1}^{n}\sum_{j=1}^{n} a_i a_j Cov(R_i, R_j) \tag{16}$$

Where a_i is the proportion of funds invested in project i. Furthermore, note that when $i = j$, $Cov(R_i, R_j) = Var(R_i)$.

Furthermore, assuming that investments are made in uniform proportions across projects, (16) may be written as follows:

$$Var(R_p) = \left(\frac{1}{n}\right)^2 \sum_{i=1}^{n}\sum_{j=1}^{n} Cov(R_i, R_j) \tag{18}$$

Separating out the projects' variance and covariance components, simplifying and then taking limits gives:

$$\lim_{n\longrightarrow\infty} Var(R_p) = \left(\frac{1}{n}\right)^2 \sum_{i=1}^{n} Var(R_i) + \left(\frac{1}{n}\right)^2 \sum_{i=1}^{n}\sum_{j=1}^{n} Cov(R_i, R_j)_{i\neq j} = \tag{19}$$

$$\lim_{n\longrightarrow\infty} Var(R_p) = \frac{\overline{Var}}{n} + \left(\frac{1}{n}\right)^2 (n^2 - n)\overline{Cov}_{i\neq j} = \tag{20}$$

$$\lim_{n\longrightarrow\infty} Var(R) = \frac{\overline{Var}}{n} + \left(1 - \frac{1}{n}\right)\overline{Cov}_{i\neq j} = \overline{Cov}_{i\neq j} \tag{21}$$

In equations (20) and (21), $\overline{Var}$ is defined to be the average variance and $\overline{Cov}_{i\neq j}$ is defined to be the average covariance when $i \neq j$.

Therefore, the total portfolio variance may be reduced, through divesification, to the average covariance of the project returns. This average covariance—the nondiversifiable risk—is referred to as the market risk of the portfolio. Observe from

(21) that if the average covariance of project returns is zero—which would be the case if all the projects were statistically independent of one another—then the portfolio variance could theoretically be reduced to zero. That is to say, all risk could be eliminated through diversification.

The striking result from equation (21) is that the unique risk of a particular R&D project does not affect the risk of a well-diversified portfolio of projects. However, the market risk of a project, which depends solely on the covariance of that project's returns with the returns from the other projects in the portfolio, does affect the risk of the portfolio. Specifically, its influence comes via its contribution to the average covariance of the portfolio. This concept is illustrated next in the Figure 2.12.

Figure 2.12

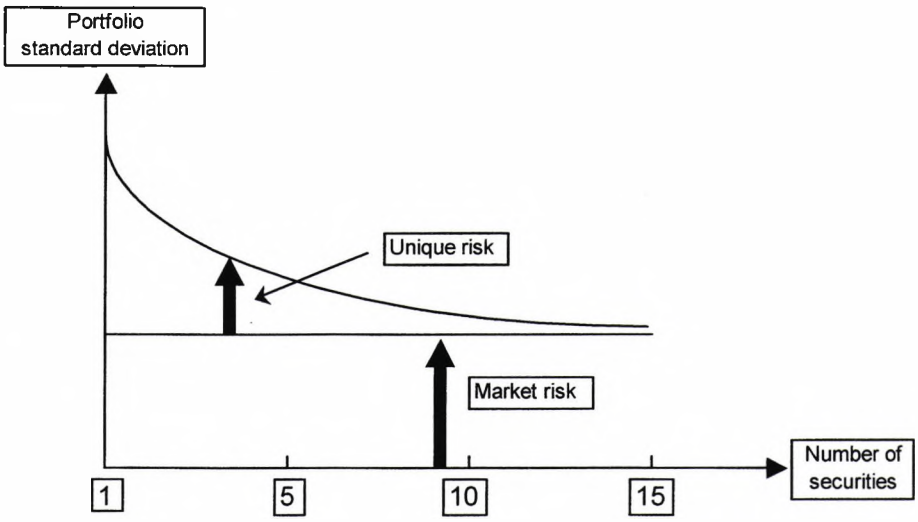


Figure 2.12 demonstrates how an investor in pharmaceutical R&D may, through diversification, eliminate all unique or project specific risk from his portfolio. However, as was shown in equation (21) and Figure 2.12, some risk cannot be eliminated. The portfolio's market risk—or the average covariance of project returns—is not diversifiable. Market risk results primarily from the fact that there are economy-wide

perils that threaten all projects and/or businesses. This results in the tendency of project returns to move together. Historical data confirm this.

Because an R&D project's specific risk may be diversified completely away, the additional risk the project contributes to a diversified portfolio of projects will depend only on how its returns are expected to co-vary with the returns from the other projects in the portfolio. It is this component of a project's risk—its market risk—which matters to potential pharmaceutical investors. Hence, the opportunity cost of capital, which is the risk-compensated expected rate of return on the project, is determined solely by the undiversifiable market risk of that project.

Equipped with a better understanding of how the risk of a specific R&D project will impact the risk of a pharmaceutical investor's portfolio—the supplier of the funds for the R&D—it now becomes necessary to address the risk-return tradeoff. That is, how much of an increase in investment returns will pharmaceutical investors expect in compensation for assuming the additional risk that the project adds to their portfolios? The answer to this question turns out to be quite simple and, as already discussed, depends on the project's covariance with the other projects in the portfolio. Specifically, the risk-return tradeoff depends on the project's *beta value.* A project's beta value, which is a measure of the project's undiversifiable risk, is a relative measure of the covariance between a project's expected returns and the expected returns from the portfolio. Specifically, a project's beta value is defined to be:

$$\beta_i = \frac{Cov(R_i, R_p)}{Var(R_p)} \tag{23}$$

Where R_p is the return from the project portfolio.

As will be discussed in a broader sense in the next section, a project's beta value is linearly related to its expected returns (i.e., its opportunity cost of capital).

Section 3.6.6: *The Linear Risk-Return Tradeoff: The Capital Asset Pricing Model (CAPM)*

Prior to discussing the CAPM, it will be helpful to view R&D projects at the firm level—that is to say, to view pharmaceutical firms as collections of R&D projects or investments. However, this is not necessary, and the following analysis is analogous to discussing individual projects, as has been done up to this point. Nonetheless, as will be discussed, there are considerable empirical difficulties in estimating the latter.

The CAPM, while not derived here, demonstrates that the expected rate of return on a particular pharmaceutical firm's stock (i.e., the equity cost of capital for the firm) is given by the following linear equation:

$$r_e = r_f + \beta(r_m - r_f) \tag{25}$$

Where,

$r_e =$	the required rate of return or opportunity cost of equity capital for the firm
$r_f =$	the rate of return on a risk-free asset
$(r_m - r_f) =$	the risk premium for the equity market as a whole
$\beta =$	the firm-specific risk premium, which is a measure of the marginal contribution of a firm's stock to the portfolio risk.

Furthermore, beta, like an individual project's *beta value*, is a relative measure of the covariance of an asset's expected returns with the expected returns from a well-diversified portfolio. In this particular case, the asset is a pharmaceutical firm's stock, and the diversified portfolio is the stock market portfolio. Therefore, it follows that beta is:

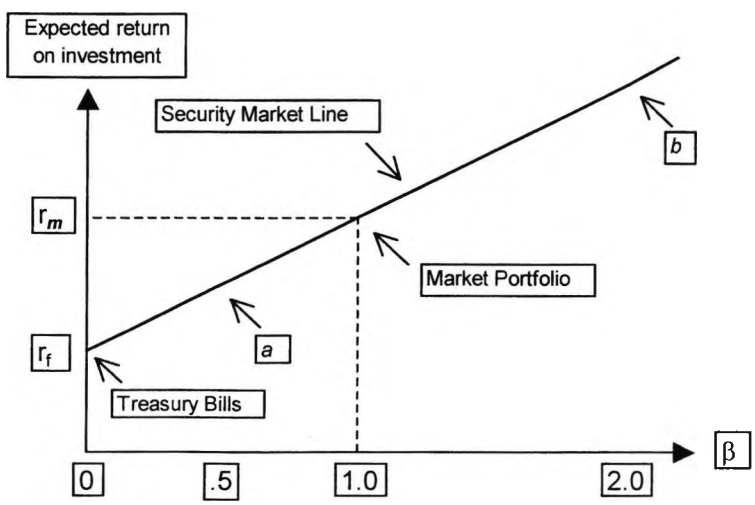
$$\beta = \frac{Cov(R_i, R_m)}{Var(R_m)} \tag{26}$$

Where R_m are the returns from the market portfolio.

On a heuristic level, in the context of a pharmaceutical firm, beta is a measure of how sensitive a pharmaceutical firm's stock price is to movements in the stock market as a whole.

The startling, yet simple, result derived from the CAPM is that the expected, and hence required, risk premium on a capital asset varies in direct proportion to the asset's equity beta, where beta is a measure of the firm's market risk or sensitivity to swings in the market. This fundamental relationship between risk and return is depicted below in Figure (2.13) on what is referred to as the security market line.

Figure 2.13



A few general observations from the CAPM should be noted:

1) A pharmaceutical firm whose stock returns have a zero covariance with the market returns will have a beta equal to zero and, consequently, will be a risk-free investment. Furthermore, the rate of return expected by those investing in the firm would be the risk-free rate r_f.

2) A pharmaceutical firm whose stock returns are perfectly associated with the returns from the market portfolio will have a beta equal to one. Consequently, the firm's market risk is average for the stock market as a whole, and investors will require a risk premium of $(r_m - r_f)$, or an expected return of r_m.

3) In general, the expected risk premium is linearly proportional to a pharmaceutical firm's beta. Therefore, firms with higher betas will be required by investors to have greater risk premiums

It is easy to see from the CAPM, that investors have requirements regarding the returns they expect from their investments based on a pharmaceutical firm's beta. Thus, pharmaceutical firms with higher betas are expected to generate higher returns so as to compensate investors for assuming more risk. Most importantly, it is this expected return which depends solely on a firm's market risk, that reflects the true opportunity cost of capital for the investment.

Additionally, it should be noted that the risk of investing in a pharmaceutical firm depends on how investors, looking into the future, view the firm's future performance. However, because no empirical data exist on future expectations, firm betas are estimated with historical data. Specifically, simple linear regression analyses are performed to estimate firm betas. The key assumption with this approach is that the market risk of a firm today is similar to its market risk over the recent past.

Equity capital, however, is only one kind of capital that pharmaceutical firms can raise. Debt financing may also be used to raise capital. However, the cost of debt financing is generally lower than the cost of equity capital. This is due to the fact that debt holders (corporate bondholders) must be paid before stockholders are paid dividends. The weighted-average cost of capital is thus a blend of the cost of equity capital and the cost of debt capital. Specifically, the weighted-average cost of capital is defined to be:

$$r^{*} = r_d(1 - t_c)(\frac{D}{V}) + r_e(\frac{E}{V}) \quad (27)$$

where r_d and r_e are the cost of debt and equity capital respectively, $\frac{D}{V}$ and $\frac{E}{V}$ are the ratios of debt and equity to the total market value of the firm, and t_c is the corporate tax rate. The reason the cost of debt is reduced by this amount is that the interest on the debt is deductible from business income and, consequently, costs the firm less than it would if there were no taxes.

However, it should be noted that pharmaceutical firms have very little debt. Therefore, a further discussion of the weighted-average cost of capital will not be undertaken. Indeed, the fact that pharmaceutical firms have very little debt implies that their weighted-average cost of capital will be very close to their equity cost of capital. This may be seen in the estimates presented below. Table 2.4 presents several 1989 cost of capital estimates for the largest pharmaceutical firms in the industry. Industry cost of capital estimates are also provided.

Table 2.4

1989 Cost of Capital Estimates for the Pharmaceutical Industry

Firm	r_D	r_E	D/V	r*
Abbot Laboratories	9.8	17.1	.04	16.8
American Home Products	9.6	15.4	.01	15.3
Bristol-Myers	9.6	15.3	.02	15.1
Johnson and Johnson	9.6	16.5	.04	16.1
Lilly (Eli) & Co.	9.6	17.8	.03	17.5
Merck and Co.	9.6	14.7	.01	14.7
Pfizer Inc.	9.6	16.3	.03	16.0
Rorer Group	10.7	18.1	.28	15.5
Schering-Plough	9.8	14.7	.05	14.4
Smith Kline-Beckman	10.1	15.7	.06	15.2
Squibb	9.8	16.4	.03	16.1
Syntex Corp.	9.8	20.0	.04	19.5
Upjohn Co.	9.8	17.7	.08	16.9
Warner-Lambert	9.8	16.2	.09	15.5

Portfolio returns (nominal)

Equally weighted	9.8	16.6	.06	16.0
Market value weighted		16.2		15.9

Portfolio returns (real)

Equally weighted	4.8	11.6	.06	11.1
Market value weighted		11.2		11.0

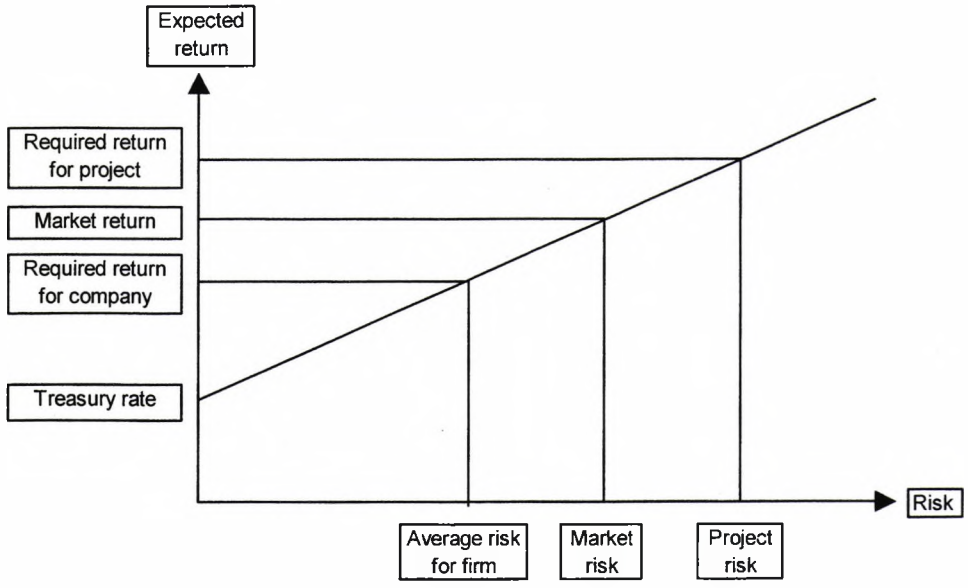
Source: Myers and Majluf (1994)

However, a firm's cost of capital estimate is an imperfect proxy for the cost of capital for an individual R&D project. This is because firm betas represent a weighted-average of betas from the various investments that the pharmaceutical firms make. Indeed, R&D is just one type of investment for the firm. For example, pharmaceutical firms may make investments in property, manufacturing plants, equipment, and

marketing. Consequently, it is unlikely that R&D project betas will be the same as the firm's weighted-average beta. Indeed, it is generally believed that R&D investment betas are much higher than the betas for the other major types of investments just mentioned. Moreover, different R&D projects are likely to have different betas. Unfortunately, however, estimating such project betas is virtually impossible due to the fact that historic data on the returns from similar projects do not exist. Thus, while it is possible to make reasonably good estimates of firm-wide betas, estimating project specific betas is not a possibility.

Finally, a few general comments should be made regarding the cost of capital for pharmaceutical R&D. Investing in pharmaceutical R&D may be thought of as purchasing an option (or opportunity) to invest in the development and manufacture of a new drug. Thus, R&D investments are in reality sequential investments that buy opportunities for future R&D. Furthermore, as a drug passes through the development stages, information is being gathered about the drug. For example, information is gathered on a drug's efficacy, its safety profile, and its commercial viability. Consequently, not only do investments in R&D produce options for future R&D, but also produce information and reduce uncertainty. Therefore, earlier R&D projects are likely to be more risky than later R&D projects and, consequently, will have a higher cost of capital. Figure 2.14 illustrates this distinction and reflects the fact that R&D projects are among the riskiest types of a pharmaceutical firm's investments.

Figure 2.14



Section 3.7.1: *Estimates of the Costs of R&D*

As was discussed in much detail in the previous section, the cost of bringing a new drug to market is highly sensitive to several factors. Specifically, these factors were identified to be:

1) The cash outlays (for both successful and unsuccessful projects) incurred while bringing the drug to market;
2) The timing of the cash outlays (the length of development time and the distribution of expenditures over this period);
3) The opportunity cost of capital appropriate for capitalizing the cash outlays up to the time of NDA approval.

In studies attempting to estimate this cost, two major methodological approaches have been used: a project-level approach and an industry-level approach. Brief overviews and summaries of the findings from the major studies in both categories will be provided.

Section 3.7.2: *Project-level Studies*

The approach employed by the project-level studies involved measuring—at each stage in the development process—each firm's total R&D expenditures and the number of drugs the firm had advancing into the next development stage. These measures were then used to estimate an average capitalized cost per NDA approval. The key advantage to this methodology is that it provides a detailed view of a project's overall development costs. However, because of the non-public nature of much of the data required by this approach, there have been very few of these types of studies. The prototypes of these project-level studies are the Hansen (1979) and DiMasi (1991) studies. The specific approach used in these studies is described briefly below.

Section 3.7.3: *The Hansen and DiMasi Studies*

In his study, Hansen examined 67 drugs that were discovered and developed by U.S. pharmaceutical firms and that entered clinical trials in humans between 1963 and 1975. Similarly, DiMasi's study examined 93 drugs that were discovered and developed by U.S. pharmaceutical firms and that entered clinical trials in humans between 1970 and 1982. Both studies examined only those drugs that were discovered *and* developed by the firms that initially discovered them. Hence, neither study included drugs that were licensed in from other firms. To estimate the average cost of bringing a drug to market, both Hansen and DiMasi capitalized total per annum R&D expenditures up to the date of FDA approval. Specifically, Hansen used an opportunity cost of capital estimate of 8%; and DiMasi used an estimate of 9%. The results from both of these studies are presented below in Table 2.5. The estimates have been inflated to 1998 dollars using the GDP implicit price deflator.

Table 2.5

The Cost of Bringing a New Drug to Market (1998 millions of dollars)

Study	Study Years (Midpoint)	Clinical Cost	Preclinical & Discovery Cost	Total Cash Outlays	Capitalized Total Cost
Hansen, 1979	1969	36.9	43.9	80.8	141.6
DiMasi, 1991	1976	66.4	90.5	156.9	319.4
Rate of Increase		79%	106%	94%	125%

While these results are not a very good reflection of the average cost to bring a drug to market today, they do provide a reasonable benchmark, at least until more contemporary studies are undertaken. Moreover, they demonstrate the trend toward higher drug development costs. Indeed, there was a 125% increase in the estimated cost of bringing a new drug to market from the time of Hansen's study (sample year midpoint = 1969) to the time of DiMasi's study (sample year midpoint = 1976). This should not be too surprising due to the fact that the average development time increased from 9.6 to 11.8 years between 1969 and 1976 (OTA, 1994). Moreover, DiMasi used a slightly higher cost of capital estimate.

Finally, because the average drug development time has increased substantially since the time of the DiMasi Study—from 11.8 years to 14.9 years—it is quite likely that the average cost of bringing a drug to market today is much higher than 319.4.

Section 3.7.4: *Industry Level Studies*

The methodological approach used by industry-level studies involved examining the relationship between the annual number of NDA approvals and lagged industry R&D expenditures. The principle advantage of industry-wide studies is that there is readily available data on both annual industry R&D expenditures and the annual number of new

drugs introduced to the market. However, there are considerable disadvantages to this type of methodology. For example, new drug introductions in a given year will be related to a very complex pattern of past R&D expenditures and other external factors like regulatory controls. This makes assigning past R&D expenditures to a cohort of recently marketed new drugs very difficult and imprecise. The two industry-level studies discussed here are the Wiggins Study (1987) and the Grabowski and Vernon Study (1990).

In his study, Wiggins examined the relationship—via standard regression techniques—between the number of per annum NDA approvals and lagged industry R&D expenditures during the 1970-1985 period. Specifically, Wiggins estimated a regression equation that predicted the annual number of new drug approvals based on lagged R&D expenditures and average NDA delay times. Wiggins, like Hansen, used an opportunity cost of capital of 8% to capitalize R&D expenditures up to the year of NDA approval. However, it should be noted that unlike Hansen's and DiMasi's sample of drugs, the Wiggins sample included licensed-in drugs as well as self-originated drugs. From his regression models, Wiggins estimated that the additional cost of bringing a new drug to market was approximately 162.2 million dollars (1998 dollars).

In the other major industry-level study, the Grabowski and Vernon Study, the authors examined NDA approvals from 1970 to 1979. To estimate the cost per NDA approval they used aggregate R&D expenditure data form 1962 to 1978. Specifically, they made assumptions about the allocation of each year's R&D expenditures to future years' NDA approvals. For example, they made the assumption that 10% of R&D expenditures in 1965 were spent on drugs receiving NDA approvals in 1970, 10% on drugs receiving NDA approval in 1971, and so on. The appropriate allocation of R&D expenditures to a future year's NDA approval was based, in part, on regression analyses. Grabowski and Vernon estimated that the average cost per approved drug between 1970 and 1979 was approximately 175.1 million dollars (1998 dollars).

The four studies on the cost of drug development, described above, are virtually the only theoretically rigorous studies that have been conducted to date. Therefore, while the methodological approaches of the studies are different, it will prove useful to compare their results in order to approximate a range for the cost of bringing a new drug to market.

Evidence seems to indicate that the average time from IND application to NDA approval was 6.5 years during the Wiggins Study (OTA, 1994). This implies that drugs in the Wiggins sample entered clinical testing in humans from 1963-1979. This is approximately the same time period examined in the Hansen study. (Hansen examined drugs entering clinical testing in humans from 1963-1975.) Consequently, the costs estimated from the two studies may be reasonably compared. Furthermore, an assumed 8-12 year total drug development time (discovery to NDA approval—see Figure 2.5) would imply that the sample of drugs examined by Grabowski and Vernon entered human testing from 1965 to 1972. This, like the Wiggins Study, is roughly equivalent to drugs in Hansen's sample. Thus, it is at least reasonable to compare the different study results. The results from the above four studies are summarized below in Table 2.6.

Table 2.6

The Cost of Bringing a New Drug to Market (1998 millions of dollars)

Study	Study Years (Midpoint)	Capitalized Total Cost (In millions of dollars)
DiMasi, 1991	1976	319.4
Hansen, 1979	1969	141.6
Wiggins, 1987	1969	162.2
Grabowski, 1990	1969	175.1

One very important thing must be kept in mind, however. As was mentioned at the beginning of this section, these development cost estimates reflect the cost of drug development for drugs entering human testing almost two decades ago. Therefore, and especially in light of the significant changes in the regulatory environment since that time, these estimates should not be viewed as contemporary estimates of a drug's total development cost. Indeed, as was mentioned earlier, this cost is likely to be substantially greater. Finally, because the costs of R&D are only meaningful when they may be compared to the returns from the projects they financed, the next section will address the returns on pharmaceutical R&D

Section 3.8.1: *Returns on Pharmaceutical R&D*

As was discussed in much detail in the last section, investors in pharmaceutical R&D put up their money because they expect, on average, to be adequately compensated for the risk and time involved in their investment. This section will explore the returns to pharmaceutical R&D. Specifically, this section will examine the evidence on the returns from pharmaceutical R&D, the key regulatory changes that have influenced these returns (or are likely to influence these returns in the future), and the overall trends in pharmaceutical profitability.

Section 3.8.2: *Estimates on the Returns from Pharmaceutical R&D*

Estimating the returns from pharmaceutical R&D, like estimating the costs of pharmaceutical R&D, is a very difficult task. One reason is the extremely long market life of many drugs. Indeed, many drugs have market lives that extend well beyond 20 years. Furthermore, the costs of producing, distributing, and marketing drugs may only be estimated imprecisely. Nevertheless, several authors have attempted to estimate these returns. Specifically, their studies attempted to estimate the *net* returns from new drug introductions. That is, they attempted to estimate both the costs attributable to new drug introductions (R&D, production, distribution, and marketing) and the returns (for which a number of assumptions had to be made regarding future sales revenue). Not surprisingly, these studies produced widely divergent results. The differences were due largely to the different time periods examined and the various assumptions made in each study. However, the two most recent studies of the returns on pharmaceutical R&D had relatively consistent findings for the same time period—1980-1984. Moreover, these newer studies had a larger sample of years with actual sales data than the earlier studies, which relied more heavily on forecasted future drug sales. The results from these studies are summarized below.

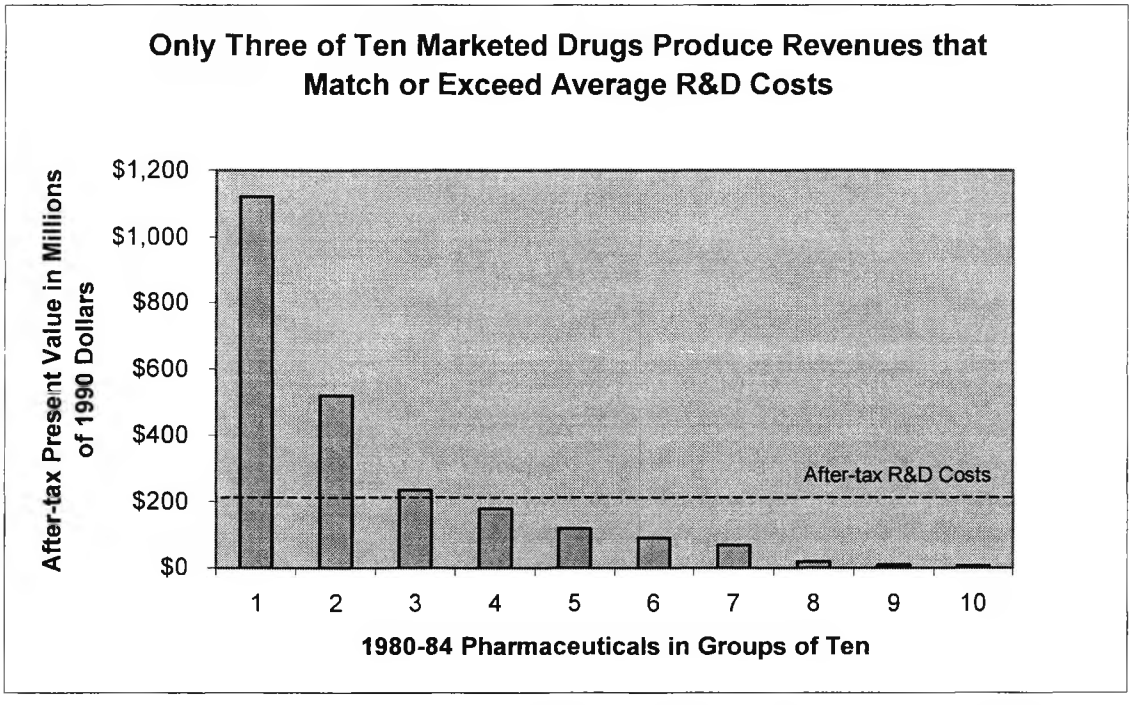
In a recent report contracted by the U.S. Congress, The Office of Technology Assessment (OTA) examined the returns from new drugs that were introduced between 1981 and 1983. The OTA found that these drugs delivered, on average, a present value cash flow (sales less production, distribution, and marketing costs) of approximately 283.7 million dollars (1998 dollars) after taxes. This present value cash flow estimate was then compared to DiMasi's estimate of 239.3 million dollars (which was adjusted to reflect tax-savings from investing in R&D and a variable cost of capital[3]) for the average capitalized cost of R&D for new drugs introduced in this same period. Henceforth, OTA concluded that the average new drug introduction in 1981-1983 had a net present value (present value after-tax revenues less capitalized R&D costs) of approximately 44.4 million dollars. Stated in slightly different way, OTA estimated that, for drugs introduced between 1981 and 1983, the present value of the cash flows generated by the average drug would be approximately 44.4 million dollars more than would be necessary to induce the investment in the R&D.

In the other study, Grabowski and Vernon (1994) found broadly similar results. In a 1994 study, they examined 67 new drug introductions in the United States between 1980 and 1984. Using a similar approach to that of the OTA, the authors estimated an average rate of return on pharmaceutical R&D of 11.1%. This return was then compared to a cost of capital of 10.5%, which was based on a recent estimate of the cost of capital for the pharmaceutical industry during the same time period (Myers and Shyam-Sunder, 1994). Indeed, these findings, like OTA's findings, appear to indicate that, at least historically, the real economic returns from pharmaceutical R&D are slightly greater than the opportunity cost of capital for the R&D. An interesting feature of the Grabowski and Vernon study was that the authors also examined the actual distribution of returns from R&D. Specifically, they divided the 67 new drug introductions into deciles and calculated the average after-tax present value of revenues for each decile. These decile

[3] The firm's effective cost of bringing a new drug to market (the appropriate cost for calculating a firm's net return from R&D) is considerably reduced by the tax savings that a firm receives when it invests in R&D. That is, the net cost of every dollar expended on R&D must be reduced by the amount of the tax burden avoided. OTA estimated this effective firm cost by taking into account both deductions and tax savings from various R&D tax credits that were available during the time period of their study. Furthermore, OTA adjusted DiMasi's estimate by allowing the cost of capital to decrease in a linear fashion from 14% to10% over the life of the R&D projects. This was done to reflect more recent estimates of the cost of capital during his period.

averages were then benchmarked against their estimate for the average capitalized value of R&D cost for all 67 drugs—all on an after- tax basis. This distribution is presented below in Figure 2.15.

Figure 2.15



Source: H. Grabowski and J. Vernon "Returns to R&D on New Drug Introductions in the 1980s," Journal of Health Economics, Vol. 13, 1994.

The striking feature from the above diagram is the skewed nature of the distribution of drug returns. For example, the top decile of new drug introductions had an estimated present value cash flow five times that of the average R&D cost. Moreover, only the top three deciles had present value returns that exceeded the average cost of R&D. Importantly, it should be noted that these estimates are based on new drug introductions in the early 1980s and, consequently, may not be reflective of the returns to R&D in more recent periods.

Section 3.8.3: *Pharmaceutical Regulation and Effective Patent Life*

One of the most important factors affecting the total revenues and hence the returns from pharmaceutical R&D is the length of a drug's effective patent life—or the drug's period of market exclusivity. That is, a drug's effective patent life is defined to be the elapsed time between FDA approval and the expiration date of the drug's last patent. Therefore, pharmaceutical patents will be the focus of this section. Generally, there are thought to be three major barriers to entry into the market for newly introduced pharmaceuticals. They are:

1) Patents
2) Brand Loyalty
3) Scale Advantages in R&D

However, patents are generally regarded as the most important of the three, because once a new chemical structure has been marketed, the cost of imitation is typically quite low. Thus, a pharmaceutical firm could spend several hundred million dollars and many years developing an important new drug only to have other firms imitate the chemical structure once it is marketed. Consequently, exclusive marketing rights are granted to the newly introduced drug via a patent. This is done in an effort to foster drug innovation by providing incentives (future drug sales) to invest in the pharmaceutical R&D. Clearly, if no such market exclusivity were awarded for new innovations, then incentives to invest would be almost nonexistent. This is the familiar public-good/free rider argument. While there is much more that could be said on this topic, it is beyond the scope and purpose of this chapter.

During this period of market exclusivity, or patent protection, firms are essentially monopolists and are able to effectively price at profit-maximizing levels. However, at the time of patent expiration, generic drugs are allowed to enter the market and compete with the brand drug. This generic competition typically results in substantial erosion of the brand drug's market share and profits. Consequently, changes in the effective patent lives of new drugs will have a substantial impact on the profitability and returns from

pharmaceutical R&D. Indeed, over the past several decades there have been a number of changes in the regulation of pharmaceuticals that have significantly impacted the effective patent life of new drugs. Specifically, the most influential regulatory changes have come via Congressional Acts and the implementation of GATT (General Agreement on Tariffs and Trade). These major regulatory changes are briefly discussed next.

Section 3.8.4: *1962 Kefauver-Harris Amendments to the Food, Drug, and Cosmetic Act*

The 1962 Amendments were an important milestone in the regulatory regime of pharmaceuticals. These Amendments required that substantial evidence of clinical efficacy be demonstrated for all new drugs prior to marketing. Furthermore, they also established the investigational new drug (IND) procedures for clinical testing. The overall impact of these new clinical requirements was longer average drug development times and hence shorter effective patent lives.

Section 3.8.5: *1984 Drug Price Competition and Term Patent Restoration Act: The Waxman-Hatch Act*

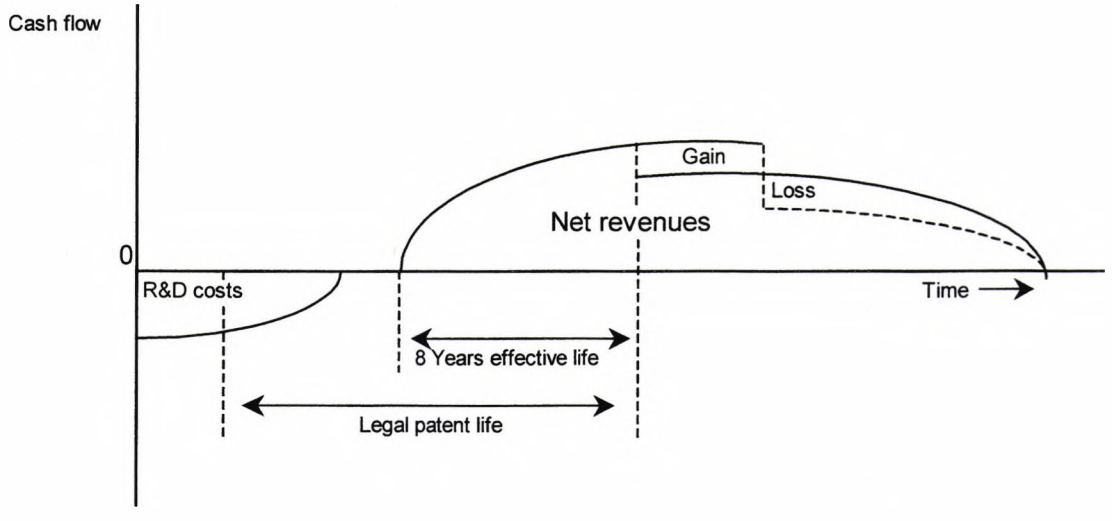
In 1984 another major legislative Act was passed that would greatly influence the effective patent lives of pharmaceuticals. Specifically, 1984 marked the passing of the Waxman-Hatch Act, which was designed to balance the competing concerns of drug innovation and generic competition. Title I of this Act established the Abbreviated New Drug Application (ANDA) for generic drugs. The ANDA process permitted generic drugs to rely on the clinical safety and efficacy results submitted to the FDA by the pioneering firm. Consequently, Title I enabled generic drugs to receive marketing approval much more quickly and inexpensively by only requiring them to demonstrate bioequivalence to the pioneer drug. In particular, this law allowed generic drug manufacturers to conduct their bioequivalence testing and have their ANDA reviewed in the pre-patent expiration period. This provided generic drugs the opportunity to enter the market almost immediately after patent expiration.

Title II of this Act provided for a partial restoration of the patent time lost by most drugs during the clinical testing and regulatory approval periods. Specifically, the law allowed for extensions in patent life equal to the sum of the length of the NDA review time and one-half the IND clinical testing time. The Act capped this patent extension time to five years and further specified that the extension could not increase a drug's effective patent life beyond 14 years. Furthermore, Title II included a very important transitional provision. Specifically, this provision capped patent extensions to a maximum of two years for patented drugs in clinical testing on the date the legislation was passed (September 24, 1984). Consequently, most new drug introductions occurring in the 1980s and early 1990s were subject to this cap.

While the effect of the 1984 Act on effective patent lives is obvious, what is not clear is the net impact on present value drug revenues, and hence returns to R&D. Figure 2.16 demonstrates the competing effects of a longer effective patent life (market exclusivity) and increased generic competition.

Figure 2.16

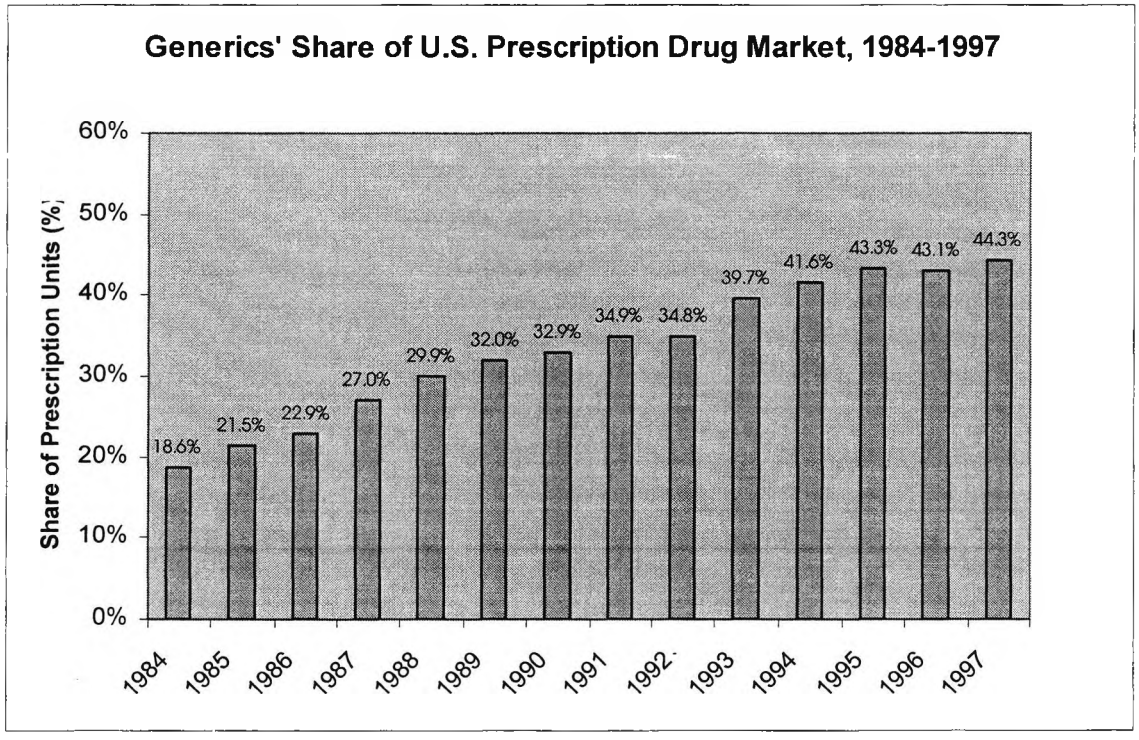
Effect of 1984 Act on Expected Revenues of Average Drug



Source: Grabowski and Vernon, "Longer Patents for Lower Imitation Barriers: The 1984 Act," American Economic Review, May 1986.

One possible way to gauge how the Waxman-Hatch Act has facilitated the growth of generic competition in the pharmaceutical industry would be to examine the trend in market shares for generic drugs since 1984. Indeed, as might be predicted, since the passing of the Waxman-Hatch Act, generic drug market shares have steadily climbed from 18.6% in 1984 to 44.3% in 1997. This trend is shown in Figure 2.17 below.

Figure 2.17



Source: IMS Health, 1998.
Note: Generic share of countable units, such as tablets.

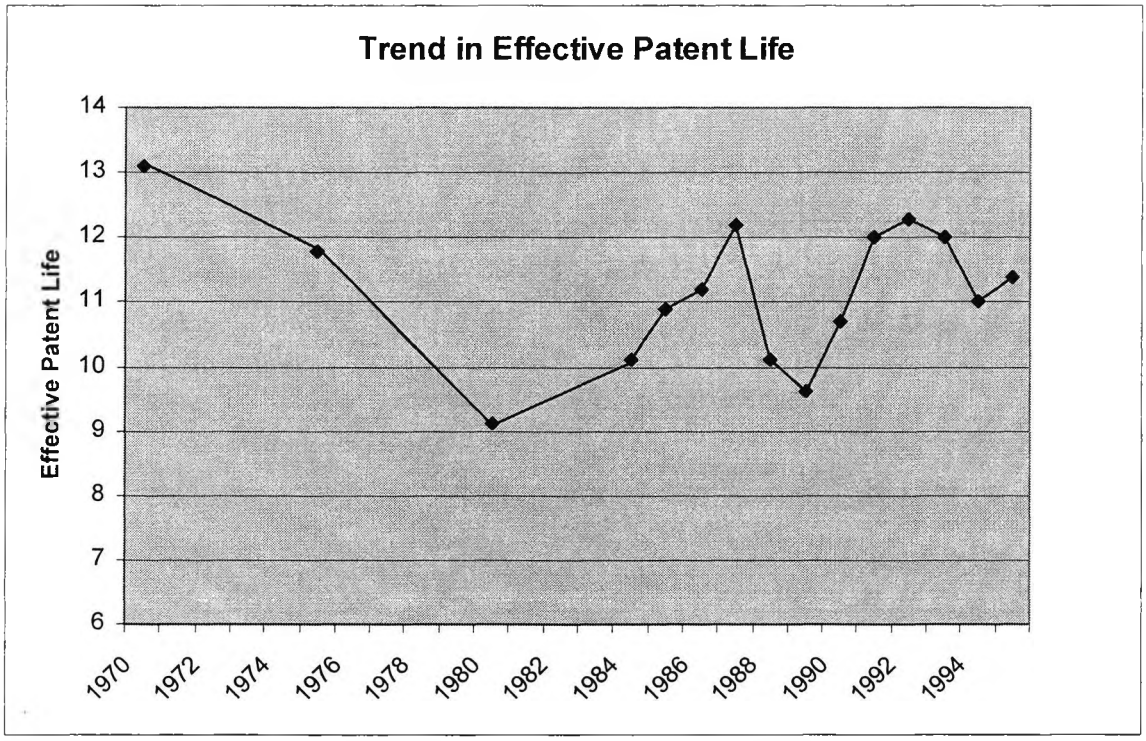
Section 3.8.6: *Implementation of GATT (General Agreement on Tariffs and Trade)*

On June 8, 1995 provisions negotiated under the GATT treaty and directly affecting patents became effective in the United States. The specific provisions granted under GATT included a change in patent terms. In particular, patent terms were

designated to be 20 years from the date of patent application rather than 17 years from the date of patent grant. Additionally, patents in effect or on file prior to June 8th were given *either* the 20-year term from application or the 17-year term from patent grant date—whichever was longer. For drugs in this transition set, a very crucial question was whether or not the 1984 Waxman-Hatch extensions could be added to the GATT-induced extensions (which would have resulted from the switch to the 20-year from file term). Initially, the U.S. patent office determined that the Waxman-Hatch extensions could not be added. More recently, however, courts have ruled that firms can add these extensions. Nonetheless, the maximum 14-year requirement under the Waxman-Hatch Act remains a binding constraint for effective patent lives under either regime.

Clearly, the result of GATT for drugs in the aforementioned transition set will be beneficial, as some patent holders will gain patent extensions and no patent holders will lose patent time. Consequently, the average effective patent life should increase. However, the impact of GATT for patents filed after June 8, 1995 will ultimately depend on the patent pendency period. Clearly, for patent pendency periods less than three years the result will be a gain in patent time. Figure 2.18 below shows how effective patent lives have changed over the past few decades.

Figure 2.18

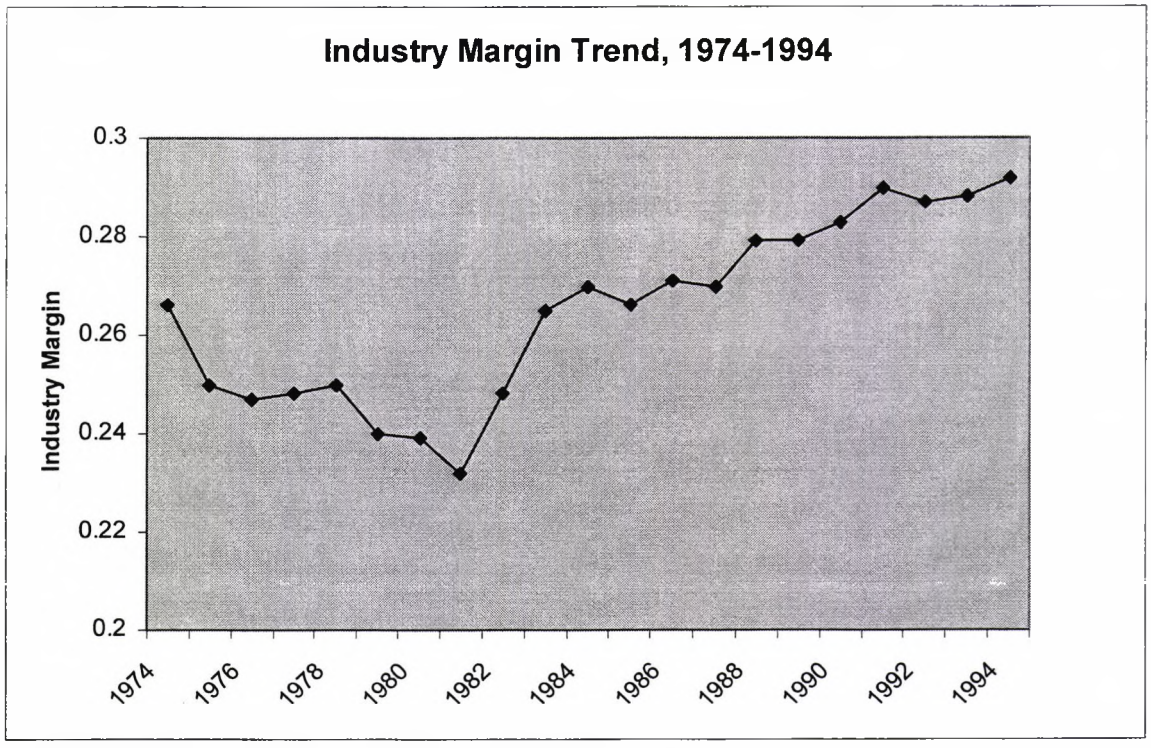


Source: Office of Technology Assessment, 1994 and Grabowski and Vernon, 1994.

Section 3.9: *Trends in Pharmaceutical Profitability Margins*

Another measure, albeit an inferior one, of the profitability of pharmaceutical R&D is the profit margin on a firm's annual pharmaceutical operations. This data is readily available on both the firm and the industry level. Figure 2.19 below illustrates how the pharmaceutical industry's "accounting" profit margin has increased rather steadily over the past couple of decades.

Figure 2.19



Source: Scrip League Tables, and Grabowski and Vernon, 1990.

However, several caveats should be mentioned regarding these profitability calculations. Accounting-based profit measures can be poor approximations of a firm's true returns. This is because accounting standards require that expenditures on R&D and advertising be recorded as current expenditures—when in reality these expenditures are investments whose payoffs are delayed or extended into future accounting periods. Additionally, financial statements frequently report income and expenses as they are accrued in accounting records. This may be very different from the actual cash flows of operations. Harvard economist F.M. Scherer expresses these points nicely:

> Under standard accounting practice, R&D and new product marketing outlays, both of which are atypically high in pharmaceuticals, are written off as current expenses. Since both, and especially R&D, affect revenue for many years to come, it would be more accurate in principle to capitalize the outlays and then depreciate them over appropriate time periods. Otherwise, the rate of return on "investment" is calculated using an asset base that improperly excludes

accumulated intangible R&D and marketing capital. Accounting figures tend to overstate the true rate of return on investment under these conditions.

In general, however, pharmaceutical R&D—at least historically— appears to generate a real rate of return that is slightly greater that the rate of return required to bring forth the investment in the R&D. The most recent published study estimated this rate of return to be, on average, approximately 11.1%, which was compared to a 10.5% cost of capital. However, there are several reasons why this rate of return should not be compared to the rates of return given in *recent* financial reports on pharmaceutical profitability. For one, this estimate is based on new drug introductions between 1981-1984. Secondly, as was just mentioned, there are many reasons why accounting rates of return distort the true economic rates of return for pharmaceutical R&D.

The pharmaceutical R&D process has gone through, and continues to go through, dramatic changes that have tremendously affected both the scientific and economic landscapes of this highly innovative and competitive industrial process. While this chapter has given a broad overview of some of the major trends and developments in pharmaceutical R&D, it is important to keep in mind that the information may not be indicative of the current R&D landscape. Nonetheless, the information provided here should serve as an adequate overview and background of the key issues surrounding the costs, the risks, and the returns of pharmaceutical R&D.

Chapter Three

The Theoretical Foundations and Rationale for Pharmaceutical R&D Financing Constraints

Section 1: Introduction

Analysis of the firm investment decision has occupied a prominent place in both the industrial organization and corporate finance literature. Indeed, the firm investment decision has been one of the most widely researched topics in all of economics. Furthermore, the majority of this research has relied heavily on the well-known neoclassical assumption that the source of investment finance (i.e., new debt, new equity, or internal funds) has no impact on the firm's investment decision (Miller and Modiglani, 1958). That is, the standard neoclassical investment model assumes that internal and external funds are perfect substitutes. Consequently, firms are assumed to be indifferent between financing investment projects with internal cash flows and financing investment projects with either new debt or new equity capital.

Over the past decade, however, many researchers have rejected this conventional view of firm investment and have developed models of business investment that incorporate a role for "financing constraints." This recent focus on the source of investment finance has been driven both by theoretical and empirical concerns and suggests that the source of finance *is* an important determinant of firm investment. Specifically, there have been recent advances, both theoretical and empirical, that provide evidence supporting the hypothesis that internal funds have a *lower* cost of capital than external funds (Hubbard, 1998).[1] This new hypothesis, which rejects the neoclassical assumption that internal and external funds are perfect substitutes, clearly implies that the availability of internal funds is a major determinant of firm investment expenditures. Therefore, because the primary hypothesis of this thesis is that internal funds are an

[1] For a recent survey, refer to Hubbard's synopsis and the references therein.

important determinant of pharmaceutical R&D expenditures, this hypothesis will be thoroughly examined and reviewed in this chapter.

The present chapter will begin by presenting a simple model of firm investment within the conventional framework of neoclassical assumptions. Specifically, the model chosen will be couched in a world with perfectly functioning, centralized, capital markets wherein internal and external funds are perfect substitutes. A discussion of how profit-maximizing firms make investment decisions under these assumptions will be presented along with several dynamic characteristics of this model, which will be referred to as the *conventional* model of firm investment.

Immediately following this presentation of the conventional model, an alternative model specification, one that presupposes the existence of capital market imperfections —i.e., financing constraints, will be presented. It will be demonstrated that in a world where capital market imperfections exist, internal and external funds are not perfect substitutes. It will be shown that in this type of world a "financing hierarchy" may exist—a hierarchy in which internal funds have a substantial cost advantage over external funds. Hence, this model will be referred to as the *alternative* model of firm investment. The alternative model—which forms the basis for much of the empirical analyses in chapters 4,5, and 6—will be examined from several theoretical perspectives. Based on these theoretical perspectives, it will be argued that the alternative model of investment is the appropriate model for describing firm investment behavior. In particular, arguments will be made for the existence of financing constraints based on transaction costs, tax advantages, asymmetric information, costs of financial distress, and agency problems. Furthermore, it will be contended that financing constraints are particularly important when analyzing pharmaceutical R&D investment behavior—the subject of this thesis.

After introducing the alternative model of investment, several of its dynamic attributes will be examined in the context of the pharmaceutical R&D decision. Following this examination, several sections will be devoted to the development of the theoretical underpinnings and microeconomic foundations of the alternative model specification—i.e., the hypothesis that financing constraints lead to a cost advantage for internal funds. Finally, after these theoretical rationales have been presented and

rigorously developed, potential policy implications for the pharmaceutical industry will be discussed.

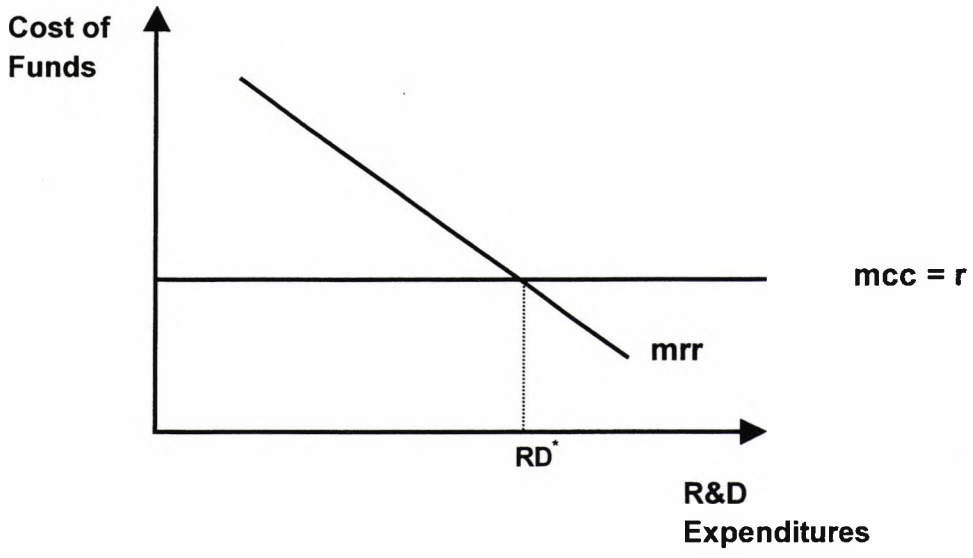
Section 2.1: The Miller and Modigliani Conventional Model of Investment without Financing Constraints

The vast majority of empirical models to date have relied heavily on neoclassical-type assumptions whereby a representative firm responds to prices set in centralized securities markets. Within this framework, all firms have equal access to capital markets and any differences in firms' responses to changes in the cost of capital or tax-based investment incentives is due solely to differences in investment demand. Thus, the conventional model of investment is based on the premise that the source of finance (i.e., new debt, new equity, or internal cash flows) is irrelevant to the firm when making its investment decision. This is because under the neoclassical assumptions of the conventional model, external funds are a perfect substitute for internal funds. More generally, such a substitution implies that within perfectly functional centralized capital markets a firm's investment decision is independent of its financial condition (Miller and Modigliani, 1958). A graphical representation of this single period investment model—in the context of the pharmaceutical R&D investment decision—is presented below in figure 3.1.[2] The quantity of R&D investment is on the horizontal axis, and the cost of capital is on the vertical axis.

[2] A single period model is used first to simplify the exposition of the theory. Following this a simple multi-period Tobin's q model will be considered. More complex dynamic models of the optimal time path for investment, using the calculus of variations, is beyond the scope of this presentation. The qualitative results will not be altered by this approach. Indeed, single period models (and modifications thereof) have been used widely in the literature for describing the optimal level of firm investment.

Figure 3.1

The Optimal Level of R&D Expenditures



In accordance with basic economic theory, Figure 3.1 demonstrates how a firm maximizes total R&D investment returns by equating the marginal rate of return from R&D with the marginal cost of capital. Stated more precisely, the optimal level of R&D is determined by solving simultaneously the expected marginal rate-of-return equation, mrr, and the expected marginal cost-of-capital equation, mcc. The mrr schedule is also referred to as the firm's investment demand schedule. Specifically, it is the firm's demand for R&D. This schedule is downward sloping, reflecting the fact that, all else held constant, increases in the cost of funds reduce the firm's desired level of R&D spending. The mcc schedule is a horizontal line representing the fact that firms may borrow and lend freely at the market rate of interest, r. In the above figure, the optimal level of investment in R&D is denoted by RD^*. The determination of this equilibrium level of R&D is developed and explained in more detail in the following sections.

Section 2.2: *The Demand for Pharmaceutical R&D: The Marginal Rate of Return Schedule (mrr)*

The *mrr* schedule for the firm is derived by arranging the firm's potential investment projects in a decreasing order with respect to each project's risk-adjusted expected rate of return. This clearly implies, all things held constant, that a firm will first choose to undertake the most profitable investment projects—those offering the highest expected rates of return. Indeed, the firm will then continue to undertake additional investment projects so long as the expected rate of return from the next project exceeds the cost of capital to finance it, i.e., if $mrr > mcc$. However, prior to ranking the potential investment projects in this manner, the firm must first formulate expectations about the future returns from each project.

The expected rate of return from a project that has a payoff after one period is simply the ratio of the expected payoff from the investment to the cost of the investment project. However, investment projects—especially pharmaceutical R&D investment projects—typically involve cash flows that occur over many periods. Moreover, these investment projects are likely to involve very complex streams of investment expenditures and returns. For these projects the appropriate measure of the expected rate of return is its expected internal rate of return, *irr*. The *irr* for a project, by definition, is the discount rate that results in the project's expected cash flow stream having a net present value equal to zero. Specifically, a firm's expectations about a project's future expenditures and returns are formulated in the period when the initial investment expenditure decision is made. For example, a firm in period $t = 0$ formulates expectations about an investment project's future expenditure requirements, the likelihood the project will advance and eventually become successful, and the returns the project will generate. Consequently, for this simple investment model, the assessment and subsequent ranking of potential investment projects are based on a firm's expectations in period $t = 0$.

Algebraically, the *irr* for a particular investment project, say project i, which has cash flows for n years, may be found by solving equation (2) for the discount rate r:

$$\sum_{t=0}^{n} \frac{E(CF_{it} \mid \Omega_{t=0})}{(1+r)^t} = 0 \qquad (2)$$

Where $E(CF_{it} \mid \Omega_{t=0})$ is the expected cash flow from project i in period t based on all available information in period $t = 0$. The information set Ω_t represents the information available to the firm in period t. It should be noted that equation (2) has no explicit algebraic solution. In general, when cash flows are variable over time, a solution to (2) must be found through an iterative process of trial and error.

Alternatively, if cash flows are better described by continuous flows, the *irr* for project i will be the discount rate that solves equation (3) below[3]:

$$\int_0^n E(CF_{it} \mid \Omega_{t=0}) e^{-rt} dt = 0 \qquad (3)$$

Section 2.3: *The Supply of Capital: The Marginal Cost of Capital Schedule (mcc)*

The *mcc* equation reflects the opportunity cost of capital incurred through investing in R&D projects on the margin. In particular, the *mcc* schedule reflects the opportunity cost of alternative investments for the firm. In the conventional, or neoclassical, model of investment this would be a horizontal line at r, the real market rate of interest (adjusted for risk).[4] This horizontal cost of capital schedule clearly demonstrates the irrelevance of the source of investment financing to the firm. The firm can lend or borrow freely at the market rate r. Hence, the method of investment

[3] In the continuous case, under certain assumptions, Newton's Method could be used to approximate the solution to equation (3).

[4] This simple version of the neoclassical investment model is used primarily for ease of exposition. Indeed, all of the models in this chapter incorporate numerous simplifying assumptions.

financing—i.e., internal funds, new debt capital, or new equity capital—has no impact on the optimal level of investment in R&D. Therefore, fluctuations in the firm's internal cash flows will in no way affect R&D spending. Clearly, the central assumption underlying the horizontal *mcc* schedule in the conventional investment model is that internal and external funds are perfect substitutes.

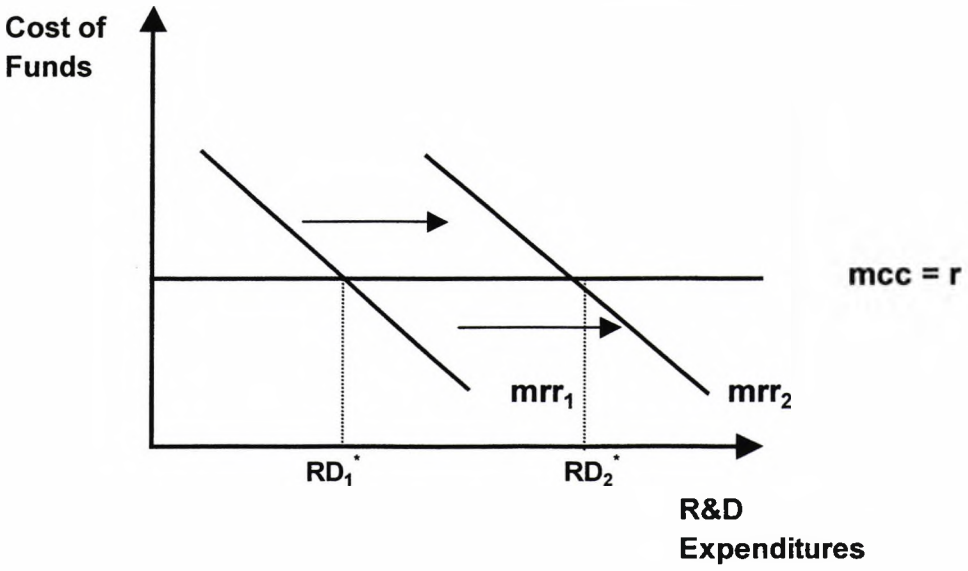
Section 2.4: *Equilibrium Investment in the Conventional Model*

As was illustrated in Figure 3.1, the equilibrium level of investment in R&D occurs at the intersection of the *mrr* and *mcc* schedules. This equilibrium quantity of R&D will necessarily be subject to changes in the demand for R&D (which may be represented graphically by shifts in the *mrr* schedule) and to changes in the cost of capital (which may be represented graphically by shifts in the *mcc* schedule). Therefore, any shift in the either of these two schedules will change the equilibrium level of R&D. For example, as Figure 3.2 illustrates below, an increase in the demand for R&D will, ceteris paribus, increase the optimal level of R&D from RD_1^* to RD_2^*. This increase in the demand for R&D, which is represented by a shift in the *mrr* schedule from mrr_1 to mrr_2, could be the result of improved pharmaceutical investment opportunities. Alternatively, this increase in the demand for R&D could be the result of greater expectations surrounding the future profitability of the firm's pharmaceutical business operations.

While these two examples are certainly closely related, there is indeed a somewhat subtle difference. The latter, while clearly a function of the expected performance of R&D, also incorporates expectations around the broader economic forces that may impinge upon the firm or industry as a whole. This distinction, which is an important component of several of the model specifications used in the forthcoming empirical analyses, will be elaborated upon in greater detail in a later chapter.

Figure 3.2

An Increase in the Demand for R&D



In general, the location of the *mrr* schedules depicted in Figure 3.2 will depend on the firm's R&D investment opportunities and their perceived future profitability. The location of the *mcc* schedule is determined by the cost of capital—which is simply the market rate of interest in the neoclassical, or conventional, model of investment. As was demonstrated in Figure 3.2, all else being equal, an increase in the expected returns to R&D will shift the *mrr* schedule to the right, increasing the firm's desired level of R&D. Similarly, it can also be shown that a decline in the expected returns to R&D will shift the *mrr* schedule to the left, decreasing the firm's desired level of R&D. On the supply side of the model, an increase in the cost of capital reduces the firm's desired level of R&D, all else being equal, while a decrease in the cost of capital increases the firm's desired level of R&D. Clearly, within the framework of the conventional model of firm investment there is no role for a firm's internal funds, or cash flows, to affect the R&D investment decision. That is, the firm perceives the opportunity cost of internal funds to be the market rate of interest.

Algebraically, the equilibrium condition for this model may be expressed by the following equation:

$$mrr(RD^*, \mathbf{X}, \mathbf{Y}) = mcc(RD^*, \mathbf{Z}) \quad (4)$$

Where,

RD^* = the optimal level of pharmaceutical R&D investment expenditures

$\mathbf{X}$ = a vector of variables influencing expected returns to pharmaceutical R&D

$\mathbf{Y}$ = a vector of variables influencing the expected costs associated with pharmaceutical R&D, and

$\mathbf{Z}$ = a vector of variables influencing the opportunity cost of capital

Therefore, the optimal level of R&D expenditures, RD^*, is implicit within equation (4) and is consequently a function of the vectors **X**, **Y**, and **Z**. Generally, we may solve the above equation to obtain the reduced form solution for the optimal level of R&D:

$$RD^* = f(\mathbf{X}, \mathbf{Y}, \mathbf{Z}) \quad (5)$$

Obviously, then, any change in one or more of the variables within the **X**, **Y**, and **Z** vectors is likely to alter the firm's optimal level of R&D expenditures. Moreover, it is important to emphasize that within the framework of the conventional model, the availability of internal cash flows has no impact on the optimal level of R&D. That is, the availability of internal funds does not influence the cost of capital in this model (i.e., the **Z** vector in the above equations), because internal and external funds are perfectly substitutable.

This very crucial assumption will be relaxed in the forthcoming specification of the alternative model of investment. The result, as will be demonstrated in the next

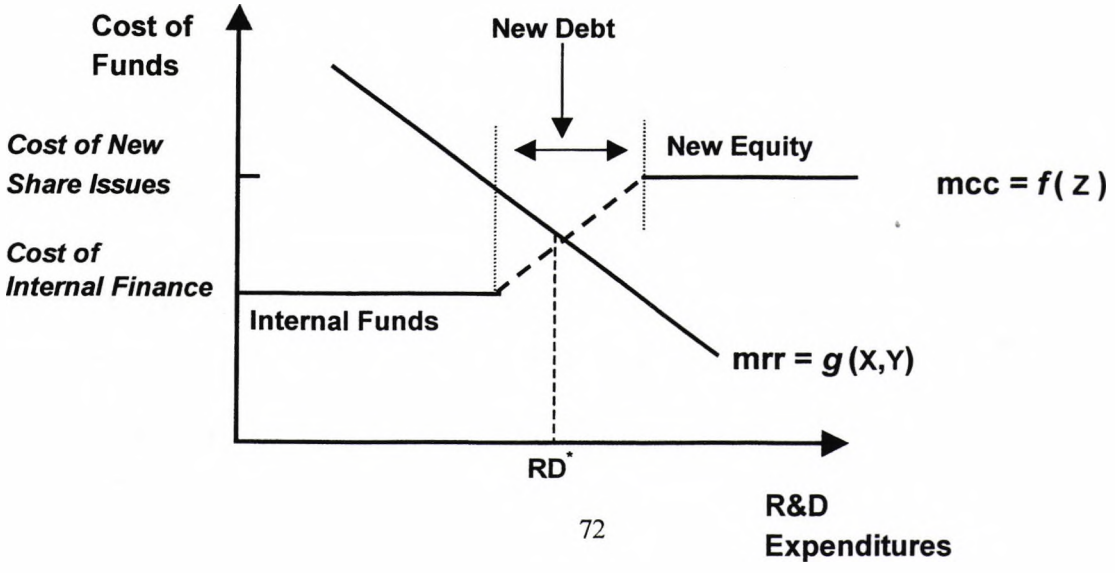
section, is a model wherein the availability of internal funds has a positive influence on the equilibrium level of investment in R&D. This is discussed next.

Section 3.1: The Alternative Model of Firm Investment: The Existence of Capital Market Imperfections and Financing Constraints

Recent work on firm investment behavior has focused on an alternative research agenda—one in which internal capital and external capital are not perfect substitutes. According to this view, the optimal level of firm investment may depend on such financial factors as the availability of internal funds, access to new debt and equity markets, or the functionality of particular credit markets. For example, a firm's optimal level of investment may be significantly influenced by the availability of internal cash flows. In other words, because capital market imperfections lead to a financing hierarchy among the sources of investment finance, internal funds may have a substantial cost advantage over new debt or equity finance. A simple graphical representation of the firm investment model—in the presence of a financing hierarchy—is presented below in Figure 3.3. Like the conventional investment model, this model is presented within the context of the pharmaceutical R&D decision.

Figure 3.3

The Optimal Level of R&D Expenditures with Financing Constraints



As was the case within the framework of the conventional model, a firm maximizes expected returns by selecting the level of R&D where $mrr = mcc$. This occurs in Figure 3.3 at RD^*. However, unlike in the conventional investment model, in the presence of a financing hierarchy, the source of investment finance becomes an important determinant of the optimal level of R&D. In particular, as Figure 3.3 illustrates, firms will begin by financing investment projects with internal cash flows. Then, only after internal funds have been exhausted, will the firm seek external sources of finance—so long as the expected returns exceed the cost of external funds.

Algebraically, this optimal level of R&D may be expressed as the following reduced form solution to equation (4):

$$RD^* = f(\mathbf{X}, \mathbf{Y}, \tilde{\mathbf{Z}}) \tag{6}$$

Where,

$\tilde{\mathbf{Z}}$ = a vector of variables influencing the cost of capital when capital market imperfections lead to a financing hierarchy for investment.

In this alternative investment model specification, the *mcc* schedule consists of two horizontal segments, one representing the cost of internal finance and the other representing the cost of external equity finance. As Figure 3.3 depicts, the horizontal segment representing the cost of internal funds is lower than the segment representing the cost of external finance, and extends out to the point where internal funds are exhausted. There have been several recent theoretical arguments presented for this expected difference in the cost of internal and external funds. These arguments, which are discussed in detail in the following sections, include transaction costs, tax advantages, asymmetric information, financial distress costs, and agency problems.

The upward sloping portion of the *mcc* schedule that connects the two horizontal segments represents new debt finance. The theoretical reasoning behind the increasing marginal cost of new debt finance is well known and is the result of financial gearing.

That is, all things held constant, as a firm becomes leveraged with more debt, the likelihood that the firm will default on its debt obligations increases. This is often referred to as financial distress. Consequently, debt holders require a higher expected rate of return on the firm's debt to compensate them for the increased risk that the firm will default on its debt payments. However, because debt finance is secured with corporate assets, and equity finance is not, the cost of new debt finance is generally less than the cost of new equity finance. More will be said on this later in the chapter.

Section 3.2: *Dynamic Characteristics of the Alternative Investment Model*

Figures 3.4 and 3.5 provide a simple graphical analysis of the two major determinants of investment in pharmaceutical R&D. Figure 3.4 shows how an increase in investment demand (an upward shift in the *mrr* schedule) leads to an increase in a firm's equilibrium level of investment in R&D.

Figure 3.4

An Increase in the Demand for R&D

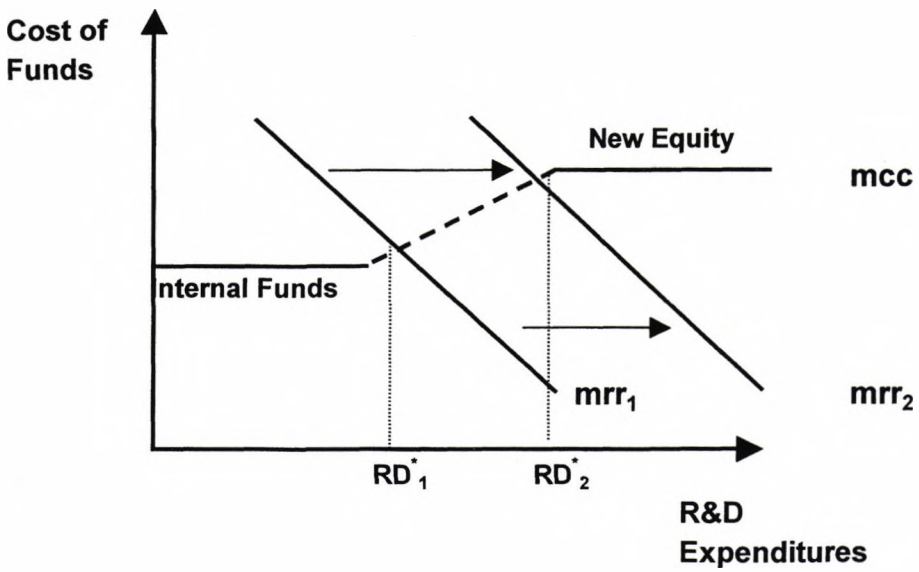
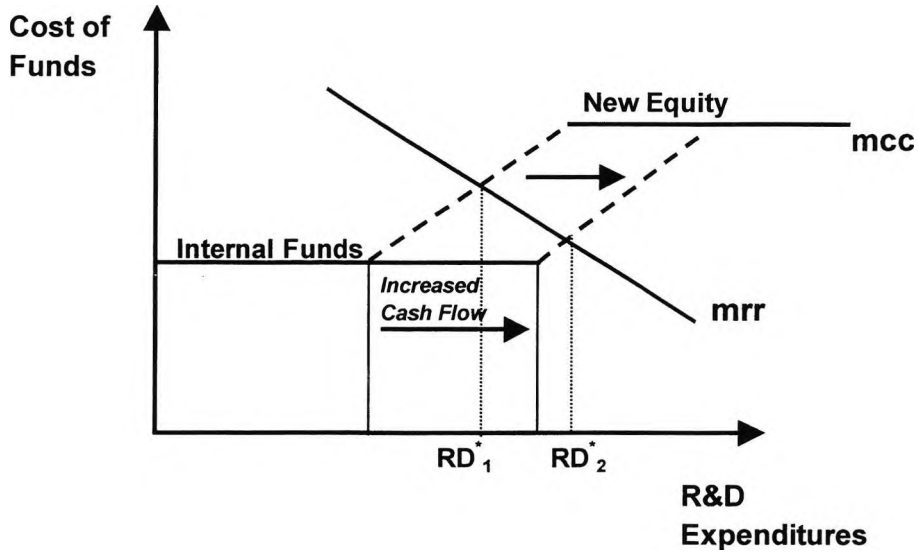


Figure 3.5 demonstrates how, in the presence of a financing hierarchy, an increase in the availability of internal funds, or cash flows, will also lead to an increase in the equilibrium level of R&D investment.

Figure 3.5

An Increase in the Level of Internal Funds



In both the conventional and alternative models of investment, an increase in the demand for R&D will, ceteris paribus, increase the optimal level of R&D. Thus, qualitatively, the conclusions drawn by the two models are identical. However, the conclusions drawn by the two models are quite different in the case of an increase in the firm's internal cash flows. In the convention model, an increase in the level of internal funds had no impact on the equilibrium level of R&D. However, as was shown in Figure 3.4, within the framework of the alternative investment model, when there was an increase in the level of internal funds, everything else held constant, investment in R&D increased in equilibrium. This hypothesized positive relationship between cash flows and R&D expenditures, as predicted within the alternative investment model specification,

forms the crux of the empirical analyses in this thesis. The following sections develop the theoretical underpinnings necessary to support this hypothesis.

Section 4: The Theoretical Rationale for R&D Financing Constraints

In order to provide a microeconomic foundation for establishing links between a firm's internal cash flows and its real R&D investment spending, it will be necessary to first establish reasons why internal and external funds are not perfect substitutes. Indeed, there have been several recent theoretical explanations given for why internal funds may be a less costly source of finance than new equity or new debt finance. The most prominent explanations have included transaction costs, tax advantages, asymmetric information, costs of financial distress, and agency problems. Therefore, to support the hypothesis that cash flows are an important determinant of a pharmaceutical firm's R&D expenditures, the aforementioned explanations will be thoroughly explored in the following sections.

In the first section evidence will be provided to support the argument that there exist substantial transaction costs associated with raising external funds. In particular, it will be shown that transaction costs typically represent between 3 and 6 percent of the total capital raised by new equity issues. In the next section, a theoretical model incorporating the effects of taxes on the cost of capital will be presented. Specifically, it will be shown that when capital gains are taxed at a lower rate than dividends, there exist substantial tax advantages to financing investment with internal funds.

Next, another model will be presented—one that is an adaptation of the aforementioned tax model. This model will be developed to incorporate a role for asymmetric information. Asymmetric information, it will be shown, can generate potentially significant cost disadvantages for external finance. In particular, this model will demonstrate that when firm managers have better information about the quality of an investment project than do potential investors—the suppliers of the funds for the project—then the investors demand a premium rate of return.

Consequently, the rate of return required by investors, who are aware of their informational disadvantage, is greater than the opportunity cost of capital for the firm's internal funds. Moreover, both of the above models will be couched within the framework of the well-known q-model of investment. Therefore, prior to developing these models, the q-theory of investment will be introduced. This will facilitate the transition into the tax and information models by providing a sound analytic framework within which to analyze the R&D investment decision.

Finally, in the last section, a brief discussion will be undertaken to explain how agency problems and financial distress can lead to an increasing marginal cost of new debt schedule. Specifically, it will be shown how agency problems can lead existing creditors to place covenants on the behavior of firm managers—particularly with respect to the issue of new debt. These covenants, it will be shown, place substantial restrictions on a firm's financial flexibility, which in turn may lead to a higher cost of new debt. Likewise, it will be demonstrated how financial distress costs—which increase with a firm's level of debt—can also lead to an increasing cost of new debt, on the margin. These aforementioned microeconomic foundations, it will be argued, provide the necessary theoretical rationale to support the hypothesis that internal funds are an important determinant of pharmaceutical R&D investment.

Section 5.1: The Transaction Costs Associated with Raising External Equity Capital

In the neoclassical, or conventional, model of firm investment, the transaction costs associated with raising new equity capital are assumed to be insignificant. This assumption is easily challenged. Despite the fact that transaction costs are not likely to be the *major* cause of the hypothesized difference between the cost of internal and external capital, these costs are certainly not insignificant. Consequently, the presence of these transaction costs is likely to contribute to a firm's incentive to finance investment with internal, rather than external, funds.

Several studies have provided substantial evidence demonstrating the existence of significant transaction costs in raising new equity capital. The most thorough and

exhaustive study to date is that undertaken by Clifford Smith (1987). Smith examined the transaction costs associated with raising new equity capital by examining filing data from the Securities and Exchange Commission (SEC) between 1971 and 1975. In his sample he obtained detailed filing data on 578 publicly traded companies. It was determined that, on average, transaction costs account for between 2.45% and 6.17% of the proceeds ultimately obtained from a new equity floatation—depending on whether the new equity was raised by means of a rights offering or through an underwritten offering. Before discussing these findings in detail, a brief description of each type of offering will be provided.

Section 5.2: *Methods of Raising New Equity Capital: Underwritten and Rights Offerings*

There are essentially two ways that a firm can raise new equity capital: an underwritten offering and a rights offering. Furthermore, rights offerings sometimes have what is known as a standby-underwriting proviso. This is basically a clause that insures the firm against an unsuccessful rights offering. Indeed, the vast majority of firms choose underwritten offerings.

In an underwritten offering, an underwriting syndicate is contracted to purchase new shares from the firm at an agreed upon price that is usually set within 24 hours of the offering. The underwriter then offers the shares to the public at an offer price—which is a price greater than what the underwriter paid to the issuing firm. Hence, this price differential serves as a commission to the underwriter for bearing the risks associated with the offering. However, if the shares cannot be sold at the offer price, the underwriting syndicate dissolves and the shares are sold for whatever price can be obtained. Thus, in an underwritten offering the firm's proceeds are guaranteed. It is the underwriter that bears the risk associated with random movements in the firm's stock price. In a rights offering, on the other hand, the issuing firm provides shareholders with rights, which are options to purchase new shares for each share owned. The right states the terms of the option, the subscription price of the new shares, the number of rights required to purchase each additional new share, and the expiration date of the option. Thus, in a rights offering there is no direct third party involvement in the flotation of new

shares. As a result, rights offerings are typically associated with lower flotation costs. Despite this fact, underwritten offerings are still the most common means by which firms raise new equity capital.[5]

In his study, Smith found that the average total transaction cost for a new underwritten offering, measured as a percent of the total proceeds from the offering, was 6.17%. This average estimate was based on a sample of 484 firms with new offerings ranging in size from less than $500,000 to 500 million dollars (in 1987 dollars). Moreover, as would be expected, the total transaction costs—measured as a percent of the total proceeds raised by the offering—decreased with the size of the offering. For example, for offerings between $500,000 and 1 million dollars, this cost was 13.74% of the total offering, on average. And for the largest offerings, those between 100 and 500 million dollars, the cost was a significantly smaller 3.95%, on average.

For new rights offerings with standby underwriting the estimated total transaction cost—as a percentage of the total proceeds raised by the offering—was 6.05%. This estimate was based on a sample of 56 firms. As was the case with new underwritten offerings, the cost estimates making up this composite average were inversely related to the size of the offering. For the smallest offerings, those less than $500,000, this cost was 8.24%, on average. And for the largest offerings, those between 100 and 500 million dollars, this cost was 4.0%, on average.

The transaction costs associated with rights offerings without standby underwriting were much less than the other two types of offerings and amounted to 2.45%, on average. Indeed, the transaction costs associated with pure rights offerings were, as was the case with the other two types of offerings, inversely related to the size of the offering. In particular, these costs ranged from 8.99% of the total offering for the smallest offerings, those less than $500,00, to 1.3% of the total offering for the largest offerings, those between 100 and 500 million dollars. These estimates were based on a sample size of 38 firms.

[5] The fact that the transaction costs associated with underwritten offerings are greater than those associated with rights offerings would seem to indicate that firms would prefer rights offerings. In fact, the opposite is true. For a theoretical discussion of this apparent paradox refer to Smith (1987).

While all three types of offerings entailed significant transaction costs, underwritten offerings and rights offerings with standby underwriting, as mentioned, were the most costly of the three. The firms in these samples reported ten categories of expenses to the Securities and Exchange Commission (SEC) by mandate of law. Furthermore, these expenses were generally incurred by all new equity offerings, albeit to varying degrees depending on the type of offering. These expense categories are summarized in the list below:

1) Commissions received by investment bankers for underwriting services (underwritten offerings only)
2) Legal fees
3) Accounting fees
4) Engineering fees
5) Trustees' fees
6) Listing fees
7) Printing and engraving expenses
8) SEC registration fees
9) Federal Revenue Stamps
10) State taxes

While the above categories of costs are certainly significant, they are by no means exhaustive. Indeed, they may not even represent the majority of the transaction costs associated with new equity offerings. Categories 1 through 10 include only those costs that are required by law to be reported to the SEC. Hence, they do not include several other key categories of costs. One such example is the use of warrants as a means of compensation to underwriters. A warrant, which is convertible into shares of the firm at a price well below the new equity's offer price, is frequently used as a supplemental payment to the underwriter. Furthermore, this form of compensation is not reported to the SEC. Another type of unreported cost is the opportunity cost of time for the firm's employees. This cost is particularly relevant to underwritten offerings. This is because top management is usually involved in lengthy negotiations over such underwriting parameters as the offer price and fee structure of the new issues. However, such negotiations should not be unexpected as the aforementioned parameters have a significant impact on the wealth of both the owners of the firm and the underwriters.

In general, the transaction costs associated with raising new equity capital are not insignificant. The fact that the majority of firms employ underwriting services indicates

that, on average, firms may be incurring transaction costs approximately equal to 6% of the market total value of a new offering. Even for the small proportion of firms that elect to raise new equity capital through a pure rights offering, the average cost incurred is still approximately 2.5% of the value of the total offering. Hence, while transaction costs may not be the primary rationale for expecting a divergence in the cost of internal and external capital, they clearly are not insignificant.

Prior to the presentation of several theoretical models that demonstrate how taxes and asymmetric information may lead to a difference in the cost of capital between internal and external funds, a q-model framework of investment will first be developed. Specifically, because the q-model of investment provides the best framework within which to analyze the impact of taxes and asymmetric information on firm investment behavior, this approach is adopted. To be consistent, the q-model will be derived in the conventional way, with a representative firm choosing in each period the profit-maximizing quantity of new investment. In this derivation, investment is investment in real capital—i.e., plant and equipment. Following this, a special interpretation will be suggested for investment in pharmaceutical R&D.

Section 6: Tobin's q and the q-Model of Firm Investment

The q-model of investment asserts that a firm's demand for capital assets varies directly with the ratio of the market value of those capital assets to their replacement value. This ratio, or q, essentially compares the yield from capital assets with the rates of return required by investors who supply the funds for the capital. Thus, values of q exceeding unity stimulate investment spending, while values of q well below unity discourage capital formation. The determinants of the demand for capital in the q-model are precisely the same as those described in the previous section on the demand for investment in R&D—i.e., the derivation of the *mrr* schedule. Indeed, the description of the demand for capital in the q-model is as old as financial theories of investment themselves. That is, firms calculate the demand price of capital by discounting the expected future returns from the capital. Likewise, the cost of producing the new capital assets is their supply price. Should shifts in technology or business conditions create

profitable investment opportunities, then the demand price for capital will exceed its supply price. This, consequently, will stimulate investment spending. Clearly, the q-model of investment is analogous in many ways to the R&D investment model presented earlier in this chapter. Therefore, the q-model framework is a natural choice for demonstrating the effects of taxes and asymmetric information on the cost of capital for pharmaceutical R&D investment. A formal derivation of the q-model of capital investment is developed below.

A firm's optimal stock of capital in any given period may be derived directly from the firm's profit maximization problem. In particular, the firm selects a program of capital formation and new investment that maximizes the present value of the firm's expected future profits. This problem is stated below in the context of the representative firm's maximization problem:

$$\underset{L_t, I_t}{Max} \quad \sum_{t=0}^{\infty} \frac{1}{(1+r)^t} [P_t Y_t - w_t L_t - \rho_t i_t] \tag{7}$$

Subject to:

$$Y_t = y(L_t, K_t) \tag{7.1}$$

$$K_{t+1} = K_t + i_t - \delta K_t = (1-\delta)K_t + i_t \tag{7.2}$$

$$\frac{\partial y}{\partial L} > 0 \;,\; \frac{\partial y}{\partial K} > 0 \tag{7.3}$$

The variables in this optimization problem are defined as follows:

L_t = the quantity of labor units employed in period t
K_t = the quantity of capital employed in period t
i_t = the investment expenditures in period t
r = the market interest rate
P_t = the market price of the firm's output in period t
Y_t = the output of the firm in period t

w_t = the wage rate or price of labor in period t
ρ_t = the rental rate or price of capital in period t
δ = the depreciation rate of the capital stock

Equation (7.1) is simply the technology constraint facing the firm—i.e., the firm's production function. Equation (7.2) is the firm's capital stock constraint, which, for simplicity, assumes a fixed depreciation rate, δ. This constraint expresses the fact that, in any given period, t, the firm uses up a fixed proportion of its capital, δK_t, in the production process, and in the same period installs new capital in the amount of i_t—which will not begin to depreciate until period $(t+1)$. Consequently, constraint (7.2) gives the firm's capital stock at the beginning of period $(t+1)$. Finally, constraint (7.3) states that the marginal product of both capital and labor is positive.

Before deriving the optimality conditions associated with this maximization problem, several points should be made. First, the firm is assumed to operate in a perfectly competitive market environment. Hence, the firm is a price-taker and P_t is exogenous to the firm's maximization problem. Secondly, in order to ease the exposition, uncertainty has been placed aside. Therefore, future profits are not written explicitly as *expected* future profits.

Because the production function holds with equality for all periods, we may substitute it into the maximand to yield the following expression for the firms present value profits:

$$\textit{Present Value Profits} = \sum_{t=0}^{\infty} \frac{1}{(1+r)^t} [P_t y(L_t, K_t) - w_t L_t - \rho_t i_t] \tag{8}$$

The re-written maximization problem now becomes:

$$\underset{L_t, K_t, i_t}{Max} \sum_{t=0}^{\infty} \frac{1}{(1+r)^t} [P_t y(L_t, K_t) - w_t L_t - \rho_t i_t] \tag{9}$$

Subject to:

$$K_{t+1} = (1-\delta)K_t + i_t \tag{9.1}$$

$$\frac{\partial y}{\partial L} > 0 \ , \ \frac{\partial y}{\partial K} > 0 \tag{9.2}$$

The problem is now set up such that the firm selects both its labor and capital inputs, L_t and K_t, respectively, and a level of new investment i_t. These endogenous choice variables are selected to maximize the present value of the firm's future profit stream subject to the multi-period capital constraint, equation (9.1). To solve this relatively simple maximization problem, the method of Lagrange multipliers is used. Consequently, the Lagrangean for this problem is:

$$\mathcal{L} = \sum_{t=0}^{\infty} \frac{1}{(1+r)^t}[P_t y(L_t, K_t) - w_t L_t - \rho_t i_t] + \sum_{t=0}^{\infty} \lambda_t [i_t + (1-\delta)K_t - K_{t+1}] \tag{10}$$

Hence, the maximization problem now becomes:

$$\underset{L_t, K_t, i_t, \lambda_t}{Max} \quad \mathcal{L} = \sum_{t=0}^{\infty} \frac{1}{(1+r)^t}[P_t y(L_t, K_t) - w_t L_t - \rho_t i_t] + \sum_{t=0}^{\infty} \lambda_t [i_t + (1-\delta)K_t - K_{t+1}] \tag{11}$$

A complete solution to this problem may be obtained by partially differentiating the Lagrangean with respect to all the endogenous choice variables (including the Lagrange multipliers) and setting these differentials equal to zero. This system of differential equations, i.e., the first order conditions, may be solved simultaneously for the optimal investment program into the infinite future. Indeed, the firm's labor demand

schedule is also easily derived in this manner.[6] The first order conditions for profit maximization are presented below:[7]

$$\frac{\partial \mathcal{L}}{\partial L_t} = \frac{1}{(1+r)^t}(P_t \frac{\partial y}{\partial L_t} - w_t) = 0 \tag{11.1}$$

$$\frac{\partial \mathcal{L}}{\partial K_t} = \frac{1}{(1+r)^t}[P_t \frac{\partial y}{\partial K_t}] + \lambda_t(1-\delta) - \lambda_{t-1} = 0 \tag{11.2}$$[8]

$$\frac{\partial \mathcal{L}}{\partial i_t} = \frac{-1}{(1+r)^t}\rho_t + \lambda_t = 0 \tag{11.3}$$

$$\frac{\partial \mathcal{L}}{\partial \lambda_t} = i_t + (1-\delta)K_t - K_{t+1} = 0 \tag{11.4}$$

In order to derive q, it is first necessary to solve for the optimal capital stock condition. This may be done by combining the equations (11.2) and (11.3). First, solving (11.3) for λ_t clearly yields:

$$\lambda_t = \frac{\rho_t}{(1+r)^t} \tag{12}$$

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[6] Rearranging (11.1) yields the very familiar condition for the optimal utilization of labor: $P_t \frac{\partial y}{\partial L_t} = w_t$. That is, labor is paid its marginal revenue product in equilibrium.

[7] Of course, to ensure that the constrained extremum is indeed a maximum, and not a minimum, one must check the second-order conditions. Specifically, the sufficiency conditions for this maximization problem require that: $(-1)^n|\overline{H}_n| > 0$, where, $|\overline{H}_n|$ is the n^{th} principal minor of the bordered Hessian matrix. That is to say, for an extremum to be a maximum, the sufficiency condition requires that the bordered Hessian is negative definite.

[8] A somewhat unusual and possibly puzzling term in this equation is λ_{t-1}. This term comes into the first-order condition because K_t is the end-of-period capital stock for period (t-1).

Then, lagging this expression one period gives the following expression for λ_{t-1}:

$$\lambda_{t-1} = \frac{\rho_{t-1}}{(1+r)^{t-1}} \tag{13}$$

Substituting the above expressions for λ_t and λ_{t-1} into equation (11.2) results in the following condition:

$$\frac{1}{(1+r)^t}\left[P_t \frac{\partial y}{\partial K_t}\right] + \frac{\rho_t(1-\delta)}{(1+r)^t} - \frac{\rho_{t-1}}{(1+r)^{t-1}} = 0 \tag{14}$$

Multiplying equation (14) through by the term $(1+r)^t$ yields another version of the optimal capital stock condition:

$$P_t \frac{\partial y}{\partial K_t} + \rho_t(1-\delta) - \rho_{t-1}\ (1+r) = 0 \tag{15}$$

Finally, equation (15) may be rearranged into the following expression for the equilibrium, or profit maximizing, level of capital:

$$\frac{[1/(1+r)][P_t \frac{\partial y}{\partial K_t} + \rho_t(1-\delta)]}{\rho_{t-1}} = 1 \tag{16}$$

The expression on the left-hand side of equation (16) is referred to as Tobin's marginal *q*. This ratio, as was described informally earlier, may be interpreted more

formally in the context of the firm's maximization problem, as follows. The numerator captures the incremental increase in the value of the firm resulting from a small increment in the firm's capital stock, discounted back to period $(t-1)$. Specifically, the term $P_t \frac{\partial y}{\partial K_t}$ is the marginal increase in the firm's sales resulting from a small increase in the capital stock, and the term $\rho_t(1-\delta)$ represents the marginal increase in the market value of the firm's capital stock.[9] This sum is then discounted back to the period $(t-1)$ by dividing by $(1+r)$. The denominator is simply the cost of acquiring a small increment to the capital stock in period $(t-1)$. Hence, Tobin's marginal q is simply the ratio of the marginal increase in the value of the firm (resulting from a marginal increase in the capital stock) to the marginal cost of adding the additional capital to the firm's capital stock. Thus, if the firm is in equilibrium, the value of q is equal to unity. This is the capital stock optimality condition described by equation (16). Therefore, all investment opportunities that add more to the present value of the firm than they cost have already been undertaken.

The q-model framework just described addresses how a firm maximizes profits by selecting the optimal quantities of labor and capital inputs over time. While this model applies to investments in real capital, these same principles may generally be applied to investment in research and development (Hall 1990, 1991, and 1992). In particular, this model may be applied to pharmaceutical R&D investment. Pharmaceutical firms are peculiar in that they employ very little real capital. In fact, the largest input into the production of new drugs is R&D. However, despite their obvious differences, R&D investment and real capital investment are quite similar—at least within the context of the specification of the aforementioned q-model. For example, R&D may be thought of as a stock flow much like real capital. That is, most research and development programs

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[9] The term $P_t \frac{\partial y}{\partial K_t}$ is the marginal revenue product of capital—i.e., this term captures the marginal revenue to the firm (P_t) obtained from employing capital on the margin (the marginal product of capital: $\frac{\partial y}{\partial K_t}$).

extend over many years and accumulate a base of knowledge over time. This is how new drugs are discovered and developed. Hence, new information does not evaporate at the end of the period or when new research agendas take precedence—this information is a valuable corporate asset and is utilized by the firm to produce new drugs. This is similar in many respects to the accumulation of real capital over time. Additionally, like the depreciation of real capital, clearly some research agendas will be completely exhausted, leaving no opportunities for future development. That is, some R&D programs will fail or produce information that has no future value to the firm.

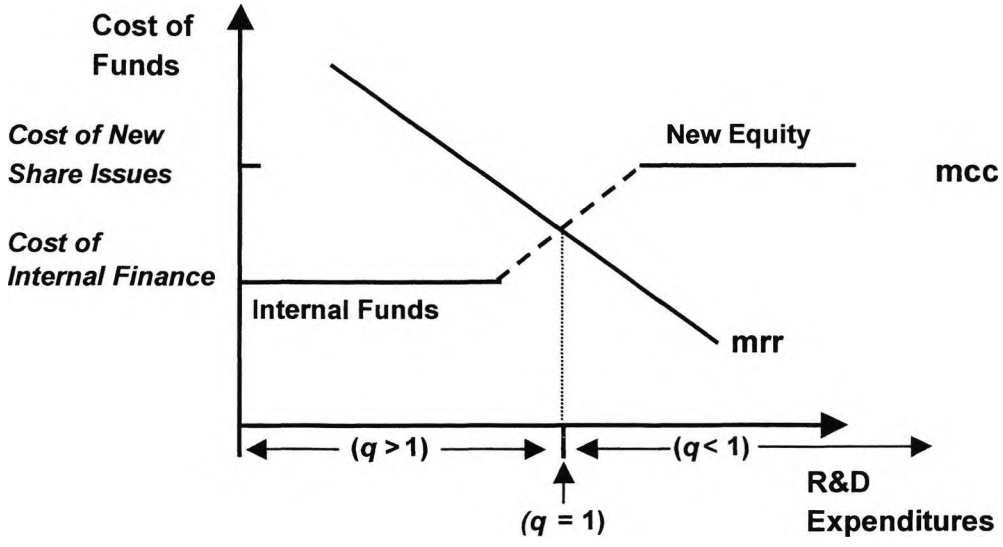
Despite their obvious differences, investment in real capital and investment in pharmaceutical R&D may be analyzed in the same way. Essentially, for profit-maximizing pharmaceutical firms considering R&D on the margin, if the ratio of the expected discounted marginal returns from the R&D to the cost of the R&D exceeds unity, the firms should undertake the prospective R&D investment. This is analogous to saying that if Tobin's marginal q exceeds unity, firms increase investment spending in real capital. Indeed, from a conceptual point of view the two statements are identical. Thus, in the context of the models presented at the beginning of this chapter (i.e., the conventional and alternative models of pharmaceutical R&D investment) marginal q may be thought of as the following:

$$q = \frac{mrr}{mcc} \tag{17}$$

The relationship between these two models, which are essentially the same model, is depicted below in Figure 3.6.

Figure 3.6

A q-Model Interpretation with Financing Constraints



Having introduced the q-model framework, the effects of taxes and asymmetric information on the cost of internal and external capital may now be addressed.

Section 7.1: The Effect of Tax Policy on Firm Investment Behavior: The Cost Advantages of Internal Finance

The structure of the corporate tax system in the United States and other countries has historically imparted a substantial cost advantage to financing investment projects with internal funds (Myers, 1984). This is because, for several years now, capital gains have been taxed at a lower rate than dividends. This lower tax on capital gains, it will be shown, can result in a substantial tax savings to the firm's shareholders when earnings are retained and realized as capital gains, instead of paid out as dividends. This is because a

dividend tax is replaced with a lower tax on capital gains. This tax-induced incentive for firms to retain earnings, in lieu of paying dividends, leads to different decision criteria for investment projects—depending on whether they are financed with internal or external funds. Specifically, the after-tax cost of internal finance is lower than that of external equity finance. On a heuristic level, this is quite intuitive and may be explained nicely within the previously developed framework of the q-model of investment.

According to Poterba and Summers (1985), because of the different tax rates, firms, acting to maximize shareholder wealth, will undertake all internally financed investment projects when:

$$q > \frac{(1-t_d)}{(1-t_c)} \tag{18}$$

Where,

t_d = the tax rate on dividends, and

t_c = the tax rate on capital gains

Thus, if the personal tax system favors capital gains, such that $t_d > t_c$, then the threshold marginal q for investment projects financed with internal funds is less than unity. This may be explained as follows. A dollar paid out in the form of dividends and taxed at the rate t_d yields shareholders $(1-t_d)$ dollars after taxes. Alternatively, if the firm retains the dollar and shareholders realize the capital gain, their after-tax yield is $(1-t_c)$ dollars. This clearly implies that shareholders will be indifferent between a dollar paid out in dividends and $(1-t_d)/(1-t_c)$ dollars retained by the firm and realized as a capital gain.[10] Consequently, a dollar in retained earnings need only generate an expected present value

[10] Algebraically, this result is derived from the following indifference condition, where x is the before-tax capital gain that equates with a before-tax \$1.00 dividend payment before taxes:

$\$1.00(1-t_d) = x(1-t_c)$. Dividing both sides by $(1-t_c)$ yields: $x = \frac{(1-t_d)}{(1-t_c)}$.

investment return slightly greater than $(1-t_d)/(1-t_c)$ to yield more in after-tax income to shareholders than a dollar paid out as a dividend. On the other hand, if this dollar were raised through a new share offering, shareholders would only benefit from those investments with a marginal q greater than unity. This is the idea behind Tobin's q. Thus, the "hurdle," or "threshold," marginal q for internally financed investments is lower than that for externally financed investments due to this distortionary effect from taxes.

Therefore, under a tax system where $t_d > t_c$, a financing hierarchy is created whereupon the threshold marginal q required for investment projects is dependent upon the source of finance. The firm's decision criteria for investments under these two financing schemes are presented below in Table 3.1.

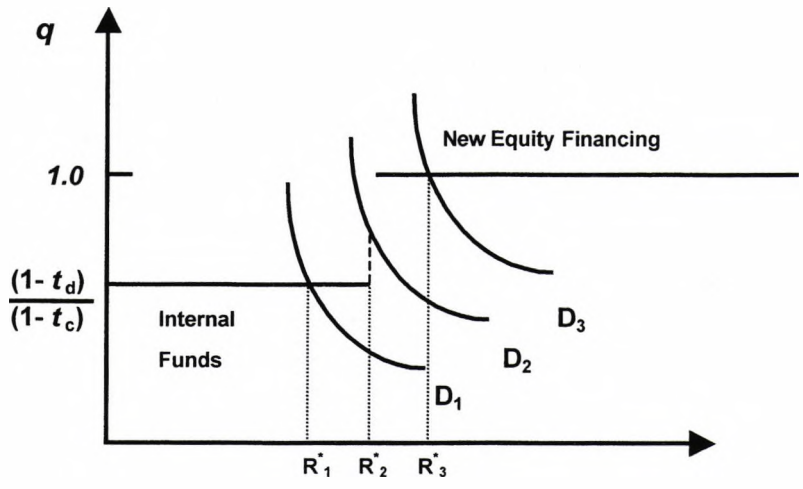
Table 3.1: R&D Investment Project Acceptance Criteria

Source of Finance	Accept Investment Project	Reject Investment Project
Internal Funds	$q \geq \frac{(1-t_d)}{(1-t_c)}$	$q < \frac{(1-t_d)}{(1-t_c)}$
External Equity	$q \geq 1$	$q < 1$

Therefore, when $t_d > t_c$, the after-tax cost of internal funds is less than the after-tax cost of external equity. The implication is clear: firms will exhaust all available internal funds before seeking external equity to finance investment—assuming, of course, that shareholders have no explicit preference for dividends. This fundamental relationship between q, t_d, and t_c is illustrated below in Figure 3.7.

Figure 3.7

A *q*-Model Equilibrium with Tax-Induced Financing Constraints



This highly intuitive result may be derived formally within the context of the representative firm's maximization problem. Specifically, firm managers, acting on behalf of shareholders, seek to maximize the after-tax present value of the firm.

Section 7.2: *A Simple Model of Equity Finance, Dividends, and Investment*

The following exposition was adapted from the seminal work of Poterba and Summers (1985). In any given period t, an existing shareholders after-tax rate return may be expressed as follows:

$$R_t = \frac{(1-t_d)D_t + (1-t_c)(_tV_{t+1} - V_t)}{V_t} \qquad (19)^{11}$$

[11] In their original article, Poterba and Summers used m and z to denote the tax rates on dividends and capital gains, respectively. However, for the sake of consistency throughout the chapter, t_d and t_c will

Where,

D_t = the dividend payment by the firm in period t

V_t = the value of the firm's equity in period t, and

${}_tV_{t+1}$ = the value in period $(t+1)$ of the shares outstanding in period t

Equation (19) expresses the fact that in any given period t, an existing shareholder's after-tax return is simply the sum of the dividend return (taxed at the rate t_d) and the capital gain (taxed at the rate t_c).

Consequently, the total value of the firm in period $(t+1)$ may be expressed as follows:

$$V_{t+1} = {}_tV_{t+1} + V_t^N \tag{20}$$

Where,

V_t^N = the value of the new share issues.

In equilibrium, shareholders earn their required rate of return so that $R_t = r^e$; therefore, equation (19) may be re-written and expressed as follows:

$$r^e V_t = (1-t_d)D_t - (1-t_c)V_t^N + (1-t_c)V_{t+1} - (1-t_c)V_t \tag{21}$$

Equation (21) is a difference equation for the value of the firm, V_t. Solving (21) for V_{t+1} yields:

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continue to be used for these tax rates. It should be noted that *t*, when appearing as a subscript, denotes the time period.

$$V_{t+1} = \left(1 + \frac{r^e}{(1-t_c)}\right) V_t + V_t^N - \left(\frac{(1-t_d)}{(1-t_c)}\right) D_t \tag{22}$$

Equation (22) may be solved forward, subject to the following transversality condition:

$$\lim_{t \to \infty} \left(1 + \frac{r^e}{(1-t_c)}\right)^{-t} V_t = 0 \tag{23}$$

The result is the following expression for the value of the firm in period t:

$$V_t = \sum_{i=0}^{\infty} \left(1 + \frac{r^e}{(1-t_c)}\right)^{-i} \left[\left(\frac{(1-t_d)}{(1-t_c)}\right) D_{t+i} - V_{t+i}^N\right] \tag{24}$$

Equation (24) demonstrates that the value of the firm in period t is the present value of the post-tax dividend stream adjusted for the present value of new equity issues that existing shareholders would be required to purchase in order to maintain their proportionate ownership of the firm.

The firm's maximization problem is consequently the following:

$$\underset{I_t, K_t, V_t^N, D_t}{Max} \quad V_t = \sum_{i=0}^{\infty} \left(1 + \frac{r^e}{(1-t_c)}\right)^{-i} \left[\left(\frac{(1-t_d)}{(1-t_c)}\right) D_{t+i} - V_{t+i}^N\right] \tag{25}$$

Subject to,

$$K_t = (1-\delta) K_{t-1} + I_t \tag{25.1}$$

$$(1-\tau)\Pi_t + V_t^N = D_t + I_t \tag{25.2}$$

$$D_t \geq 0 \tag{25.3}$$

$$V_t^N \geq \overline{V}^N \ , \ \overline{V}^N \leq 0 \tag{25.4}$$

The first constraint, (25.1), is the firm's capital accumulation constraint. This constraint, as was previously described, maps out the evolution of the firm's capital stock. Constraint (25.2) is the cash flow identity. This constraint equates the sources of funds with the uses of funds. Therefore, $\Pi_t = \Pi(K_t)$ is the firm's pre-tax profit, which is a function of the current period's capital stock, and τ is the corporate tax rate.[12] The two inequality constraints, (25.3) and (25.4), are restrictions on the firm's financial policies. In particular, constraint (25.3) ensures dividends are nonnegative, and constraint (25.4) requires that new share issues be greater than some minimum level $\overline{V}^N$. The condition $\overline{V}^N \leq 0$ restricts the firm's ability to repurchase shares or engage in transactions that have the same tax consequences.

This maximization problem may be re-written using the method of Lagrange multipliers as follows:

$$\underset{I_t,K_t,V_t^N,D_t,\lambda_t,\mu_t,\eta_t,\xi_t}{Max} \mathcal{L} = \sum_{t=0}^{\infty}\left(1+\frac{r^e}{(1-t_c)}\right)^{-t}\left\{\left[\left(\frac{(1-t_d)}{(1-t_c)}\right)D_{t+1} - V_{t+1}^N\right]\right. \tag{26}$$

$$-\lambda_t\left[K_t - (1-\delta)K_{t-1} - I_t\right]$$

$$-\mu_t\left[(1-\tau)\Pi(K_t) + V_t^N - D_t - I_t\right]$$

$$\left.-\eta_t(V_t^N - \overline{V}^N) - \xi_t D_t\right\}$$

Where λ_t, μ_t, η_t, and ξ_t are the Lagrange multipliers associated with the aforementioned constraints. The first-order necessary conditions for an optimal program are presented below:[13]

[12] The specification of the firm's profit function presumes that profits are solely a function of the current period's capital stock. Thus, labor is excluded from this particular specification. This is a simplifying assumption to minimize the algebra of the optimization problem—the qualitative results will not be affected.

[13] To ensure that the capital investment program satisfying the first-order conditions is indeed at maximum, the bordered Hessian must be negative definite. That is, the principal minors of the bordered Hessian must alternate signs such that $(-1)^n\left|\overline{H}_n\right| > 0$.

$$\frac{\partial \mathcal{L}}{\partial I_t} = \lambda_t + \mu_t = 0 \tag{26.1}$$

$$\frac{\partial \mathcal{L}}{\partial K_t} = -\lambda_t + \left(1 + \frac{r^e}{(1-t_c)}\right)^{-1} \lambda_{t+1} - \mu_t (1-\tau)\frac{d\Pi}{dK_t} = 0 \tag{26.2}$$

$$\frac{\partial \mathcal{L}}{\partial V_t^N} = -1 - \mu_t - \eta_t = 0 \qquad \eta_t (V_t^N - \overline{V}^N) \leq 0 \tag{26.3}$$

$$\frac{\partial \mathcal{L}}{\partial D_t} = \left(\frac{(1-t_d)}{(1-t_c)}\right) + \mu_t - \xi_t = 0 \qquad \xi_t D_t \leq 0 \tag{26.4}$$

These optimality conditions may be used to interpret the marginal value of an additional unit of capital in equilibrium (i.e., marginal q) for capital financed with retained earnings. In particular, for mature firms that have after-tax profits in excess of desired investment expenditures, their marginal source of finance for investment will be retained earnings. Consequently, dividends are determined as a residual and equal to the excess of profits over investment. This is shown below in equation (27).[14]

$$D_t = (1-\tau)\Pi_t - I_t + \overline{V}^N \tag{27}$$

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[14] When firms cannot find tax-free channels to transfer income to shareholders, the $V^N = \overline{V}^N$ constraint binds and dividends are determined as a residual. This well-known feature of the above model implies that it will never be optimal for firms to issue new shares and pay dividends simultaneously when $t_d > t_c$. In particular, if a firm follows a financial policy such that both $D_t > 0$ and $V_t^N > \overline{V}^N$ in any period, there would exist a feasible perturbation in financial policy such that share values could be raised without affecting investment or profits. Specifically, this perturbation involves a policy of dividend reductions compensated for by a reduction in new share issues, where these reductions would be governed by the identity $dV_t^N = dD_t$ to ensure investment and profits are unaffected by the policy. From this identity and equation (24), the maximand in the firm's maximization problem (i.e., the present value of the firm), it is easily demonstrated that when $t_d > t_c$ reducing dividends whenever feasible will raise the present value of the firm. Consequently, firms with sufficient profits in excess of investment needs should reduce new share issues and repurchase outstanding shares whenever possible. Hence, $V^N = \overline{V}^N$ binds and dividends equal $D_t = (1-\tau)\Pi_t - I_t + \overline{V}^N$.

For a firm in this situation it is known that $D_t > 0$. Consequently, this implies that $\xi_t = 0$, which results in the following expression for (26.4):

$$\mu_t = -\left[\frac{(1-t_d)}{(1-t_c)}\right] \tag{28}$$

Substituting (28) into (26.1) yields the following first-order condition for investment:

$$\lambda_t = \left[\frac{(1-t_d)}{(1-t_c)}\right] \tag{29}$$

The Lagrange multiplier in equation (28) may be interpreted in the usual way. Specifically, λ_t represents the marginal, or shadow, value of an addition unit of capital to the firm. That is, it reflects the incremental, after-tax increase in the present value of the firm attributable to an incremental increase in the firm's capital stock. This is Tobin's marginal q. Furthermore, when $t_d > t_c$ the following condition holds:

$$\lambda_t = \left[\frac{(1-t_d)}{(1-t_c)}\right] < 1 \tag{30}$$

Hence, the marginal q of investment in equilibrium is less than unity. As was described earlier, firms will continue to invest in capital until shareholders are indifferent on the margin between receiving a dollar in dividends and having the firm reinvest the dollar. That is, when a firm pays a dollar in dividends, shareholders receive $(1-t_d)$ dollars after taxes. Alternatively, if the firm retains the dollar and uses it to purchase new capital, the firm's share value will increase by q dollars. Consequently, shareholders will receive $q(1-t_c)$ dollars after taxes in the form of capital gains. Therefore, investors are indifferent between these two alternatives in equilibrium, giving the following indifference condition:

$$(1-t_d) = q(1-t_c) \tag{31}$$

Thus, it is clear that the marginal q in equilibrium, q^e, is less than unity.

$$q^e = \left[\frac{(1-t_d)}{(1-t_c)}\right] < 1 \tag{32}$$

This formal result confirms the intuitive argument made earlier regarding the impact of a higher tax rate on dividends relative to capital gains, i.e., when $t_d > t_c$. In particular, as was summarized in Table 3.1, investments financed with external funds will benefit shareholders only if their marginal q exceeds unity. On the other hand, as equation (32) demonstrates, shareholders will benefit from investments financed with internal funds as long as $q > [(1-t_d)/(1-t_c)] < 1$. Consequently, the after-tax cost of internal finance will be lower than the cost of external equity finance. However, the quantitative impact of this tax advantage for internal finance is probably not that large. There have been several tax reforms over the past few decades that have reduced the personal tax advantage of capital gains. Nonetheless, as was the case with transaction costs, this tax-induced incentive to finance investment projects with internal funds, while possibly only a minor incentive, cannot be dismissed.

Probably the strongest argument for the existence of a significant difference in the cost of capital between internal and external finance is based on asymmetric information. This is discussed in the following section.

Section 8.1: Asymmetric Information and the Cost of External Equity Capital

There are many markets that may be characterized by informational asymmetries between buyers and sellers. In financial markets this asymmetry is likely to be particularly pronounced. For example, in financial markets the borrowers of funds

typically know their collateral, technology, industriousness, and moral rectitude far better than the prospective lenders of the funds do. Hence, borrowers possess "inside" information about the prospects of their investment projects that lenders do not have. This is particularly true for investments in research and development, and especially true for pharmaceutical R&D—as was discussed earlier in this chapter. This asymmetry of information can create a significant deviation between the cost of internal and external capital—one whereby external capital is at a significant cost disadvantage. This is because rational investors, aware of their informational disadvantage, demand a premium—which is referred to as a "lemons" premium—on the capital they supply to finance investment.

This section will build upon the last section and incorporate asymmetric information into the model of firm investment. First, however, a discussion will be provided to describe the theoretical rationale for financing constraints based on asymmetric information.

The core theoretical argument behind the "lemons" premium draws heavily on the pioneering work first presented by George Akerlof (1970). Essentially, the argument is that sellers, because they possess "inside information" about the quality of their product, are unwilling to accept the terms offered by a less informed buyer. The result can be a complete breakdown in the market—or at least a situation in which the seller is forced to sell the product at a lower price than what would have been obtained if there were symmetric information. This basic idea may be applied to financial markets very easily. The result, as will be shown, is a financial hierarchy, or pecking order, whereupon internal funds have a significant cost advantage over external funds.

In the well-known Myers and Majluf model (1984), which extended Akerlof's ideas about asymmetric ideas into financial markets, the authors considered the case in which investors could not distinguish between the different qualities of firms.[15] As a consequence, investors valued each firm at the population average. The resulting implication—it was shown—was that investors required a premium rate of return on the

[15] Certainly, with time the true value of the firm will eventually be revealed. However, new shares will likely need to be issued before that, or the investment opportunity will be lost. This type of situation is particularly realistic for firms in industries undergoing rapid technological advancement. The pharmaceutical industry is clearly one such industry (refer to Chapter Two).

new equity issues of above-average-quality firms, or good firms. This premium compensated the investors for their losses—which they incurred by financing the low-quality firms, or "lemons". This, in turn, was shown to raise the cost of equity capital above that of internal funds—for the good firms.

The intuition behind the lemons premium may be explained nicely within the framework of the q-model of investment. As was demonstrated in an earlier section, the q-model of investment establishes that investments will only be undertaken if they increase the present value wealth of the existing shareholders. In particular, the Myers and Majluf model demonstrated that for good firms, new shares will be issued only when:

$$\frac{R'}{I} \geq \frac{R}{V} \tag{33}$$

Where,

R = the true gross returns from assets in place;
R' = the returns from a potential new investment project;
I = the cost of the new investment;
V = the market value assigned to both good firms and lemons alike.

As Fazzari, Hubbard, and Petersen (1988) pointed out, condition (33) is equivalent to requiring that a new project's marginal q be at least equal to the ratio of the firm's true average q (represented by Q) to the average q assigned to all firms by the market—the population average (represented by $\overline{q}$) [16]. That is,

$$q \geq \frac{Q}{\overline{q}} \tag{34}$$

---

[16] A firm's average q, sometimes expressed as Q, is simply the average return on capital investment. Indeed, assuming constant returns to scale for capital, marginal q and Q are equal.

If information is symmetric, such that firm managers have no inside information about the quality of an investment project, then

$$\frac{Q}{\bar{q}} = 1 \tag{35}$$

Consequently, the threshold marginal q for investments financed with new equity will be unity. However, in the presence of asymmetric information, when investors cannot distinguish between good firms and lemons, this ratio will exceed unity for the good firms. Specifically,

$$\frac{Q}{\bar{q}} > 1 \tag{36}$$

In particular, when there is asymmetric information this ratio depicts how much dilution occurs when a good firm issues new shares. Furthermore, subtracting one from this quantity yields the lemons premium, which is denoted by Ω.

$$\Omega = \frac{Q}{\bar{q}} - 1 \tag{37}$$

Incorporating the lemons premium, and hence asymmetric information, into the previously developed model is quite simple, and is done in the next section.

Section 8.2: *Financing Hierarchies and Investment: A Model of Taxes, Dividends, and Asymmetric Information*

Adapting the firm's maximization problem to incorporate a lemons premium may be done by modifying the maximand in equation (24). Specifically, the present value of

the firm V_t is reduced by the quantity Ω_t per each additional dollar of new equity issued, where again Ω_t, the lemons premium, reflects the additional dollar value that new investors demand per share from above-average firms to compensate them for unknowingly funding lemons.

Therefore, according to Fazzari, Hubard, and Petersen (1988), the firm's new maximization problem should be re-stated as the following:

$$\underset{I_t,K_t,V_t^N,D_t}{Max} \quad V_t = \sum_{i=0}^{\infty}\left(1+\frac{r^e}{(1-t_c)}\right)^{-i}\left[\left(\frac{(1-t_d)}{(1-t_c)}\right)D_{t+i} - V_{t+i}^N(1+\Omega_{t+i})\right] \tag{38}$$

Subject to,

$$K_t = (1-\delta)K_{t-1} + I_t \tag{38.1}$$

$$(1-\tau)\Pi_t + V_t^N = D_t + I_t \tag{38.2}$$

$$D_t \geq 0 \tag{38.3}$$

$$V_t^N \geq \overline{V}^N \ , \ \overline{V}^N \leq 0 \tag{38.4}$$

Re-writing this maximization problem to obtain the Lagrangean yields:

$$\begin{aligned}\underset{I_t,K_t,V_t^N,D_t,\lambda_t,\mu_t,\eta_t,\xi_t}{Max} \quad \mathcal{L} = \sum_{i=0}^{\infty}\left(1+\frac{r^e}{(1-t_c)}\right)^{-i}\Bigg\{&\left[\left(\frac{(1-t_d)}{(1-t_c)}\right)D_{t+i} - V_{t+i}^N(1+\Omega_{t+i})\right] \\ &- \lambda_t\left[K_t - (1-\delta)K_{t-1} - I_t\right] \\ &- \mu_t\left[(1-\tau)\Pi(K_t) + V_t^N - D_t - I_t\right] \\ &- \eta_t(V_t^N - \overline{V}^N) - \xi_t D_t\Bigg\}\end{aligned} \tag{39}$$

Where λ_t, μ_t, η_t, and ξ_t are the Largrange multipliers associated with the constraints. The first-order necessary conditions for an optimal program are presented below:[17]

$$\frac{\partial \mathcal{L}}{\partial I_t} = \lambda_t + \mu_t = 0 \tag{39.1}$$

$$\frac{\partial \mathcal{L}}{\partial K_t} = -\lambda_t + \left(1 + \frac{r^e}{(1-t_c)}\right)^{-1} \lambda_{t+1} - \mu_t (1-\tau)\frac{d\Pi}{dK_t} = 0 \tag{39.2}$$

$$\frac{\partial \mathcal{L}}{\partial V_t^N} = -1(1+\Omega_t) - \mu_t - \eta_t = 0 \qquad \eta_t (V_t^N - \overline{V}^N) \leq 0 \tag{39.3}$$

$$\frac{\partial \mathcal{L}}{\partial D_t} = \left(\frac{(1-t_d)}{(1-t_c)}\right) + \mu_t - \xi_t = 0 \qquad \xi_t D_t \leq 0 \tag{39.4}$$

This set of optimality conditions may be used to interpret firm behavior when asymmetric information prevails in the market and when firms must issue new equity to finance investment. In particular, when firms exhaust internal funds and seek investment finance in external equity markets, firms will not be paying dividends. That is, as was explained in the previous section, it is never optimal for firms to issue new shares and pay dividends simultaneously. Consequently, the knowledge that a firm is financing investment with new shares implies $D_t = 0$. Therefore, because $(V_t^N - \overline{V}^N) > 0$, the inequality in (39.3) implies $\eta_t = 0$. Consequently, equation (38.3) may be solved for μ_t to yield:

$$\mu_t = -1 - \Omega_t \tag{40}$$

[17] Again, one needs to ensure that the capital investment program satisfying the first-order conditions is indeed at maximum, i.e., the bordered Hessian must be negative definite. That is, the principal minors of the bordered Hessian must alternate signs such that $(-1)^n \left|\overline{H}_n\right| > 0$.

Substituting (40) into (39.1) yields the following optimality (i.e., equilibrium) condition for investment:

$$\lambda_t = 1 + \Omega_t \tag{41}$$

Where λ_t, the Lagrange multiplier, is interpreted as the marginal, or shadow value, of an additional unit of capital. As was discussed earlier, this is simply the marginal q. Consequently, asymmetric information will lead some firms to turn down investment projects offering positive net present values. This is because the project's marginal q is greater than unity, but less than one plus the lemons premium. This situation is described by equation (42) below.

$$1 < q < (1 + \Omega_t) \tag{42}$$

Therefore, pooling the results from the last two sections, one may express the following investment decision rules within the q-model framework. These decision rules are summarized below in table 3.2.

Table 3.2: R&D Investment Project Acceptance Criteria Under Asymmetric Information

Source of Finance	Accept Investment Project	Reject Investment Project
Internal Funds	$q \geq \frac{(1-t_d)}{(1-t_c)}$	$q < \frac{(1-t_d)}{(1-t_c)}$
External Equity	$q \geq (1 + \Omega_t)$	$q < (1 + \Omega_t)$

These results are also illustrated graphically in Figure 3.8 below.

Figure 3.8

A q-Model Equilibrium with Taxes and Asymmetric Information

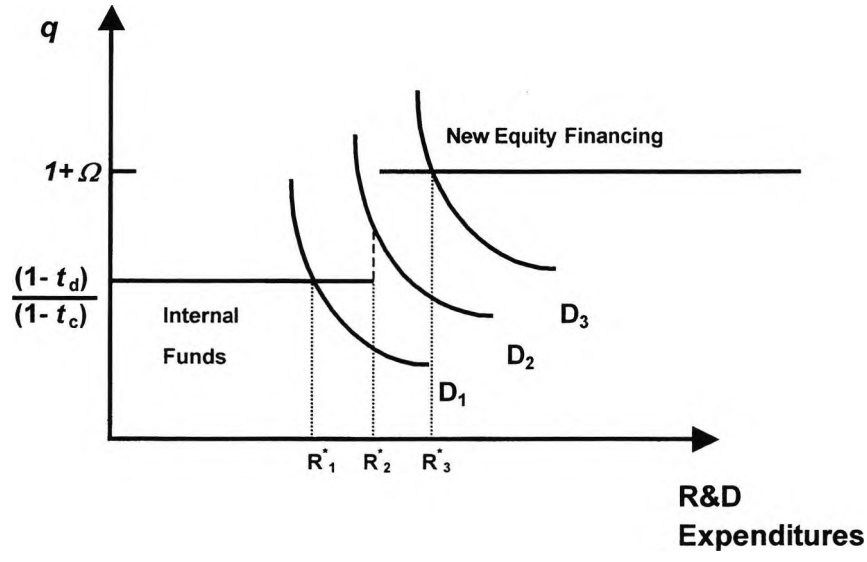


Figure 3.8 demonstrates a financing hierarchy resulting from the combined effects of both taxation and asymmetric information. It should be noted that firms finance investment with external equity only after all internal funds have been exhausted, and only then if the marginal q of the potential investment project exceeds $1+\Omega_t$. Furthermore, whereas externally financed investment projects must have a marginal q greater than $1+\Omega_t$, internally funded investment projects need only have a marginal q that exceeds $(1-t_d)/(1-t_c)$. Consequently, internal funds are clearly an important determinant of the firm's profit maximizing level of R&D. This was shown previously in Figure 3.5.

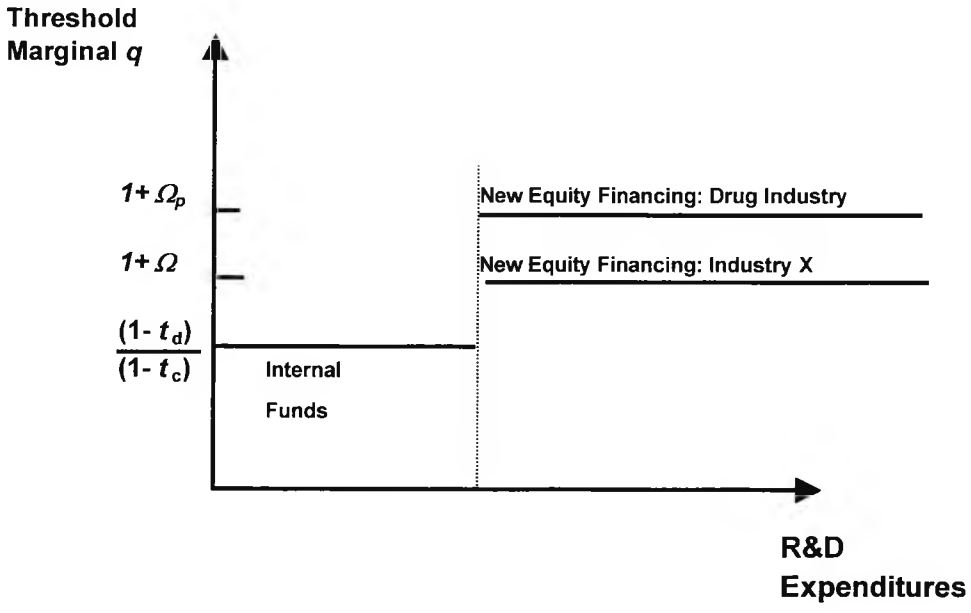
The relative position of the two horizontal segments in figure (3.8), which represent the threshold marginal qs for internally and externally financed investments, is determined by the difference between the tax on dividends and capital gains and the

extent of the informational asymmetries. In particular, as the difference between the tax rate on dividends and capital gains approaches zero, the horizontal segment representing the threshold marginal q for internal funds shifts upward and approaches unity. In a similar fashion, as the extent of informational asymmetries is reduced, the horizontal segment representing the threshold marginal q for equity funds shifts down and also approaches unity. It will equal unity when all asymmetries have been eliminated and information is symmetric between investors and firm managers. Hence, to the extent that dividends and capital gains are taxed at the same rate and no informational asymmetries exist, capital markets will, ceteris paribus, function perfectly, and no financial hierarchy will be present.

In the pharmaceutical industry, asymmetries of information are likely to be particularly important. This is because new information obtained from R&D is the primary means of competition among firms in the pharmaceutical industry. As such, this proprietary information plays the central role in the race to patent and develop new compounds. This is likely to lead to considerable information gap between firm managers and potential investors. This information gap is likely to be accentuated by the high degree of uncertainty and long development times that characterize pharmaceutical R&D. The result may be higher threshold marginal q for pharmaceutical R&D projects than for other investment projects—when these projects are financed with new equity. This potential scenario is depicted below in Figure 3.9.

Figure 3.9

Asymmetric Information in the Pharmaceutical Industry

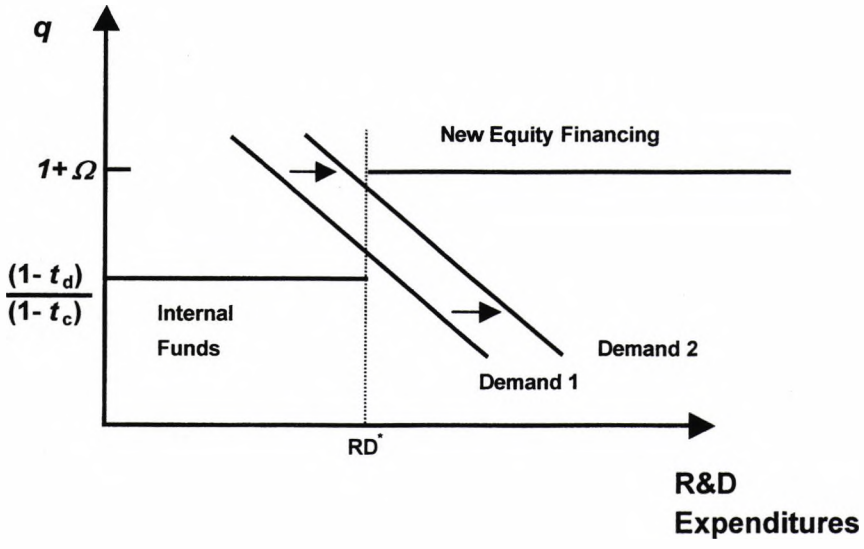


Dynamic analysis within this *q*-model framework (when debt finance is not considered) may also be illustrated. Moreover, this may be a more appropriate framework within which to analyze the pharmaceutical R&D investment decision, because pharmaceutical firms, on average, carry very little debt. Indeed, the total market value of most pharmaceutical firms is made up almost entirely of equity—most firms have less than 5% debt (refer to Table 2.5 in Chapter Two). One possible reason for this low debt to equity ratio may be the fact that the production of pharmaceuticals requires relatively little physical capital—which typically secures the firm's debt issues. Indeed, the primary input into the production of pharmaceuticals is R&D—which employs relatively little real capital. Therefore, when considering only internal funds and new equity, the cost of capital schedule—which is proxied by the firm's threshold marginal *q* schedule—has a discontinuity at the point where a firm exhausts its internal funds. The *qualitative* results obtained from this *q*-model specification are identical to those obtained

earlier from the alternative investment model. Specifically, the only difference is that new debt finance is not considered. This does, however, lead to one very interesting possibility. Under certain circumstances, without access to new debt, a change in the demand for R&D, or a change in the level of firm cash flows, will not affect the equilibrium level of firm R&D spending. Indeed, the greater the disparity between the cost of internal and external funds, the greater the likelihood of this phenomenon occurring. This possibility is demonstrated in Figure 3.10, which shows how an increase in demand for R&D may lead to no change in the firm's optimal level of R&D spending[18].

Figure 3.10

A *q*-Model Equilibrium with Taxes and Asymmetric Information



However, the consideration of new debt issues as a possible source of finance for new investment may easily be incorporated into the model. This is briefly discussed in the following section.

[18] Along similar lines, if a firm is financing some of its investment with external equity, an increase in cash flows may not impact the optimal level of R&D. However, in the pharmaceutical industry, R&D is financed almost exclusively with internal funds.

Section 9: The Rising Marginal Cost of New Debt: Financial Distress and Agency

Incorporating new debt finance into the investment model may also be particularly important for firms that rely heavily on debt financing. As was mentioned earlier in this chapter, debt finance would be represented graphically by an upward sloping line segment that connects the two horizontal line segments associated with internal and external equity. Insofar as new debt is secured, or obtained from lenders like commercial banks that specialize in monitoring the borrower, information asymmetries will be less severe in debt markets than in equity markets. Hence, the cost of new debt will be less than the cost of new equity[19]. However, the marginal cost of new debt will be greater than that of internal finance and will increase as the quantity of new debt issued by the firm rises. The theoretical rationale for the increasing marginal cost of new debt is largely based on financial distress and agency problems.

Financial distress costs arise when a firm encounters difficulties meeting its debt obligations. In particular, the firm has difficulties meeting its principal and interest obligations. In the extreme case the firm would be forced to file for bankruptcy. Hence, all things held constant, as a firm becomes leveraged with more and more debt, the likelihood that the firm will default on its debt payments increases. This is also referred to as financial gearing. Consequently, debt holders require a higher expected rate of return on the firm's debt to compensate them for the increased risk the firm will default on its debt payments. Furthermore, informational asymmetries aside, because debt finance is secured with corporate assets and equity finance is not, the cost of new debt finance is generally less than the cost of new equity finance.

Agency costs arise out of the limited-liability feature of most debt contracts. This feature may create incentives for firm managers—who are acting on behalf of firm shareholders—to act counter to the interests of the firm's debt-holders. This will be particularly true as a firm becomes more leveraged with debt. The result may be the acceptance of investment projects with negative net present values or the failure to accept projects with positive net present values. Furthermore, firm managers will have the

[19] Debt financing will also be less costly than equity financing because debt financing reduces a firm's tax liability. That is, interest on the debt is deductible from before-tax income.

incentive to issue new debt that will raise the riskiness and lower the value of existing debt. Debt-holders, who are well aware of this conflict of interest, will consequently set restrictive covenants on the firm's management—especially with respect to new debt issues. Frequently these covenants will stipulate a target debt-to-equity ratio and hence limit management's choices among potential investment projects. Moreover, if these covenants place restrictions on working capital such that the supply of funds available to finance investment is reduced, shocks to working capital (such as debt deflation or a decline in cash flows) will make debt finance more costly at the margin. Indeed, the theoretical arguments behind financial distress and agency costs, and how these costs lead to an increasing marginal cost of debt schedule, are quite old and well documented in the finance literature.

In summary, capital market imperfections may arise for any number of reasons. For example, transaction costs, taxes, asymmetric information, financial distress and agency problems may all lead to a breakdown in financial markets. The result may be a significant difference between the cost of internal and external funds, i.e., a financing hierarchy. Consequently, this financing hierarchy is likely to have an effect on the investment practices of some firms. Specifically, it may result in internal cash flows being a major determinant of investment spending. Hence, fluctuations in firm cash flows are likely to be accompanied by fluctuations in firm investment spending. As was discussed previously, this relationship may be particularly important to pharmaceutical R&D investment. This conclusion is in direct contrast with the neoclassical belief that real investment spending is independent of a firm's financial condition. This is because the neoclassical view maintains that internal capital and external capital are perfect substitutes.

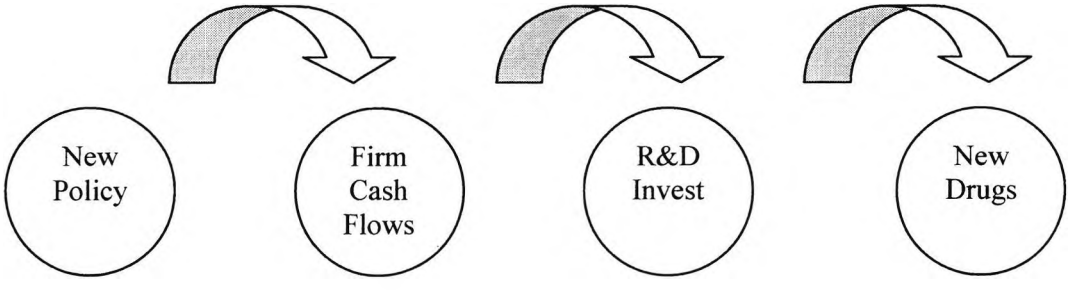
If a financing hierarchy does exist for R&D investments in the pharmaceutical industry, then there may be some very important policy implications as a result.

Section 10: Policy Considerations

As was addressed previously, there are several reasons to believe that financing constraints may be more prevalent in the pharmaceutical industry. That is, in the pharmaceutical industry, R&D investment is characterized by above average uncertainty and extremely long development times (the average length of the R&D process is 14.9 years—see Chapter Two). Moreover, unlike fixed investment in plant and equipment, the product of drug R&D is simply new knowledge that may have no resale value. For these reasons, as was discussed, the difference between the cost of internal funds and external funds may be especially large for pharmaceutical R&D (refer to Figure 3.9). This difference between the cost of internal and external funds has a number of important policy implications. In particular, any government intervention affecting the returns to R&D, and hence the supply of funds needed to undertake the R&D, will necessarily impact new drug innovation. That is, if firms rely heavily on internal cash flows to finance their R&D—due to the presence of a financing hierarchy—then any policy intervention affecting these cash flows will necessarily affect R&D expenditures, which in turn will affect new drug innovation. This causal relationship is illustrated below in Figure 3.11[20]

Figure 3.11

The Potential Impact of a New Policy on Drug Innovation



[20] It is important to note that the extent to which innovation will be stifled depends heavily on firm efficiency and the marginal productivity of the R&D. For example, a 25% reduction in R&D investment will reduce innovation by 25% only if the R&D production function is homogeneous of degree 1 (i.e., it exhibits constant returns to scale). It is very likely, however, that there are diminishing returns to R&D

There are a number of policy interventions that may affect firm cash flows and hence the supply of funds to undertake pharmaceutical R&D. These interventions include, for example, pre-market regulatory controls, drug price and reimbursement controls, regulation affecting the effective pharmaceutical patent lives, tax policies, and policies affecting product formulary decisions. A recent example of a government proposal affecting pharmaceuticals was the 1994 Clinton Health Care Reform Act. This Act would have extended government price controls over a large portion of the pharmaceutical market place. While the Clinton Administration commissioned several studies to gauge the impact of price controls on such things as Medicare drug budgets and the demand for pharmaceuticals, very little attention was paid to the potential long-term affects such price controls would have on pharmaceutical R&D and, consequently, new drug innovation. Given the important role pharmaceutical R&D plays in new drug innovation, which in turn influences economic welfare and economic growth, it would seem important that prospective analyses be undertaken to ascertain the potential impact of such governmental policies. Therefore, one of the primary objectives of the next several chapters of this thesis is to better understand the relationship between cash flows and pharmaceutical R&D. Hopefully, a better understanding of this key relationship will shed light on the potential economic repercussions of various government regulations and policies on the pharmaceutical industry.

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investment; hence, a 25% reduction in R&D investment will result in less than a 25% reduction in innovation.

Chapter Four

The Determinants of Pharmaceutical R&D and the Role of Internal Funds in Firm Investment Behavior: A Study of Eleven Leading U.S. Firms

Section 1: Introduction

Having developed the theoretical rationale for investment financing constraints, and their particular relevance to investment in pharmaceutical R&D, it is now appropriate to study the empirical role such constraints play in a firm's R&D decision. More specifically, to test the hypothesis that financing constraints impart a substantial cost advantage to internal funds (over external equity and debt), several models of the determinants of pharmaceutical R&D will be estimated.

This chapter will estimate several models of the determinants of pharmaceutical R&D using data from eleven leading U.S. pharmaceutical firms from 1976 to 1996. As a result, this analysis will be the most contemporary empirical study of the determinants of pharmaceutical R&D to date. Furthermore, in addition to using more recent data, the analyses in this chapter will differ from the earlier studies in two principle ways. First, the current models will be based on a more complete data sample than was used in the earlier studies. In particular, the earlier studies were hampered by limited data on one of the key independent variables in their regression models.[1] Secondly, the model specifications estimated in the current analyses will be substantially different from those of the earlier studies. For example, all of the early studies relied strictly on classic ordinary least squares (OLS) estimation techniques—the models in this chapter will not be so restrictive. Furthermore, as will be explained later in the chapter, several other innovations were made to both the model specifications and variable formulations in the

[1] The earlier studies relied upon linear interpolation for missing values of one of the key independent variables. In fact, so severe was the limited availability of this variable, that some models—which were based on 15-year time series—were estimated using only one or two observations per firm.

present analysis. Hence, it is hoped that the results reported here will more accurately reflect the true determinants of pharmaceutical R&D.

The collection of empirical analyses undertaken in this chapter should sufficiently test the hypothesis that cash flows, because of capital market imperfections, are an important determinant of pharmaceutical R&D. Furthermore, because of the more complete data sets employed, the more contemporary time periods studied, and the multiple refinements made to the previously employed model specifications, several new facts and details regarding the influence of internal funds on firm R&D investment should be uncovered.

Section 1.2: *Why Only U.S. Firms?*

All previous studies of the determinants of pharmaceutical R&D have been based exclusively on U.S. firm data. Therefore, for comparability reasons, an empirical investigation using recent U.S. firm data will be undertaken *first*. This will allow for more direct comparisons with, and critiques of, the earlier studies of the determinants of pharmaceutical R&D. Furthermore, and of central importance to this thesis, this study of U.S. firms will provide a bridge into the global R&D models that will follow in subsequent chapters—which will be based on a substantially larger *and* international sample of firms.

It is clear why this study will *begin* with U.S.-firm based models, but why have all previous studies been based exclusively on U.S. firm data? The principle reason is because U.S. firm data is readily available from many sources; the U.S. Securities and Exchange Commission (SEC) mandates that publicly traded firms disclose detailed financial information on a regular basis. Primarily, this information is submitted to the SEC in the form of 10-K and 10-Q reports—which are detailed annual and quarterly financial reports. Because 10-K and 10-Q filings are publicly available, it has been relatively easy, and of low cost, for researchers to gather the necessary U.S. firm data for a wide range of analyses. On the other hand, however, for firms not publicly traded on the U.S. financial exchanges—i.e., most non-U.S. firms—such detailed financial information is not readily available (at a low cost, anyway). In fact, due to the vastly

different disclosure requirements across most non-U.S. countries, much of the data procurable for U.S. firms is not available for non-U.S. firms. As a result, studies of the determinants of pharmaceutical R&D have historically been limited to analyses using strictly U.S. pharmaceutical firm data. This, however, will not be the case for the analyses in this thesis. As will be elaborated on in greater detail in the following chapters, the empirical models in this thesis will be based upon a strikingly larger data sample—one that actually contains a greater number of non-U.S. firms than U.S. firms. However, as was already mentioned, there are good reasons to begin the empirical analyses with U.S.-firm data.

This chapter proceeds as follows. First, a description of the firm selection criteria is provided. This is then followed by an overview of the resulting data sample and firms selected for the present analyses. Following this is a discussion of plausible model specifications and variable formulations. In particular, a brief review of the theoretical model is presented, and a justification for an intensity measure of R&D investment (the dependent variable in the forthcoming model specifications) is established. A review of the earlier studies, model specifications, and empirical findings is conducted along with the general model specification used in this analysis. Finally, the empirical findings are presented and discussed.

Section 2: Data Sample

The majority of the data used in this chapter were obtained from Standard and Poor's Compustat data. In particular, financial data were obtained on 11 of the largest U.S. pharmaceutical firms over the period from 1976-1996.

The firm selection criteria that resulted in this sample were dictated by four key factors:

1) Market capitalization
2) Years of established operations
3) Mergers
4) Percent of total firm sales accounted for by pharmaceutical sales

Therefore, for a firm to be included in the sample, the firm had to be, essentially, a major U.S pharmaceutical firm. This criterion generally excluded both biotech and smaller pharmaceutical firms from the sample. It was felt that, at least for a first analysis, it would be better to concentrate on the major pharmaceutical firms, and then expand the sample size in subsequent analyses by including smaller biotech and pharmaceutical firms. The second criterion excluded firms without a substantial number of years of pharmaceutical operations—a minimum of twenty years was required. This restriction was imposed for two principle reasons. First, because the first criterion considerably limited the number of firms remaining in the sample, it was necessary to have a substantial number of years of data on each firm in the sample in order to bolster the sample size. Secondly, and along the same lines, because several of the model specifications contained lagged variable formulations, a substantial number of years of data were required in order to maintain a reasonable sample size. The third criterion eliminated firms that went through significant mergers during the years in this study. It was believed that such mergers would substantially alter the internal capital structure of the merging firms and, consequently, compromise the integrity of the data. Finally, in order for a firm to be included in the sample, at least 30% of the firm's total sales had to be accounted for by pharmaceutical sales. That is, the firm's involvement in the pharmaceutical industry had to account for roughly one-third of the firm's total business operations. Most firms' pharmaceutical sales, did, however, account for over 50% of total firm sales.

The firms meeting the above criteria were identified to be the following:

1) Abbott Laboratories
2) American Home Products
3) Bristol Myers
4) Johnson & Johnson
5) Eli Lilly
6) Merck
7) Pfizer
8) Schering-Plough
9) Syntex
10) Upjohn
11) Warner-Lambert

Section 3.1: Model Specifications and Variable Formulations

Before presenting the model specifications used in the forthcoming analyses, a brief overview of the theoretical model will be provided. This model was presented in full detail in the preceding chapter.

Section 3.2: The Optimal Level of R&D Intensity: A Rate of Return Analysis

The optimal level of research and development may be determined by simultaneously solving an expected marginal rate-of-return equation, *mrr*, and an expected marginal cost-of-capital equation, *mcc*. The marginal rate of return on R&D investment may be thought of as the expected rate of return on the next R&D project. Specifically, the expected rate of return on the next project is assessed by the firm to be the expected present value revenues from the next project *less* the expected present value operating costs from the next project all *divided* by the present value R&D expenditures for that project. This is expressed algebraically by equation (1).

$$mrr_i = \frac{E(R_i) - E(C_i)}{RD_i} \qquad (1)$$

The subscript i denotes the *i*th R&D project in the firm's R&D project portfolio. Refer to Chapter Three for a more rigorous development of this expected marginal-rate-of-return concept. Projects are arranged in the R&D project portfolio in a decreasing order with respect to their risk-adjusted expected rate of return.

The *mcc* equation similarly reflects the opportunity cost of capital incurred through investing in R&D on the margin. The opportunity cost of capital is the expected rate of return on the next best alternative investment of similar risk. As has been previously discussed, the focus of this research, and consequently the model specifications that follow, will be devoted to testing the hypothesis that capital market imperfections exist and result in a lower cost of capital for internal funds relative to external funds (i.e., new debt and equity finance). This, as was elaborated on in Chapter

Three, results in a positive relationship between firm R&D expenditures and changes in a firm's cash flow. Explanations of why internal finance may be less costly than the issuance of new shares or debt abound and have already been rigorously developed in this thesis. To summarize, these explanations include:

1) Transaction Costs
2) Tax Advantages
3) Asymmetric Information
4) Agency Problems
5) Costs of Financial Distress

Algebraically, the general form of this model may be expressed as follows:

$$MRR(RD^*, \mathbf{X}, \mathbf{Y}) = MCC(RD^*, \mathbf{Z}) \qquad (2)$$

Where,

RD^* = the optimal level of pharmaceutical R&D investment expenditures
$\mathbf{X}$ = a vector of variables influencing expected returns to pharmaceutical R&D
$\mathbf{Y}$ = a vector of variables influencing the expected costs associated with pharmaceutical R&D, and
$\mathbf{Z}$ = a vector of variables influencing the opportunity cost of capital

Hence, it is clear that the optimal level of R&D is implicit within the above equation and is a function of the vectors **X**, **Y**, and **Z**.

Generally, we may solve the above equation to obtain the reduced form solution for the optimal level of R&D expenditures:

$$RD^* = f(\mathbf{X}, \mathbf{Y}, \mathbf{Z}) \qquad (3)$$

Equation (3) clearly implies that any change in one or more of the variables contained in the **X**, **Y**, or **Z** vectors is likely to alter the optimal level of R&D.

Section 3.3: *Rate-of-Return Analysis and the Specification of the Dependent Variable: R&D Intensity (R&D-to-Sales)*

One consideration regarding the rate-of-return analysis just mentioned is that firm managers may not be reasonably capable of assessing the expected steam of revenues and costs associated with a given R&D project during the very preliminary development stages. For example, in the preliminary stages of development, numerous tests must be conducted on laboratory animals before a firm applies to the U.S. FDA for clinical trials of a product on humans. The attrition rate during this stage is extraordinarily high; on average, only one out of several hundred new chemical entities (NCEs) makes it to the clinical stage for trials with humans. For this reason, rate-of-return analyses are virtually impossible to conduct at this preliminary development stage.

Partially mitigating this problem is the fact that R&D costs do not start to escalate significantly until after these very preliminary stages of development. Once a product makes it beyond the earliest stages of drug development, a rate-of-return analysis is possible. Information regarding the efficacy and safety of a compound in human subjects gives firm managers more insight into the probability of FDA approval, the costs of subsequent tests and clinical trials, and the expected future revenues from, and costs of, the compound. The attrition rate after a compound reaches this stage in drug development is much less—approximately one in eight NCEs eventually gains FDA approval and is launched on the market (PhRMA 1998).

Moreover, even though firms may not be able to assess project-specific future revenues and costs in the earliest stages of drug development, they will nevertheless be sensitive to industry-wide changes and expectations, such as new tax laws, new FDA regulations, or industry-wide economic conditions. Theoretically, such factors will be highly influential variables within the **X**, **Y**, and **Z** vectors previously specified.

Additionally, firm managers have been reported to deal with the aforementioned uncertainties by following a "rule of thumb" relationship between R&D and sales (Grabowski 1968, Grabowski and Vernon 1981). This short-run management device enables firms to avoid unstable expansions or contractions of their R&D departments. Furthermore, because there is considerable variance in R&D intensities over time and

across firms, this rule-of-thumb investment model appears to be highly plausible. Consequently, in the model specifications that follow, the dependent variable will be defined as the ratio of R&D-to-sales to reflect management's rule-of-thumb approach to R&D allocation.

Section 4.1: Past Research on the Determinants of Pharmaceutical R&D: The 1960's, 1970's, and 1980's

Section 4.2: Earlier Model Specifications: The 1960's and 1970's

In modeling the determinants of R&D intensity for the period from 1959 to 1975, Grabowski (1968) and Grabowski and Vernon (1981) specified four variables thought to be deterministic of the allocation of funds to R&D. Their model specification was of the general form:

$$RDS_{it} = f(NR_{it}, DVR_i, CFM_{it}, PC_{it}) \qquad (4)$$

Where,

RDS_{it} = the ratio of R&D expenditures to total firm sales for the ith firm in year t.

NR_{it} = an index of past R&D success—in particular, it equals the sales of a firm's new product introductions, during the first three years of the product's commercial life, for all of a firm's introductions in years: 0, -1,-2,-3,-4, all divided by R&D expenditures in year -2.

DVR_i = a Herfindahl-type index of firm diversification that equals $1 - \sum_{j=1}^{n} s_j^2$, where s_j equals the fraction of a firm's ethical drugs sales in the jth class, calculated at the midpoint year of the sample.

CFM_{it} = firm i's cash flow margin in year t—in particular it equals lagged profits after taxes plus depreciation divided by sales (a two-year lag was utilized).

PC_{it} = the percentage of the ith firm's total sales accounted for by ethical drug sales during year t.

The rationale for the formulation of the above variables is quite intuitive and captures many of the theoretical considerations presented in detail in Chapter Three. Because the models in this chapter will be based on similar specifications to the above model, a brief explanation of this specification is provided below.

A primary factor in the decision to allocate funds to R&D must be the expected returns from the R&D[2]. Grabowski and Vernon measured this expectation with their NR_{it} variable. This variable was designed to be a rough "productivity of R&D" measure at the firm level.[3]

Additionally, it was posited that scientifically diversified firms would have higher profit expectations than less scientifically diversified firms. The basic idea underlying this assumption was that a more diversified firm would have a greater capacity to exploit serendipitous research findings than would a firm with a more specialized research and development program. Theoretically, this variable, while appropriate for the time period studied here, would be much less likely to affect profit expectations in more recent times. This is because of the advent of rational drug design. As was discussed in Chapter Two, in the late 1970's the rational drug design technology was emerging rapidly and changing the way drugs were being discovered. Firms were no longer randomly testing and screening large volumes of chemicals—firms were instead beginning to design molecules

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[2] Firm R&D expenditures, per SEC regulation, include all expenses associated with the different stages of drug discovery and development described in detail in Chapter Two.

[3] This variable formulation clearly implies that firm managers form their expectations of the returns from R&D based on past returns from R&D. Contemporary thought, however, would challenge this assumption on the grounds that such adaptive expectations ignore the possibility that a firm's future prospects may be completely unrelated to its past performance. In fact, a firm manager forming expectations about the future returns to R&D would theoretically only consider contemporaneous information. Consequently, in theory, firm decision-makers will not base future expectations on the success (or failure) of the firm's past R&D investments. This is the well-known Rational Expectations (REH) Hypothesis first put forth by John Muth (1961) and later developed fully by Robert Lucus.

with known chemical or biological responses (refer to Chapter Two). A major effect of the arrival of rational drug design was the elimination of most serendipitous drug discoveries—which characterized the major drug discoveries in the pre-1975 period. Hence, for more contemporary time periods, a variable similar to DVR_t would theoretically be inappropriate for models of the determinants of R&D.

A cash flow variable designed to estimate a firm's internal cash flow was also hypothesized to be an explanatory variable in this model. As was argued extensively in Chapter Three, firms are likely to impute a lower cost of capital to internal funds. Hence, increases in the level of internal funds were expected to positively affect R&D investment. This is likely to be the case for the reasons sited earlier: transaction costs, tax advantages, asymmetries of information, agency problems, and the costs associated with financial distress.

Finally, because the firms in this study were diversified across several industries, the pharmaceutical industry being just one of these industries, it was necessary to include the variable PC_{it}. This variable was defined as the ratio of pharmaceutical sales to total firm sales, and was designed to control for the varying levels of firm involvement in the pharmaceutical industry. In particular, because the pharmaceutical industry is one of the most research intensive industries in the world (refer to Figure 2.3 in Chapter Two), the more concentrated a firm is in the pharmaceutical business the higher the anticipated level of total R&D spending.

Clearly, all of the aforementioned variables were hypothesized to have positive signs. In a series of simple linear regressions, Grabowski and Vernon found all the variables to be statistically significant with the exception of the DVR_t variable. A summary of these empirical results is provided below in Table 4.1. Coefficient t-statistics are reported in parentheses.

Table 4.1[4]

Summary of Linear Regression Results from the Grabowski and Vernon 1981 Study

Equation Sample N	Intercept	CFM	NR	DVR	PC	R^2/F	Time Period
1.1 N=140	-.051 (-1.86)	.268 (6.07)	.019 (3.80)	.045 (1.73)	.063 (5.11)	.49/32.6	1962-1975
1.2 N=140	-.005 (-.73)	.224 (6.16)	.015 (3.36)		.064 (5.18)	.48/41.9	1962-1975
1.3 N=70	-.057 (-1.36)	.282 (4.38)	.016 (2.49)	.035 (.88)	.084 (5.01)	.53/18.9	1962-1968
1.4 N=70	-.021 (-1.81)	.249 (4.76)	.013 (2.45)		.085 (5.10)	.53/25.1	1962-1968
1.5 N=70	-.033 (-.85)	.255 (3.81)	.029 (1.96)	.042 (1.09)	.041 (2.18)	.44/13.1	1969-1975
1.6 N=70	.007 (.72)	.209 (4.01)	.030 (2.01)		.043 (2.30)	.43/17.1	1969-1975

These results demonstrate a highly robust model—one in which expected returns and cash flows play an important role in a firm's allocation of funds to R&D.

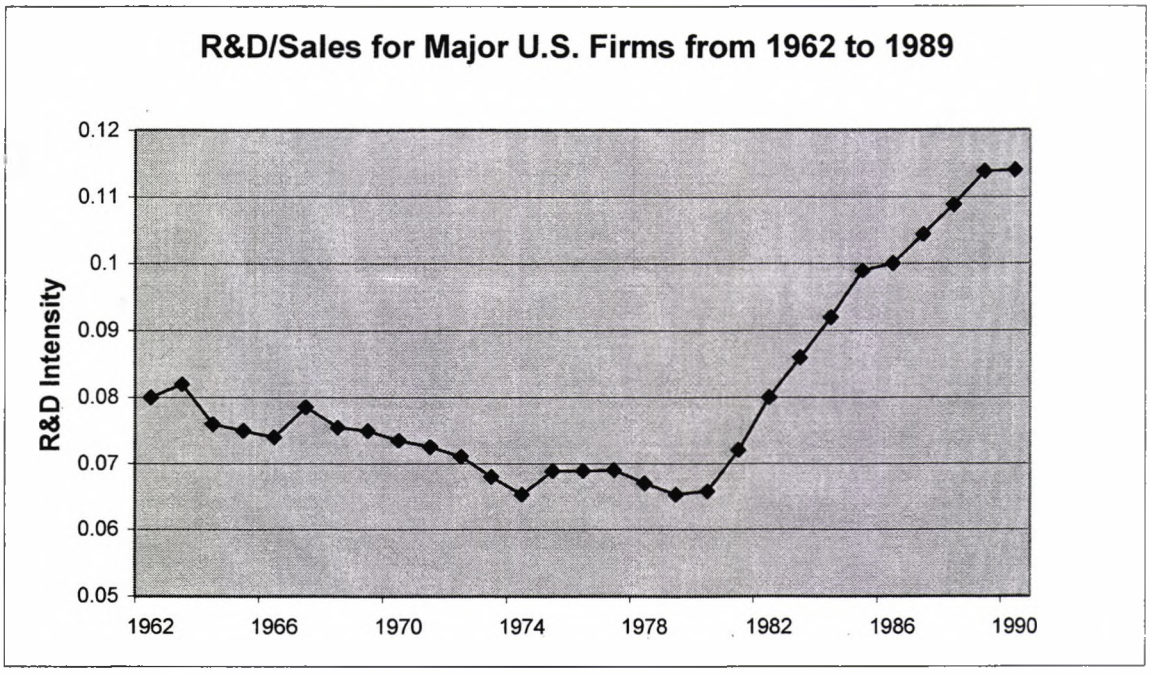
Section 4.3: *The Models of the 1980's*

The decade of the 1980's was a particularly interesting period for the pharmaceutical industry. During this period, absolute R&D spending increased dramatically. In fact, not only did absolute R&D spending increase, but the intensity of R&D spending (defined as the ratio of R&D expenditures to total firm sales) rose significantly as well. Figure 1 depicts the aggregate R&D-to-sales ratio for seven major U.S. firms that reported R&D data over the full 27-year period, 1962 to 1989.[5]

[3] The firms in this study were Abbott, Eli Lilly, Merck, Pfizer, Robins, Schering-Plough, SmithKline, Syntex, Upjohn, and Carter-Wallace.

[5] The seven firms are Abbott, Bristol Myers, Eli Lilly, Merck, Pfizer, Schering-Plough and Upjohn.

Figure 4.1



This unprecedented climb in the allocation of funds to pharmaceutical R&D stimulated much new research in the area of the determinants of R&D investment. Out of this research came several competing hypotheses for the observed increase in R&D intensity during this period. In particular, McCutchen (1993), Jensen (1994), and Vernon (1995) all utilized new variables in their model specifications, variables that were not included in the earlier Grabowski and Vernon specification, to test their respective hypotheses. These variables and hypotheses are discussed next.

In her 1988 study of the determinants of pharmaceutical R&D, Jensen used a time trend variable to capture, what she argued were, the increasing levels of scientific knowledge that were evolving during the eighties. She contented that a dramatic expansion in scientific knowledge was beginning around the turn of the decade, one that opened up an unprecedented number of new avenues for research and development. It was this expansion in scientific opportunities—she hypothesized—that was primarily responsible for the dramatic rise in R&D activity during the 1980s.

In his 1993 study, McCutchen utilized a tax dummy variable that was devised to capture the impact of the R&D tax credits that were instituted in the early 1980s. McCutchen argued that it was the advent of pharmaceutical R&D tax credits, which were established by the Economic Recovery Tax Act of 1981, that was responsible for rising R&D expenditures during the 1980s. This Act provided a 25% tax credit on all increases in R&D expenditures. Even though the tax credits expired on December 31, 1985, subsequent legislation extended them throughout the decade. In fact, a 20% R&D tax credit is still in effect for all increases in R&D expenditures.

Finally, Vernon, in his 1995 research, focused on a new "rational" expectations variable—one that was designed to more accurately capture the expected returns from R&D. He argued that the rising expectations of the returns to R&D were responsible for the higher R&D spending. He used this new variable to replace Grabowski and Vernon's adaptive expectations variable—which he found to be only marginally statistically significant in models of determinants of pharmaceutical R&D in the 1980's. Specifically, he argued that firms formed profit expectations by looking at the current *industry* profit margin, in which the industry profit margin was defined to be the weighted-average, pre-tax, price-cost margin for the pharmaceutical divisions of the largest U.S. pharmaceutical firms. The basic idea behind his formulation was based on the fact that firms, which often have parallel paths of research and spillover opportunities, are well aware of the performance of their peers. Consequently, they view current pharmaceutical profit margins as a reasonable proxy for the future returns to their *own* current R&D expenditures.

This rational-expectations variable was clearly quite different from the Grabowski and Vernon variable, which presumed that firms based future profit expectations on their *individual* past successes or failures. Furthermore, Vernon argued that the industry margin was a better proxy for expected returns to R&D because it was subject to much less variability than an individual firm's past successes or failures. He concluded that the mis-specified profit expectations variables used by Jensen and McCutchen—which utilized Grabowski and Vernon-type adaptive expectations formulations—resulted in an overestimation of the influence of the tax credits and new research opportunities, which he found to be statistically insignificant in the majority of his models. Grabowski and

Vernon largely replicated these results in their later 1997 study of the determinants of pharmaceutical R&D. For this reason, their empirical findings for the decade of the 1980's will be presented next.

Section 4.4: *The Grabowski and Vernon 1980's Model*

Using a slightly modified specification from their earlier model, one that included Vernon's forward looking profit expectations variable, Grabowski and Vernon estimated several models of the determinants of R&D intensity for the decade of the 1980's. Their general model specification was the following:

$$RDS_{it} = f(IRR_t, CFM_{it}, PC_{it}) \qquad (4)$$

CFM_{it} and PC_{it} were the same variables from their earlier study, and IRR_t was a profit expectations variable which had two new, and slightly modified, formulations. These expectation variables are defined below:

Newsal = an index of past R&D success—in particular, it equals *industry* sales of new product introductions, during the first three years of the product's commercial life, for all *industry* introductions in years: 0, -1, -2, -3, -4 all divided by *R&D* expenditures in year -2.

Imarg = the industry profit margin—the weighted-average, pre-tax, price-cost margin for the pharmaceutical divisions of the largest U.S. pharmaceutical firms.

The formulation of the *Newsal* variable was similar to Grabowski and Vernon's earlier NR_{it} variable, except NR_{it} measured an individual firm's past successes rather

than industry-wide successes. By using this industry-wide variant of expected R&D productivity, they argued it partially mitigated the theoretical problems associated with adaptive expectations. In particular, they argued that rationale firm managers formed expectations by looking at the overall industry performance with respect to R&D, not simply their own past performance. This was deemed highly plausible due to the high degree of parallel research activities and spillover opportunities amongst pharmaceutical firms during this period.

Furthermore, Grabowski and Vernon, much like Vernon, found little evidence to suggest that either a time trend variable (designed to capture expanding scientific knowledge) or R&D tax credits were influential in the determination of R&D intensity. The results from their linear regression analyses, which were very similar to Vernon's 1995 findings, were quite robust and are reported below in Table 4.2.

Table 4.2[6]

Summary of Linear Regression Results from the Grabowski and Vernon 1997 Study

Equation Sample N	Intercept	Imarg	Newsal	CFM	PC	R^2/F	Time Period
2.1 N=176	-0.20 (-7.00)	0.74 (6.58)		0.27 (9.88)	0.05 (4.57)	0.71/140.8	1974-1989
2.2 N=110	-0.17 (-4.75)	0.62 (4.46)		0.29 (8.01)	0.05 (3.65)	0.72/91.6	1980-1989
2.3 N=176	-0.06 (-8.04)		0.17 (7.95)	0.28 (11.05)	0.04 (4.58)	0.74/159.2	1974-1989
2.4 N=110	-0.07 (-4.02)		0.19 (3.55)	0.31 (8.40)	0.04 (3.25)	0.70/84.2	1980-1989

The results from both of the Grabowski and Vernon studies indicate a broadly consistent role for cash flows in the determination of firm investment spending on pharmaceutical R&D. Not only was the cash flow variable highly significant in every model estimated, but also the coefficient for this variable was relatively stable over both

[6] The firms in this study were Abbott, American Home Products, Bristol-Myers, Johnson & Johnson, Eli Lilly, Merck, Pfizer, Schering-Plough, Syntex, Upjohn and Warner-Lambert.

different time periods and different model specifications—ranging from 0.21 to 0.31. Indeed, this was true despite the vastly different industrial climates that characterized the different time periods. For example, during the 1962 to 1975 time period, R&D intensity was declining, whereas during the latter time period, R&D intensity was increasing dramatically. This was demonstrated previously in Figure 4.1.

Before presenting the new and more contemporary U.S. firm models, it should be mentioned that the earlier studies were based on a somewhat limited data sample. Specifically, these studies were constrained by a limited number of observations on annual firm *pharmaceutical* sales (as opposed to total firm sales)—a variable necessary for the computation of the previously discussed PC_{it} variable. In fact, Grabowski and Vernon's 1962-1975-study had only two years of data on this variable—1970 and 1975. Their 1974-1989-study had only one year of data—a 1980 observation.[7] Therefore, in their first study, the 1970 values of PC_{it} were applied to all years prior to 1970, and linear interpolation was used to obtain values for the years between 1970 and 1975. In their 1974-1989-study, the 1980 PC_{it} values were applied to every year in the sample. This data deficiency may have led to an imperfect measure of a firm's involvement in the pharmaceutical industry over time. It is unlikely, however, that it significantly affected their empirical results. This is because the majority of the variability in the PC_{it} variable was across firms—not over time. Nonetheless, the models estimated in this chapter will be based on a more complete data sample—one that *does* contain annual data on the firm pharmaceutical sales, and hence annual data for the PC_{it} variable.[8]

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[7] However, because the two studies contained different samples of firms, the 1975 PC_{it} values from the first study could not be used in the later study.

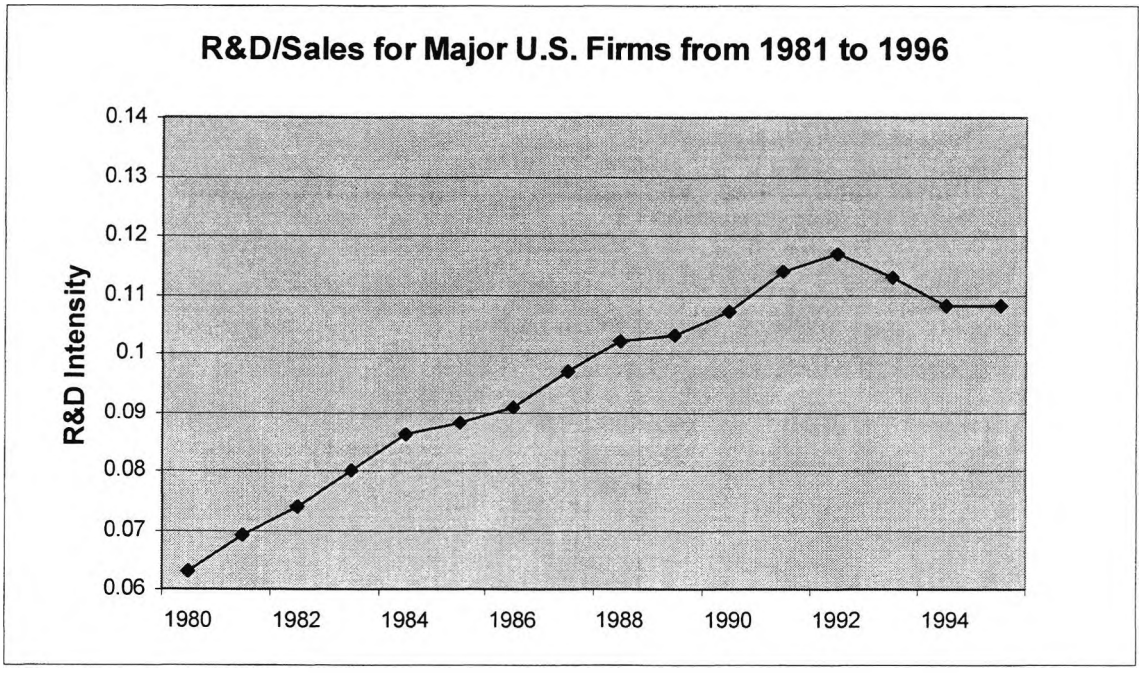
[8] These data were obtained from Scrip Annual Company League Tables. These reports are not generally available to the public. More will be said about this data source in the next chapter.

Section 5.1: New Research Findings and Empirical Models

Section 5.2: *The New Models and the 1990's: Specifications and Statistical Findings*

The 1990's have witnessed a continued growth in pharmaceutical R&D expenditures. In fact, R&D expenditures have grown at a real rate of more than 10% each year since the turn of the decade. R&D-to-sales percentages also continued to climb in the early 1990's before declining slightly in 1994 (for the firms in this sample). This aggregate R&D intensity variable is plotted below in Figure 4.2. The firms used to construct this graph are, for comparability reasons, the same firms as those used in the Figure 4.1.[9]

Figure 4.2



[9] Upjohn was excluded from the sample due to its 1995 merger with Pharmacia.

To test the primary hypothesis of this thesis that market imperfections exist in the capital markets for pharmaceutical R&D—and consequently impart a substantial cost advantage to R&D financed with internal funds, several different model specifications of the determinants of pharmaceutical R&D will be estimated. In particular, models similar to Grabowski and Vernon's earlier specifications will be employed. The empirical results that follow should, however, more accurately reflect the influence of cash flows on firm R&D intensity due to the more complete and contemporary data sets used in these analyses.

Section 5.3: *Econometric Issues and Model Specifications*

Before delving into the various model specifications and empirical findings in this and other sections, a brief discussion should be undertaken regarding the econometric analyses of pooled data samples. In general, there exist three approaches to model estimation when using a pooled data set: classic ordinary least squares (OLS), fixed effects, and random effects. The basic framework of the regression model can be represented by the following equation:

$$y_{it} = \alpha_{it} + \beta' X_{it} + \varepsilon_{it} \qquad (5)$$

Where α_{it} is the intercept term, β is the coefficient vector, X_{it} is the matrix of regressors, and ε_{it} is the vector of the classic linear regression model disturbance terms (i.e., error terms).

Section 5.4.1: *The OLS Model*

The general form of the classic OLS model assumes a common intercept term for all cross sections—i.e., $\alpha_{it} = \alpha$. Hence, the general form of the classic OLS model is:

$$y_{it} = \alpha + \beta' X_{it} + \varepsilon_{it} \quad (6)$$

With the standard assumptions made about the disturbance terms:

$$E(\varepsilon_{it}) = 0 \quad (7)$$

$$E(\varepsilon_{it}^2) = \sigma^2 \quad (8)$$

$$Cov(\varepsilon_{it}, \varepsilon_{js}) = 0 \quad \text{if } t \neq s \text{ or } i \neq j \quad (9)$$

Equations 7-9 imply that the disturbance terms in equation (6) have an expected value of zero, a constant variance (i.e., they are homoskedastic), and are independent (i.e., they are not contemporaneously or serially correlated). Furthermore, the disturbance terms are assumed to be normally distributed around zero—their expected value. An alternative—but equivalent—expression for these assumptions may be represented by the following:

$$\varepsilon_{it} \sim IN(0, \sigma^2) \quad (10)$$

All previous studies of the determinants of pharmaceutical R&D have strictly utilized this classic OLS model specification. The analyses in this chapter, however, will explore several other model specifications.

Section 5.4.2: *Fixed-Effects Models*

Another specification that may be employed is the fixed-effects model. This model specification allows for a separate constant term to be estimated for each cross-sectional unit—i.e., $\alpha_{it} = \alpha_i$. Consequently, this specification is commonly referred to as the least squares dummy variable model (LSDV) and is represented by the following equation:

$$y_{it} = \alpha_i + \beta' X_{it} + \varepsilon_{it} \tag{10}$$

Like the classical OLS model, the standard assumptions about the disturbance terms (equations 7-9) are also presumed to hold. From a theoretical perspective, the fixed-effects model is a reasonable specification if it is believed that there exist *systematic* differences between cross-sectional units (firms in this study). If this is believed to be the case, a separate constant term is estimated for each cross-sectional unit and the differences between units (i.e., firms) are viewed as parametric shifts of the regression function.

The fixed-effects model has a number of limitations, however. First, the results from models using this specification should only be interpreted within the context of the cross-sectional units in the study. Hence, generalizing the findings beyond the data sample is inappropriate (Green 1993, Kennedy 1992). Therefore, the appropriateness of the fixed-effects model depends on the context of the data and the intended use of the empirical findings. If the data exhaust the population—for example all of the firms in a particular industry—then the fixed-effects specification may be reasonable. However, if the data represent only a portion of the entire population—i.e., only a few firms in a particular industry, and the objective is to draw inferences about the entire population — i.e., the entire industry—then this model specification may no longer be appropriate. Secondly, the fixed-effects model cannot deal with regressors that are time invariant (or cross-sectionally invariant variables if a two-way fixed-effects model is assumed). More will be said on this limitation shortly. Finally, and from a more practical perspective, fixed effects models generally take up a large number of degrees of statistical freedom—especially when the number of cross sectional units is large. For this reason, for data sets that have a large number of cross sectional units and relatively few time periods, it is often unreasonable to estimate a fixed-effects model. Under these circumstances a random-effects model is typically selected.

Section 5.4.3: *Random-Effects Models*

The random-effects model, unlike the fixed-effects model, assumes that the individual specific constant terms are randomly distributed across the cross-sectional units in the sample. That is, there exists a true population constant term about which the individual cross-sectional units' constant terms are randomly distributed. Hence, the differences in the intercept values across cross-sectional units are due to a *random* process—not a *systematic* process, as was assumed by the fixed-effects model. In particular, the random-effects model assumes that α_{it} is generated by the following stochastic process:

$$\alpha_{it} = \alpha + u_i \tag{11}$$

u_i is the random disturbance term characterizing the *i*th observation—which is assumed to be constant over time. Consequently, this model can be represented by the following equation:

$$y_{it} = \alpha + \beta' X_{it} + u_i + \varepsilon_{it} \tag{12}$$

Where the following assumption are made about the two disturbance terms:

$$\mathrm{E}(\varepsilon_{it}) = \mathrm{E}(u_i) = 0 \tag{13}$$

$$\mathrm{E}(\varepsilon_{it}^2) = \sigma_\varepsilon^2 \tag{14}$$

$$\mathrm{E}(u_i^2) = \sigma_i^2 \tag{15}$$

$$\mathrm{E}(\varepsilon_{it} u_j) = 0 \quad \text{for all } i, t, \text{ and } j \tag{16}$$

$$\mathrm{E}(\varepsilon_{it} \varepsilon_{js}) = 0 \quad \text{if } t \neq s \text{ or } i \neq j \tag{17}$$

$$\mathrm{E}(u_i u_j) = 0 \quad \text{if } i \neq j \tag{18}$$

There exists one major drawback to the random-effects model presented here, however: it assumes that the random effects associated with each cross-sectional unit are uncorrelated with the other regressors in the model—this may be difficult to justify. This assumption, however, may be tested econometrically to determine the appropriateness of the random-effects model specification. Clearly, the obvious appeal of this model, especially for models estimated using a large number of cross-sectional units, is that it does not use up very many degrees of statistical freedom. Sometimes this practical consideration outweighs more theoretical considerations in applied econometric research (Greene 1993, Kennedy 1994).

Less frequently, two-way fixed and random-effects models are estimated. These models are an extension of the previously discussed fixed and random-effects models in that they allow for the possibility of time-specific effects. While the analyses in this chapter will not focus on these two-way-effect models, a brief description is nonetheless provided. The two-way fixed-effects model can be represented by the following equation:

$$y_{it} = \alpha_i + \gamma_t + \beta' X_{it} + \varepsilon_{it} \tag{19}$$

α_i is the systematic cross-sectional effect (i.e., the constant term for the *i*th cross sectional unit) and γ_t is the systematic time effect (i.e., the constant term for each time period).

Similarly, the two-way random-effects model can be represented by the following equation:

$$y_{it} = \alpha + \gamma + \beta' X_{it} + \varepsilon_{it} + u_i + \omega_t \tag{20}$$

Where α_i and γ_t are generated by the following stochastic processes:

$$\alpha_i = \alpha + u_i \quad \text{and} \quad \gamma_t = \gamma + \omega_t \tag{21}$$

Furthermore, the disturbance term ω_t is assumed to have a set of properties analogous to those depicted previously by equations (12)-(17).

The key question that remains is the following: which model specification is appropriate for testing the hypothesis that internal cash flows are an important determinant of pharmaceutical R&D intensity? In some cases, the choice of model specification will largely be driven by the structure of the data set employed for a given analysis. For example, because several of the independent variables in the forthcoming models were either time-invariant or cross-sectionally invariant, the utilization of various fixed-effects models was not possible. Furthermore, because some of the data samples used in the next chapter were very wide (i.e., they contain a large number of cross-sectional units, or firms), with relatively few time periods, fixed-effects models were generally not estimated for practical reasons. That is, it was too costly in terms of the number of degrees of freedom that had to be given up. A further discussion of this point will be deferred until Chapter Five.

With these considerations in mind, the approach followed in this chapter will be that suggested by Greene (1993). Models will first be estimated using the classical OLS. Then, both fixed-effects and random-effects models will be estimated—when reasonable. Econometric tests will be performed to assess the appropriateness of each specification. Specifically, the estimated models will be inspected for cross-sectional heteroskedasticity, for contemporaneous correlation, and within group serial correlation. When—and if—detected, the appropriate estimation technique will be employed in an attempt to correct for the econometric problems identified—i.e., the identifiable violations of the properties imposed upon the disturbance terms in the classical linear regression model. A full discussion of the diagnostic tests and estimation procedures undertaken will be provided along with each model estimated.

The general model used to estimate the determinants of pharmaceutical R&D for the 1976 to 1996 time period is presented below:

$$RDS_{it} = f(E\pi_t, CF_{it-1}, Pct_{it}) \quad (22)$$

Where,

RDS_{it} = research and development expenditures divided by total firm sales for the *i*th firm in year *t*.

$E\pi_t$ = an index of the expected profitability of *R&D* investments.

CF_{it-1} = cash flow for firm *i* in period *t*-1 divided by sales in period *t*-1.

Pct_{it} = the percentage of the *i*th firm's sales accounted for by pharmaceutical sales in year *t*.

A brief description of the formulations of the dependent and independent variables is provided next.

Section 5.5.1: *Research and Development Intensity*

The ratio of R&D to sales was selected as the dependent variable for two principal reasons. First, as was mentioned earlier, because firm managers use this ratio as a budgetary device when making R&D allocation decisions, it makes sense to use this intensity measure instead of absolute R&D expenditures. Secondly, by expressing the variables as intensity measures (or size-deflated ratio variables), one often—but not always—may avoid the econometric problem of heteroscedasticity that is present in most cross-sectional models estimated using absolute values.

Section 5.5.2: *Expected Returns to R&D: The Profit Expectations Variables ($E\pi_t$)*

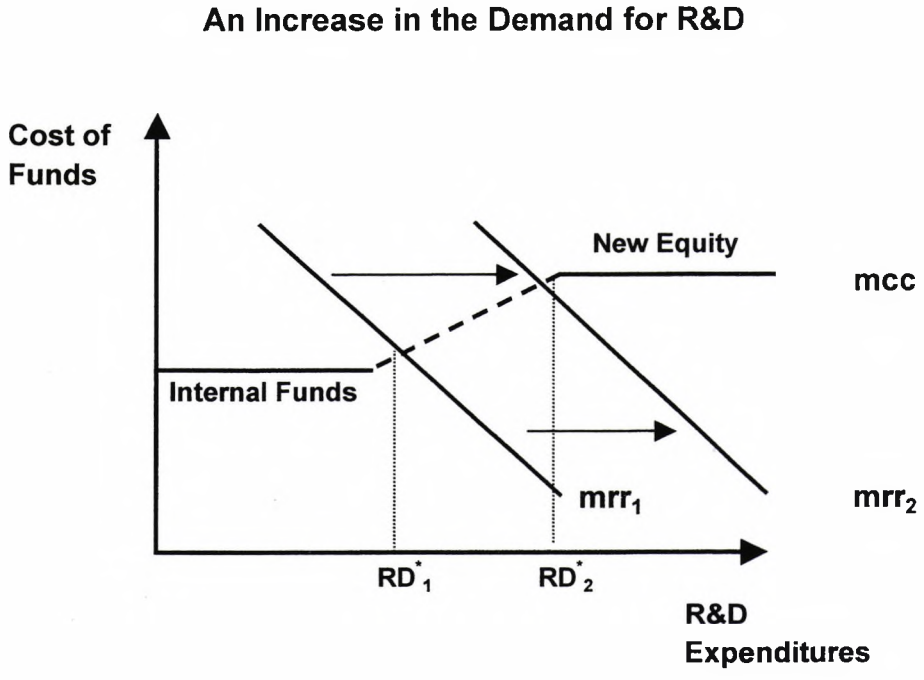
Specifically, two formulations of the expected returns to R&D expenditures were utilized. The first of these was *PharMarg*. This variable was defined to be the weighted-average, pre-tax, profit margin for the pharmaceutical divisions of the industry's largest

firms. This variable is different from Grabowski and Vernon's *Imarg* variable in two principle ways. Firstly, it was based on a larger sample of firms—making it a more representative measure of the industry's economic climate. Secondly, this variable was lagged one period. Lagging this variable allowed it to enter into the model exogenously; it also resulted in less co-linearity with the other variables in the model. Moreover, from a statistical standpoint, the one-period lag formulation of this variable performed marginally better than the other variable formulations tested.

The other profit-expectations variable was *NewRxs*. This variable, like the previously discussed *NewSal* variable, was designed to be a rough measure of the industry's R&D productivity. Specifically, this variable was defined to be the first three years of new product sales for drugs introduced in years –1, -2, -3, -4, -5, all divided by total industry R&D expenditures in year –3. New drug sales data and industry R&D expenditures were converted into constant dollars using the GDP deflator. Data on the annual sales of new drug introductions were obtained from IMS America.

These two profit-expectations variables may be viewed as substitutes. However, they may also be thought of as capturing different aspects of the expected returns to R&D. In particular, *NewRxs* may be thought of as an industry-level measure of R&D productivity—where R&D productivity is measured by the sales of new drug introductions. Hence, *NewRxs* reflects the productivity of R&D. *PharMarg*, however, while certainly a function of R&D performance, is likely to capture a different aspect of the expected returns to R&D. This variable is likely to reflect the broader economic forces impinging upon the industry, and hence the profitability of R&D. For this reason, models will be estimated using both of these expectations variables separately as well as together. As was discussed in Chapter Three, profit expectations will impact the optimal level of R&D through changes in the demand for R&D. This, as was previously demonstrated mathematically in Chapter Three, may be represented graphically as a shift in the expected marginal rate-of-return schedule for R&D. This is seen below in Figure 4.3.

Figure 4.3



Figures 4.4 and 4.5 plot the values of these profit expectations variables over the 1976-1996 time period.

Figure 4.4

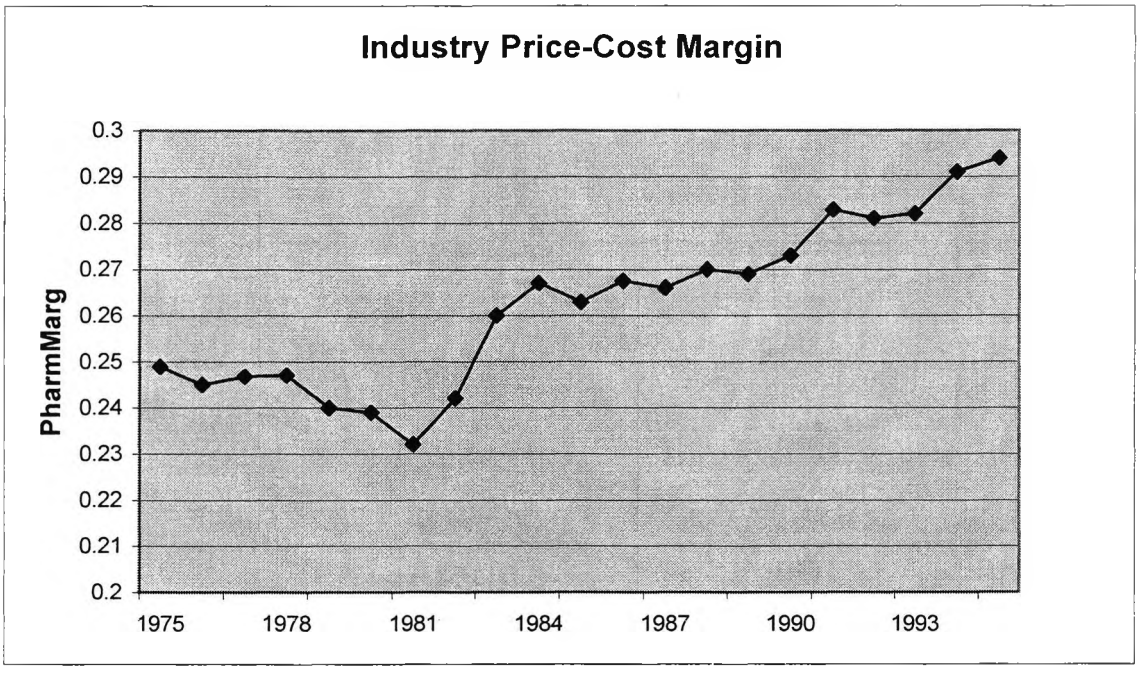
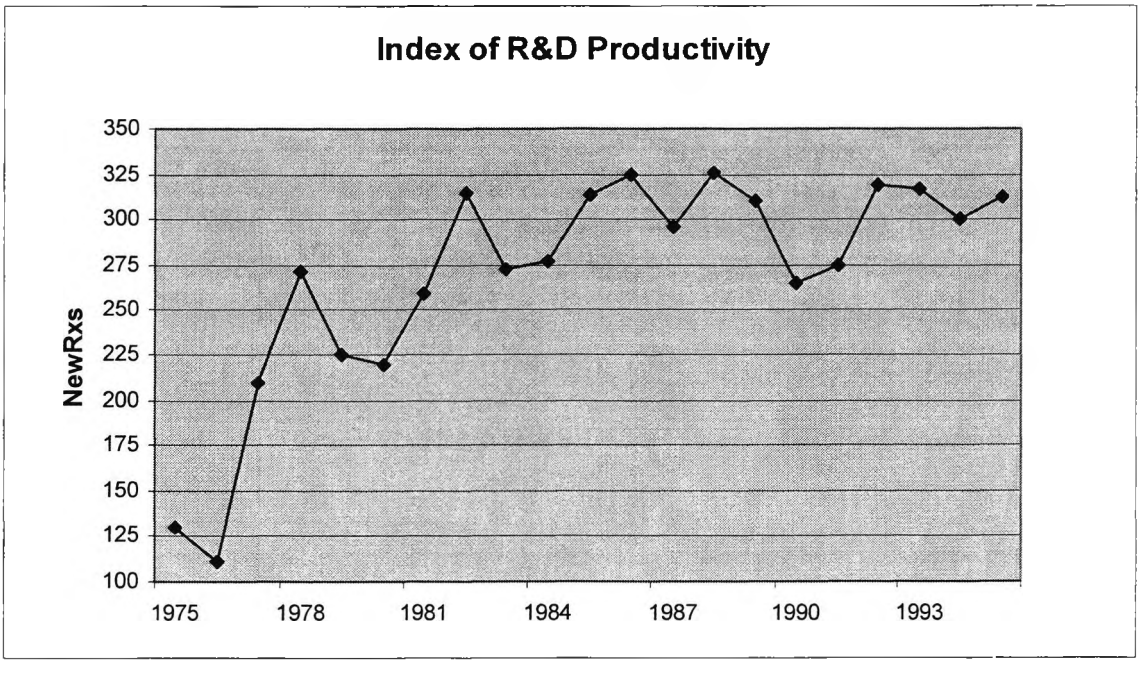


Figure 4.5



It should be mentioned that in addition to estimating models with these profit-expectations variables, a third variable was also tested; however, it was not found to be statistically significant in the majority of the models estimated. Specifically, following the approach taken by Grunfeld (1958) and Grunfeld and Griliches (1960) in their classic study of investment demand using data for 10 major U.S. corporations, firm market value was tried as a measure of the profit expectations. Theoretically, as was discussed in detail in Chapter Three, the value of a firm's securities is the discounted stream of the firm's *expected* future profits. Hence, the market value of a firm's securities at, say, the beginning of the year, should be a reasonable proxy for expected returns to investment spending (Grunfeld and Griliches 1960). It is possible that this variable did not perform well because the market value of a firm's securities reflects the expected future earnings for *all* of the firm's business operations—not simply its pharmaceutical operations. Consequently, in an attempt to mitigate this problem, a new variable was created. This variable was defined to be the product of a firm's market value in year (t-1) and the proportion of its total sales accounted for by pharmaceuticals in year (t-1)—a proxy for its pharmaceutical industry involvement (i.e., the previously discussed Pct_{it} variable). Hence, for a firm that has no operations outside of the pharmaceutical industry (i.e., its Pct_{it} is equal to 1) the market value of the firm's securities may reasonably reflect the expected profitability of the firm's pharmaceutical activities. On the other hand, for a firm whose pharmaceutical operations account for only one-half of the firm's business activities, the market value of the firm's securities will be a reflection of profit expectations made up of two components. One is the expected future profit from the firm's pharmaceuticals operations, the other the expected earnings from the firm's non-pharmaceutical operations. For this reason, it seemed reasonable to begin by assuming that profit expectations were uniform across business activities—hence justifying this multiplicative formulation. Following this approach, the statistical performance of this variable improved considerably.[10] However, this variable still did not perform as well

[10] In addition to imposing uniform expectations across business activities, different weighting schemes were also tried. For example, to allow for the possibility that a firm's pharmaceutical operations may contribute more to the expected profitability of the firm than other business operations, a weight greater than unity was applied to *Pct* prior to multiplying it by the firm's market value. Various

statistically as the *NewRxs* and *PharMarg* variables. Therefore, this variable was not included in the final analyses. Several of the regression equations that were estimated using variants of this variable are reported in Appendix 1.

Section 5.5.3: *Internally Generated Funds: The Cash Flow Variable*

Because the primary hypothesis of this research is that cash flows are an important determinant of pharmaceutical R&D investment, lagged cash flows were also entered into the model as an explanatory variable. This cash flow variable was intended to measure a firm's internally generated funds before investment in R&D, other capital assets, and the payment of dividends. Specifically, it consisted of the sum of after-tax net income, depreciation, and after-tax R&D outlays. Because R&D is expensed for tax purposes (hence it receives an implicit subsidy compared to other capital assets), it was necessary to add-back after-tax R&D expenditures to after-tax income and depreciation in order to obtain a firm's pre-investment cash flow. This method of estimating firm cash flows has been well documented in the literature (Hall 1992, Grabowski and Vernon 1997). A flat tax rate of 33% was used to estimate after-tax R&D outlays.

The reasons why internal funds may affect investment in R&D were rigorously developed in Chapter Three and included arguments based on transaction costs, tax advantages, asymmetric information, agency problems, and the costs of financial distress. Specifically, the aforementioned reasons are likely to result in a substantial cost advantage to financing R&D with internal funds instead of external debt or equity. Hence, increases in a firm's internally generated cash flows are hypothesized to increase R&D investment. This, as was demonstrated in Chapter Three, may be illustrated graphically. This is seen below in Figure 4.6.

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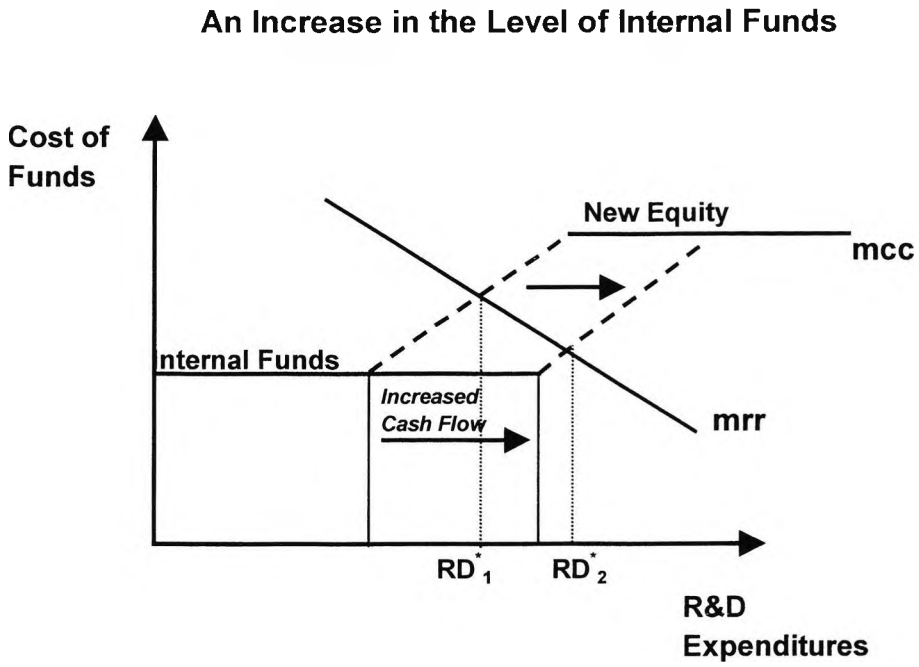
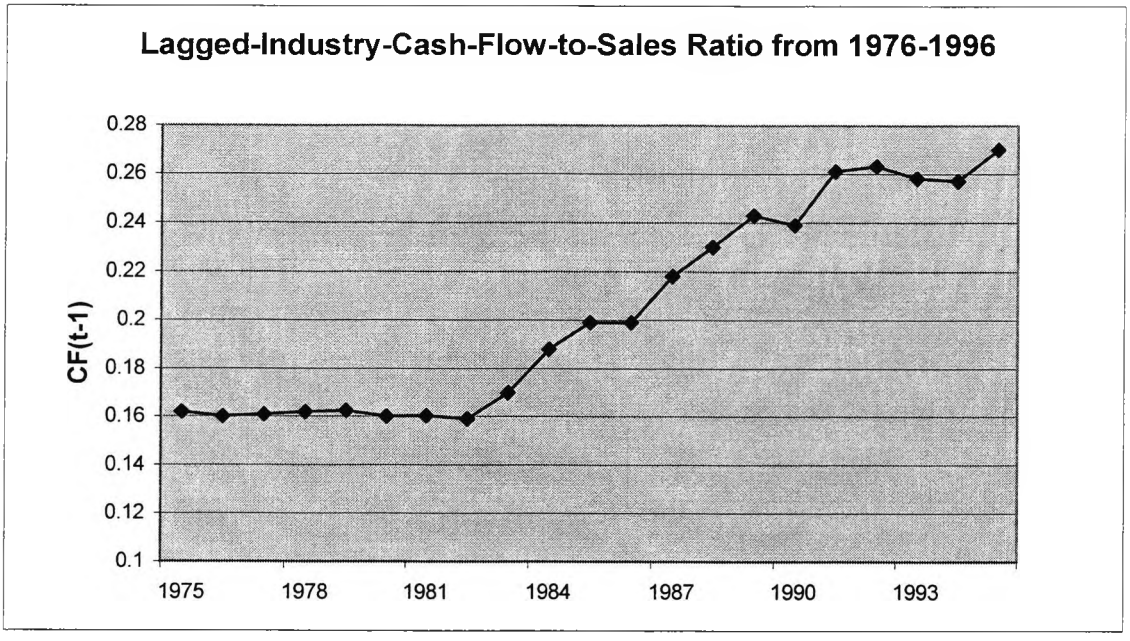
weights were tested, but this had little impact on the results.

Figure 4.6



This cash flow variable, aggregated over all firms in this sample, is presented below in Figure 4.7.

Figure 4.7



Section 5.5.4: *Firm Pharmaceutical Concentration and Industry Involvement*

Pct_{it} was included as a regressor in the model to control for the fact that firms have secondary, but not insignificant, operations in other industries that are likely to affect a firm's research intensity. Because the pharmaceutical industry is among the most research-intensive sectors of the U.S. economy, diversification into other industries will generally imply a lower overall research intensity. As was mentioned previously, the Pct_{it} data used in this analysis is a vast improvement over that which was used in the earlier studies. Therefore, it is expected to perform as a better control variable. This will presumably improve the estimates of the other coefficients in the model. While the majority of the variance in this variable was across firms, and not over time (recall that some of the earlier studies used a time invariant estimate of this variable), there were several firms whose involvement in the pharmaceutical industry *did* change considerably over time. For example, in 1980 Warner-Lambert's pharmaceutical sales accounted for only 36 % of their total firm sales—by 1989 this percentage was 64%. Similarly, over

the same time period, the Shering-Plough and Syntex Pct_{it} values rose from 54 and 66 % to 77 and 84 %, respectively. Hence, by only using the 1980 value for this variable for all the years in their last study, Grabowski and Vernon may have introduced bias into their models. This may be particularly true for their models estimated over the 1980-1989 time period (equations 2.2 and 2.4 in Table 4.2).

Aside:

A tax variable reflecting the R&D tax credits that were initiated in 1981, and periodically amended throughout the1980's and 1990's, was also tested in these models, and was found to be statistically insignificant. Several approaches were employed. The first approach was similar to McCutchen's, and utilized year dummy variables. The other approaches were different from McCutchen's. In particular, both statutory and *effective* R&D tax credits were tested in the models. Effective tax credits were tested as a variable because the implicit assumption behind McCutchen's use of a tax dummy variable was that the incentives to increase R&D spending on the margin were uniform throughout the decade.[11] This, theoretically, should not be the case. While the legislated, or statutory, tax credit remained relatively constant over the decade, the *effective* R&D tax credit was changing significantly (Baily and Lawrence 1990). The first of these R&D tax credits came under The Economic Recovery Tax Act of 1981 and provided a 25 % tax credit for all increases in R&D expenditures. Despite the fact that this particular tax credit expired on December 31, 1985, subsequent legislation, such as The Tax Reform Act of 1986, extended the tax credit at a 20 % rate. This tax credit was extended on an annual basis throughout the 1980's and 1990's. In fact, the 20 % R&D tax credit is still in effect today. The major findings from the Baily and Lawrence study are summarized below in Table 4.3.

[11] Obviously, this approach is applicable only to models estimated over time periods that span both the pre- and post-tax credit eras—i.e., models estimated over the *entire* 1976-1996 time period. For models estimated over the 1980's and 1990's, this approach would clearly be inappropriate.

Table 4.3

Statutory versus Effective R&D Tax Credit Rates[12]

Year of tax law change	Statutory tax credit	Baily and Lawrence effective tax credit estimate
1981	25%	9.3%
1986	20%	6.1%
1988	20%	4.0%
1989	20%	13%

However, as was previously mentioned, this variable did not perform well statistically. This was the case for every formulation tested. Specifically, in addition to estimating models with McCutchen's dummy variable, models were estimated using both statutory and effective tax rates. Consequently, this variable was dropped from the model.

In sum, the expected signs for the explanatory variables in the current models are the following:

$\frac{\partial RD}{\partial E\pi} > 0$ Increases (decreases) in the expected returns from R&D increase (decrease) the optimal level of R&D.

$\frac{\partial RD}{\partial CF} > 0$ Increases (decreases) in the level of internal cash flows increase (decrease) the optimal level of R&D.

$\frac{\partial RD}{Pct} > 0$ The greater (lesser) the degree of firm specialization in pharmaceuticals, the greater (lesser) the level of R&D.

[12] The reasons why the effective marginal credit rates differ from the statutory tax rates are the following.
1) Interactions of the tax credit with other provisions of the internal revenue code.
2) Future tax savings are discounted to their present value.
3) Not all firms have sufficient tax liabilities to use the tax credits in the same year they are earned.

Section 5.6: *Empirical Results*

Using data from the 11 aforementioned pharmaceutical firms, several models of the determinants of R&D were estimated over two different time periods: 1976 to 1996 and 1983 to 1996.[13] The regression results and statistical diagnostics are reported and discussed for each model. Full regression and diagnostic results, however, are provided in Appendix 1. Coefficient t-statistics are reported in parentheses underneath the coefficient estimates. Finally, in order to simplify the presentation of results, the *NewRxs* variable was scaled down by a factor 0.001.

All regressions were estimated using EViews Pooled data estimation techniques (Quantitative Micro Software, Irvine California). EViews was formally known as Micro TSP.

Table 4.4

Classic OLS Linear Regression Results for 11 U.S. Firms

Equation Time Period	Intercept	PharMarg	NewRxs	CF	Pct	R^2/F
4.1 1976-1996	-0.14 (-6.50)	0.48 (5.64)		0.22 (8.06)	0.08 (8.44)	0.73/206
4.2 1976-1996	-0.06 (-8.32)		0.16 (6.95)	0.24 (10.06)	0.08 (8.46)	0.75/225
4.3 1976-1996	-0.11 (-5.45)	0.27 (2.85)	0.13 (4.81)	0.21 (8.03)	0.08 (8.94)	0.76/176
4.4 1983-1996	-0.10 (-3.47)	0.34 (3.08)		0.22 (6.38)	0.08 (7.46)	0.70/117
4.5 1983-1996	-0.05 (-2.99)		0.13 (2.38)	0.25 (8.05)	0.08 (7.11)	0.70/113
4.6 1983-1996	-0.10 (-3.54)	0.28 (2.20)	0.06 (1.06)	0.22 (6.41)	0.08 (7.42)	0.69/88

[13] This time period was selected because the global models of R&D investment in the next chapter were estimated over a similar time period, hence, allowing for more direct comparisons to be made between models.

Table 4.5

Linear Regression Results for 11 U.S. Firms (Fixed Effects Model Specification)

Equation Time Period	PharMarg	NewRxs	CF	Pct	R^2/F
5.1 1976-1996	0.62 (7.42)		0.17 (5.77)	0.08 (6.67)	0.89/842
5.2 1976-1996		0.16 (9.36)	0.24 (11.64)	0.08 (8.32)	0.90/957
5.3 1976-1996	0.47 (6.21)	0.13 (8.31)	0.13 (5.08)	0.07 (6.92)	0.91/763
5.4 1983-1996	0.58 (6.55)		0.10 (2.90)	0.06 (5.47)	0.91/732
5.5 1983-1996		0.08 (1.84)	0.23 (9.40)	0.08 (6.04)	0.89/556
5.6 1983-1996	0.57 (6.26)	0.03 (0.81)	0.09 (2.92)	0.06 (5.36)	0.91/487

The pooled regression results reported in Tables 4.4 and 4.5 appear to indicate a highly robust model, one with similar results to those reported by the earlier studies. However, the OLS model specifications employed by these analyses implicitly assume a number of restrictions on the variance-covariance matrix of the error terms—i.e., the classical error term assumptions depicted by equations (7)-(10). Therefore, in order to determine the appropriateness of these assumptions, and hence the validity of the regression results reported in Tables 4.4.and 4.5, several diagnostic tests were employed.

First, the models were examined for the presence of cross-sectional heteroskedasticity. Because the models were estimated using size-deflated values instead of absolute values, it was anticipated that cross-sectional heteroskedasticity would not be a major problem. This, however, turned out not to be the case. To determine whether or not the error terms were cross-sectionally heteroskedastic, the null hypothesis of equality in error term variance across firms was tested. EViews reports three test statistics for this purpose: the Bartlett Test, the Levene Test, and the Brown-Forsythe Test.

Briefly, the Bartlett Test compares the logarithm of the weighted-average variance with the weighted-sum of the logarithms of the variances. The joint null hypothesis assumes that the cross-sectional variances are equal, and the samples are

normally distributed. This test statistic is approximately distributed as chi-squared with *i*-1 degrees of freedom—where *i* is the number of cross-sectional units in the sample. The Levene Test is based upon an analysis of variance (ANOVA) of the absolute value of the difference from the mean. Specifically, the Levene statistic has an approximate F-distribution with *i*-1 numerator degrees of freedom and N-*i* denominator degrees of freedom under the null hypothesis of equal variances in each cross-section. The Brown-Forsythe Test is a modification of the Levene test in that the absolute mean difference is replaced with the absolute median difference.

Diagnostic testing overwhelmingly rejected the null hypothesis of equal variance across firms. A summary of the test results for each model specification estimated is provided below in Table 4.6. Full results from these tests, along with residual tables, are provided in Appendix 1.

Table 4.6

Diagnostic Tests for Cross-sectional Heteroskedasticity

Equation	Bartlett Test	Levene Test	Brown-Forsythe Test
4.1	33.83***	3.63***	3.02**
4.2	26.05**	1.99*	1.47
4.3	25.33**	1.97*	1.72
4.4	28.75**	3.18***	2.88**
4.5	34.40***	3.94***	3.04**
4.6	32.69***	3.55***	3.09**
5.1	33.33***	3.45***	2.85**
5.2	24.96**	1.94*	1.46
5.3	33.73***	2.66**	2.37*
5.4	39.38***	3.99***	3.33***
5.5	35.75***	4.02***	3.19***
5.6	40.31***	4.09***	3.45***

* significant at the .05 level
** significant at the .01 level
*** significant at the .001 level

The results in Table 4.6 are especially important because the earlier studies, which only estimated models using classic OLS, assumed that that cross-sectional heteroskedasticity was not present in the data. This was assumed because many of the variables were deflated by firm sales—a frequent remedy to the problem of heteroskedasticity in cross-sectional models (Greene 1993, Maddala 1992, and Kennedy 1994). The presence of cross-sectional heteroskedasticty has important implications for the OLS estimators. In particular, while the OLS parameter estimates will remain unbiased, they will no longer be efficient. That is, OLS estimators will no longer have the minimum variance among all linear unbiased estimators. To correct for this problem, models have to be estimated using feasible generalized least squares (FGLS).

This feasible generalized least-squares approach first estimates the error term variances for each cross-sectional unit using first-stage pooled OLS—i.e., the equations estimated in Tables 4.4 and 4.5:

$$\hat{\sigma}_i^2 = \frac{1}{T}\sum_{t=1}^{T}(y_{it} - \hat{y}_{it})^2 \qquad (23)$$

Estimates of σ_i^2 are then used to transform the data—using standard generalized least-squares (GLS) techniques—in order to obtain a new coefficient vector $\hat{\beta}$. This coefficient vector, also referred to as β^{GLS}, can be shown to be the best linear unbiased estimator in its class. Hence, unlike the OLS estimated coefficient vector β^{OLS}, this estimator is both unbiased *and* efficient.

Before presenting the models estimated using FGLS, it is necessary to note that like the earlier Grabowski and Vernon Studies, it was determined that cross-sectional correlation and within-group serial correlation were not present in the models. A visual inspection of the residuals, correlograms, and cross correlograms was undertaken first. This revealed no cross-sectional or temporal associations among the residuals. Formal testing subsequently confirmed these initial inspections. In particular, the Lagrange multiplier test developed by Breusch and Pagan (1980) was employed to test for cross-sectional correlation, and Durbin-Watson statistics were examined to test for first-order

serial correlation.[14] Both tests failed to reject the null hypotheses of no cross-sectional correlation and within group serial correlation, respectively. The results from these diagnostic tests for the OLS and FGLS fixed-effects models are reported in Appendix 1.

The re-estimated models—corrected for cross-sectional heteroskedasticity—are presented below in Tables 4.7 and 4.8.

Table 4.7

FGLS Linear Regression Results for 11 U.S. Firms (Common Intercept)

Equation Time Period	Intercept	PharMarg	NewRxs	CF	Pct	R^2/F
7.1 1976-1996	-0.14 (-8.76)	0.51 (7.70)		0.22 (10.33)	0.08 (9.70)	0.84/395
7.2 1976-1996	-0.05 (-10.17)		0.15 (8.21)	0.25 (12.93)	0.07 (9.51)	0.86/468
7.3 1976-1996	-0.12 (-7.80)	0.32 (4.62)	0.11 (5.59)	0.20 (10.16)	0.08 (10.49)	0.86/353
7.4 1983-1996	-0.10 (-5.25)	0.36 (4.65)		0.21 (8.61)	0.08 (9.56)	0.91/495
7.5 1983-1996	-0.05 (-4.58)		0.12 (3.40)	0.27 (11.84)	0.08 (9.08)	0.93/676
7.6 1983-1996	-0.10 (-5.24)	0.29 (3.23)	0.06 (1.55)	0.22 (8.77)	0.08 (9.49)	0.92/414

[14] The Breusch-Pagan statistic has the following general form: $\lambda_{LM} = T\sum_{i=1}^{n}\sum_{j=1}^{i-1} r_{ij}^2$

Where r_{ij} is the ijth residual correlation coefficient. The large sample distribution of this statistic is chi-squared with $n(n\text{-}1)/2$ degrees of freedom—where n is the number of cross-sections in the sample and T is the number of years in the sample. Furthermore, due to the implicit assumption of a single parameter vector, the appropriate residuals for computing this statistic are those from the groupwise heteroskedastic model presented in Tables 4.7 and 4.8 (Greene 1993).

Table 4.8

FGLS Linear Regression Results for 11 U.S. Firms (Fixed Effects Specification)

Equation Time Period	PharMarg	NewRxs	CF	Pct	R^2/F
8.1 1976-1996	0.65 (8.99)		0.17 (6.62)	0.06 (5.80)	0.87/739
8.2 1976-1996		0.15 (10.18)	0.23 (11.84)	0.09 (8.54)	0.91/1110
8.3 1976-1996	0.55 (8.48)	0.13 (9.12)	0.11 (4.91)	0.06 (6.67)	0.93/925
8.4 1983-1996	0.65 (9.13)		0.09 (3.39)	0.05 (5.67)	0.97/2180
8.5 1983-1996		0.08 (2.44)	0.24 (10.31)	0.07 (5.85)	0.96/1697
8.6 1983-1996	0.63 (8.62)	0.04 (1.30)	0.09 (3.48)	0.05 (5.52)	0.97/1489

Lastly, models were estimated using the random-effects specification. This specification, because of its composite error term (which results in a particular type of heteroskedasticity), is estimated using the previously discussed FGLS. These results are presented in Table 4.9.

Table 4.9

Linear Regression Results for 11 U.S. Firms (Random Effects Model Specification)

Equation Time Period	**Intercept**	**PharMarg**	**NewRxs**	**CF**	**Pct**	**R^2**
9.1 1976-1996	-0.16 (-9.50)	0.60 (7.59)		0.18 (6.27)	0.08 (7.31)	0.88
9.2 1976-1996	-0.06 (-8.38)		0.16 (9.53)	0.24 (11.78)	0.09 (8.57)	0.90
9.3 1976-1996	-0.14 (-9.52)	0.43 (5.97)	0.13 (8.13)	0.14 (5.74)	0.08 (7.76)	0.91
9.4 1983-1996	-0.11 (-5.87)	0.53 (6.13)		0.11 (3.53)	0.07 (6.20)	0.91
9.5 1983-1996	0.03 (-1.88)		0.08 (1.84)	0.23 (9.60)	0.08 (6.40)	0.88
9.6 1983-1996	-0.12 (-5.72)	0.51 (5.79)	0.03 (0.76)	0.11 (3.59)	0.07 (6.13)	0.91

Section 5.7: *Random Effects or Fixed Effects?*

Before undertaking a full discussion of the results, one very important question needs to be addressed first: which, if any, of the regression models estimated in this section are appropriate for drawing inferences around the role cash flows play in a firm's R&D investment decision? More specifically, which specification, fixed effects or random effects, is appropriate for this study of U.S. firms? A number of important considerations to both approaches have already been discussed. For example, if the data do *not* exhaust the population, how will the results be used? Will they be used to make generalizations beyond the data sample? If so, a fixed-effects model specification is inappropriate (Greene 1993, Kennedy 1994). However, if it is believed that certain institutional factors exist, and result in, a systematic—not random—difference across units (i.e., firms), then clearly the fixed-effects model *is* required, and inferences are strictly limited to the sample.

Mundlak (1978), on the other hand, has argued that the distinction between fixed effects and random effects is an erroneous interpretation, and that a random-effects model should always be used. This, he argues, is because the fixed-effects model is simply a model estimated conditionally on the effects present in the sample. From a purely practical standpoint, the random-effects specification has a very appealing characteristic: it saves a lot of degrees of freedom—especially if the data sample has a large number of cross-sectional units.

Clearly then, arguments can easily be made for one specification or another based on various theoretical considerations. For the models estimated here, because the sample of firms used does not exhaust all the firms in the pharmaceutical industry, a random-effects model would have the advantage of being generalizable to the industry at large.[15,16] However, as was discussed previously, the random-effects model has one *major* drawback. Unlike the fixed-effects model, the random-effects model assumes that

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[15] Indeed, several of the major U.S. pharmaceutical firms are not contained in this sample—due to the reasons sited previously in the data section.

[16] For this particular sample, a fixed-effects model only uses up ten additional degrees of freedom. Hence, the practical advantage of a random-effects model—based on the number of degrees of freedom—is only marginal.

the random errors associated with each cross-sectional unit are uncorrelated with the other regressors in the model. This is something that often is not the case. Thus, the random-effects model may suffer from inconsistency due to omitted variables (Greene 1993, Hausman and Taylor 1981, and Chamberlain 1978). Therefore, to test for orthogonality between the random effects and the regressors and, hence, the appropriateness of the random-effects model for this study, a test developed by Hausman (1978) will be employed.

Hausman devised a test statistic based on the following idea. Under the null hypothesis of no correlation between the random effects and regressors, the random-effects model is appropriate, and the FGLS estimator is consistent and efficient. Under the alternate hypothesis, the FGLS estimator is efficient but *inconsistent*. Furthermore, the OLS estimator in the fixed-effects model is consistent under both the null and alternate hypotheses. Consequently, the two estimates should not differ systematically, and a chi-squared test can be based on this difference to see if it is significantly different from zero. Hausman's test is based on the following Wald statistic:

$$W = \left[\beta^{OLS} - \beta^{FGLS}\right]'\left[Var(\beta^{OLS}) - Var(\beta^{FGLS})\right]^{-1}\left[\beta^{OLS} - \beta^{FGLS}\right] \qquad (24)$$

This statistic is asymptotically distributed as chi-squared with K degrees of freedom—where K is equal to the number of regressors in the model.

The Hausman test results are reported in Table 4.10 and are based on the regressions in Tables 4.5 and 4.9—the OLS fixed-effects models and the random-effects models. The results clearly suggest that the random-effects model should be favored over the fixed-effects model.

Table 4.10

Hausman Test for Random Effects Model

Equation Number	Wald Statistic (d.f.s)
1	5.71 (3)
2	6.48*(3)
3	5.02 (4)
4	3.93 (3)
5	5.19 (3)
6	3.15 (4)

* significant at the .10 level

Section 6: Discussion

The results reported in this chapter clearly support the hypothesis that cash flows are an important determinant of firm R&D investment intensity[17]. In all of the model specifications and time periods examined, the cash flow variable was found to be statistically significant. Furthermore, the estimated coefficients for this variable were relatively stable—ranging from 0.09 to 0.25. This range, however, was slightly wider than the coefficient range reported by Grabowski and Vernon in their earlier studies (0.20 to 0.31). This is not surprising, however, because of the vastly different, and numerous, model specifications estimated in present analyses. In fact, the coefficient range obtained from the classical OLS equations (Table 4.4) was remarkably narrow (0.21-0.25)—well

[17] It should be acknowledged that while the results apper to be very robust, there are important caveats to be considered. In particular, as Hubbard (1998) has pointed out, a signficant cash flow variable does not necessarily indicate the presence of capital market imperfections. For such a finding to support the capital market imprefections hypothesis, the model must adequately control for investment opportunities; because investment opportunities are associated with profitability which, in turn, determines cash flows. Hence, failure to appropriately control for firm investment opportunities could led to a significant cash flow variable in an environment with perfectly functioning capital markets. Similarly, the same finding could be the result of a reverse causality (or simultaneity) between cash flows and profitability. These issues are explored in detail in Appendix 2.

within the range of the estimates reported by Grabowski and Vernon, which used similar OLS specifications.

An interesting feature of these results—compared to the results of the earlier studies—is the smaller coefficients on the cash flow variable found in some of the fixed and random-effects models. In particular, regressions that contained the *PharMarg* variable tended to report both lower coefficients and t-statistics. This was probably due to the higher correlation between the cash flow variable and *PharMarg* (0.52) than between the cash flow variable and *NewRxs* (0.41). Furthermore, in models that contained both demand-effect variables, this coefficient was particularly low.

Equations were also estimated using other lag formulations of the cash flow variable. Specifically, two and three period lags were investigated. These lagged variables were entered both separately and simultaneously into the different equations. In each equation estimated, the three different lag specifications had virtually identical coefficients; but the one-period lag performed marginally better in terms of statistical significance. Furthermore, the one-period lag performed better when all three lagged terms were entered simultaneously. Interestingly, when this was done, the sum of their respective coefficients approximately summed to the value observed when these terms were entered separately.

In general, the preceding results seem to favor the hypothesis that—at least for models based on U.S. firm data—cash flows are a major determinant of firm R&D investment intensity. Therefore, it seems reasonable to conclude that market imperfections exist in the capital markets for pharmaceutical R&D.

Over the 1976-1996-time period, the estimated coefficients on both of the demand-effects variables, *PharMarg* and *NewRxs,* carried the theoretically correct algebraic sign and were highly significant statistically. This was true even when both of these variables were entered into the model simultaneously to capture different aspects of the expected returns to R&D. However, the *NewRxs* variable did not perform as well statistically in the models covering the shorter time period from 1983-1996. In fact, *NewRxs* was statistically significant at the 5% level in only three of the models estimated (equations: 4.5, 7.5, and 8.5). One explanation for this may be the emergence of rational drug design in the early 1980's. This new technology made past R&D successes—even

at the industry level—a poor indicator of future successes due to the vastly different, and dynamic, scientific environment—at least during the evolutionary phase of this technology.[18] That is, for several decades prior to the 1980's, pharmaceutical firms discovered and developed drugs in very much the same way, randomly screening large volumes of chemicals with little or no a priori research strategy to guide the process. Hence, in the years prior to the early 1980's, past returns generated by this type of R&D activity might be a reasonably good indicator of potential future returns. However, with the advent of rational drug design, this random discovery process quickly became obsolete—possibly making the returns generated by the older type of discovery process less indicative of the anticipated returns from rational drug design. Thus, while appropriate for earlier time periods, *NewRxs* appears less appropriate for more current periods.[19] While the merit of this argument may certainly be challenged, it seems at least plausible.

Furthermore, because the formulation of the *NewRxs* variable was quite arbitrary (a five-year moving average), several other formulations were also investigated. In particular, shorter time intervals were tested (two, three, and four years), but from a statistical perspective, the five-year formulation performed marginally better. Polynomial and geometric lag formulations were also tested. However, these formulations did not perform very well statistically. The five-year moving average formulation was consequently selected for these reasons. Moreover, because the earlier studies utilized a similar five-year formulation (they used a slightly different lag structure), direct comparisons between models was more appropriate.

The *Pct* variable—which indicates the percentage of total firm sales accounted for by pharmaceutical sales—also carried the correct algebraic sign and was highly significant in every equation estimated. In fact, as was hypothesized, this variable

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[18] Presumably, if—and when—firms became fully acquainted with this new technology—and the returns it was capable of generating—an adaptive expectation formulation would be more appropriate (insofar as such a formulation is appropriate in the first place). It is likely that it took many years for firms to fully realize both the financial and scientific impact rational drug design would have. This fact may have made *NewRxs* a poor expectations variable for most of the years in the 1983-1996 models.

[19] In fact, when tested in models using a larger sample of firms (and over the same time period), *NewRxs* was found to be statistically insignificant in every specification. More will be said on this in the next chapter.

appears to perform better as a control variable than the version of this variable used in the earlier studies. In particular, in the directly comparable classical OLS models, the t-statistics for this variable were considerably higher (ranging from 7.11 to 8.94 versus 2.18 to 5.18) and the coefficients remarkably more stable (ranging from 0.077 to 0.080 versus from 0.040 to 0.084).

For comparability with the analyses in forthcoming chapters, models were also estimated over a shorter time horizon—from 1983 to1996. These results largely replicated the findings of the longer time period. However, as was discussed earlier, over the shorter time period *PharMarg* statistically outperformed *NewRxs* in every model estimated. In fact, in the models that contained both variables, *NewRxs* was consistently found to be statistically insignificant.

Section 7: Conclusions

The analyses undertaken in this chapter mark the most contemporary empirical study to date of the determinants of pharmaceutical R&D. Hence, these results are likely to be more reflective of the current industrial climate for pharmaceutical R&D investment. Furthermore, these analyses made several refinements to the earlier models of R&D investment. In particular, a more complete data sample was employed, and, several new, and more appropriate, model specifications were estimated.

The regression results in this chapter provide substantial evidence to support the hypothesis that internally generated funds are an important determinant of pharmaceutical R&D. In fact, in every model estimated, a statistically significant and stable positive relationship was found between firm research intensities and their lagged cash flow margins. This was the case both for models estimated over different time periods and for models estimated using different specifications. This finding is consistent with the theoretical model developed in Chapter Three. The results from the different models estimated are summarized below in Tables 4.11 and 4.12. However, diagnostic testing revealed that the random-effects model specification is likely to be the most appropriate specification for testing our hypothesis. Therefore, caution should be exercised when

considering the other models. In addition to reporting the estimated coefficients for the cash flow variable, the elasticity of R&D intensity with respect to cash flow is also reported for each model. In order to estimate this elasticity, sample means were calculated for both R&D intensity and cash flow margin.

Table 4.11

Summary of Empirical Findings on the Role of Cash Flows in Firm R&D Investment Behavior: 1976-1996

Model	Cash Flow Coefficient Range	Mean RD/Sales for the Sample	Mean CF/Sales for the Sample	Cash Flow Elasticity
Classic OLS	0.21-0.24	0.085	0.213	0.525-0.600
Classic LSDV Fixed Effects	0.13-0.24	0.085	0.213	0.325-0.600
FGLS (Common Intercept)	0.20-0.25	0.085	0.213	0.500-0.625
FGLS Fixed Effects	0.11-0.23	0.085	0.213	0.275-0.575
Random Effects	0.14-0.24	0.085	0.213	0.350-0.600

Table 4.12

Summary of Empirical Findings on the Role of Cash Flows in Firm R&D Investment Behavior: 1983-1996

Model	Cash Flow Coefficient Range	Mean RD/Sales for the Sample	Mean CF/Sales for the Sample	Cash Flow Elasticity
Classic OLS	0.22-0.25	0.099	0.259	0.576-0.654
Classic LSDV Fixed Effects	0.09-0.23	0.099	0.259	0.235-0.602
FGLS (Common Intercept)	0.21-0.27	0.099	0.259	0.549-0.706
FGLS Fixed Effects	0.09-0.24	0.099	0.259	0.235-0.623
Random Effects	0.11-0.23	0.099	0.259	0.288-0.602

The results from the classic OLS models summarized in Tables 4.11 and 4.12 are highly consistent with the earlier findings reported by Grabowski and Vernon—who used a similar specification. In particular, Grabowski and Vernon estimated this range from 0.21 to 0.31.[20] The range found in this study—which was based on more current data—was from 0.21-0.25. However, as was discussed previously, the classic OLS specification may be too restrictive. At least in this study, this was found to be the case—due to the econometric problems identified earlier in the chapter

These findings have some very important policy implications. In particular, because both R&D and cash flows are deflated by total firm sales, the coefficient on the cash flow variable represents the average reduction in R&D investment that is associated with a $1 loss in cash flow. Hence, the coefficient ranges reported in Tables 4.11 and 4.12 are of great importance when considering how a new policy, which results in reduced firm cash flows, may impact total R&D investment and, consequently, new drug innovation. One relevant example would be policies that mandate pharmaceutical price controls.

Pharmaceutical price controls have been a widely discussed issue in recent years. This has been due largely to the possibility of including expanded coverage for prescription drugs under various health care reform proposals, and the perceived need for accompanying price controls. While more will be said on the impact of pharmaceutical price controls in a later chapter, one thing appears certain: a substantial reduction in firm cash flows, for whatever reason, is likely to be accompanied by declines in R&D investment, which in turn would affect innovation.

In sum, the results presented in this section generally confirm the investment models estimated in the earlier studies and provide further evidence to suggest that cash flows are an important determinant of pharmaceutical R&D investment. However, it is important not to generalize these results to the global pharmaceutical marketplace. The current analyses, as well as all previous analyses, have been based solely on relatively small samples of U.S. firms. Consequently, it is unclear what role, if any, cash flows

[20] This range was based on all of their previous studies.

play in the larger global pharmaceutical marketplace. In order to sufficiently test the hypothesis that cash flows positively influence R&D investment, it will be necessary to estimate models based on a more representative sample of firms—a sample that contains both U.S. and non-U.S. firms. Therefore, the following chapter will be devoted to this objective and will estimate models similar to those presented here, using dramatically larger and more diverse samples.

Chapter Five

The Determinants of Pharmaceutical R&D and the Role of Internal Funds in Firm Investment Behavior: A Study of 60 of the World's Leading Pharmaceutical Firms

Section 1: Introduction

The empirical results estimated in Chapter Four, which utilized exclusively U.S. firm data, provide compelling evidence to support the hypothesis that internally generated cash flows have a positive—and quite substantial—impact on the level of firm R&D investment (intensity). This is because of their lower cost of capital relative to external debt and equity. These new results, which are consistent with the earlier studies of the determinants of pharmaceutical R&D, have one major limitation: they are based on a relatively small sample of exclusively U.S. firms. Consequently, it may be inappropriate to generalize the results reported in Chapter Four—and the results reported in the earlier studies—to the global pharmaceutical industry at large. For this reason, Chapter Five will estimate several models of the determinants of pharmaceutical R&D using different sub-samples of 60 of the *world's* largest drug firms. This dramatic increase in the number of firms studied—which results in a more representative sample of the global pharmaceutical marketplace—will make the forthcoming analyses the first empirical examination to date of the determinants of pharmaceutical R&D investment using non-U.S. firm data. Consequently, these analyses should provide additional empirical tests of the thesis that cash flows are an important determinant of pharmaceutical R&D investment.

This chapter will proceed as follows. Section 2 will estimate models using data from 32 of the largest U.S. and European pharmaceutical firms during the period from 1984 to 1997. Specifically, models will be estimated over two different time periods. The first time period is from 1984 to 1997 and will be based on data from 24 firms. The second time period studied—for which all of the 32 firms had complete, or near complete, data—is from 1991 to1997. In this latter period, because much of the European-firm data were available only after 1990, separate models for U.S. and

European firms will also be estimated. Following this, Section 3 will estimate models based on data from 28 of the largest Japanese pharmaceutical companies using data from 1994 to1997—the only years for which sufficient data could be obtained for these firms. Section 2 will also combine all of the aforementioned firms and estimate cross-sectional models for the entire industry over the period from 1994 to1997. As previously mentioned, these sections will be based on a considerably larger data set, one with an international focus. Consequently, these analyses will mark the first empirical study ever made of the determinants of pharmaceutical R&D with a global perspective. Lastly, Section 4 will discuss the findings and conclusions that may be drawn from this new research.

The collection of empirical analyses undertaken in this chapter should sufficiently test the hypothesis that cash flows, because of capital market imperfections, are an important determinant of pharmaceutical R&D. Furthermore, because of the markedly expanded number of firms (both U.S. and non-U.S.), the more complete data sets employed, and the more contemporary time periods studied, several new facts and details regarding the influence of internal funds on firm R&D investment behavior are expected to be uncovered.

Section 2.1: The Determinants of Pharmaceutical R&D: A Study of the Leading U.S. and European Drug Makers

All of the studies of the determinants of pharmaceutical R&D to date have been based exclusively on small samples of U.S. firms. In order to gain a fuller understanding of how cash flows affect R&D investment, a larger and more representative sample of international firms is needed. Consequently, this section contains several models estimated using data from 32 of the world's leading U.S. and European pharmaceutical firms over the period from 1983 to 1997.

This section begins by presenting the firms in the sample and discussing the data characteristics. Following this, model specifications are outlined and empirical results reported. The results are then discussed and conclusions drawn.

Section 2.2: *Data Sample*

The majority of the data in this sample were obtained from Scrip Pharmaceutical Company League Tables and Scrip Annual Reports[1]. These publications are not generally available to the public, and very few complete sets of these volumes exist. In fact, discussions with the publisher (PJB Publications, Ltd.) revealed that only eleven complete sets of these publications are held by external institutions—all but one of these being large pharmaceutical firms. This is not surprising given the fact that each volume costs approximately $900 and the information contained in each is highly specific to the pharmaceutical industry. All but one of the variables required for the forthcoming models were obtained from these reports. The variable not available in these reports was the firm depreciation variable—which was needed to calculate firm cash flows. (Refer to Chapter Four for details on how this variable was calculated.) Therefore, firm depreciation values were obtained from a large number of independent sources, such as company annual reports, SEC filings (when applicable), and various online financial databases (e.g., Hoovers, Edgar Online, PRARS, and CAROL). Sufficient data were available to estimate models based on the following sample of 32 firms:

1) Abbott (U.S.)
2) Akzo Nobel (Netherlands)
3) Alza (U.S.)
4) American Cynanamid (U.S.)
5) American Home Products (U.S.)
6) Amgen (U.S.)
7) Astra (Sweden)
8) Bayer (Germany)
9) Block Drug (U.S.)
10) Bristol Myers (U.S.)
11) Carter-Wallace (U.S.)
12) Dow Chemical (U.S.)
13) E Merck (Germany)
14) Forest Labs (U.S.)
15) Hoechst (Germany)
16) Johnson & Johnson (U.S.)
17) Eli Lilly (U.S.)
18) Glaxo (U.K.)
19) Merck (U.S.)
20) Monsantos (U.S.)
21) Mylan (U.S.)
22) Pfizer (U.S.)
23) Pharmacia (Sweden)
24) Rhone Poulenc (France)
25) Roche (Switzerland)
26) Sandoz (Switzerland)

[1] These data are somewhat less reliable due to the fact that they are self-reported, and hence not subjected to the rigorous regulatory requirements of officaial financial data reporting (i.e., SEC filings).

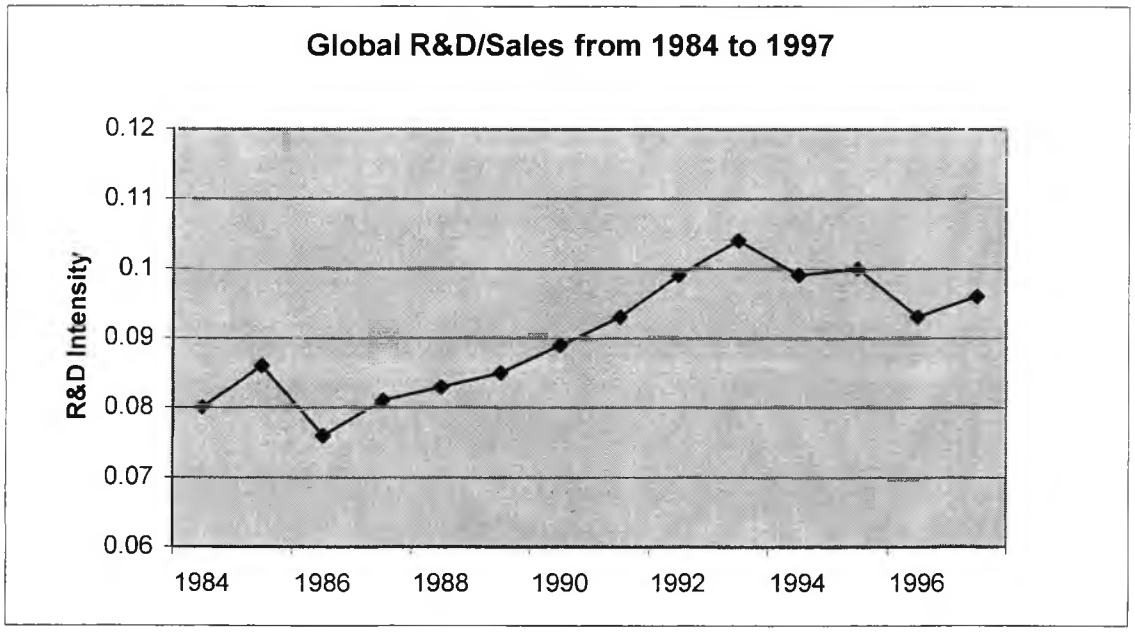
27) Shering-Plough (U.S.)
28) SmithKline Beecham (U.K.)
29) Solvay (Belgium)
30) Syntex (U.S.)
31) Warner-Lambert (U.S.)
32) Zeneca (U.K.)

It should be noted that many of the U.S. firms listed above were *not* included in the empirical analyses undertaken in Chapter Four. This was because of the more restrictive firm selection criteria used in the last chapter. Specifically, in Chapter Four the market capitalization criterion eliminated many of the smaller U.S. firms that are included in the present sample. In general, after converting foreign currencies to U.S. dollars, it was determined that in order to have a sufficient sample size, the threshold market capitalization level had to be lowered.

Of the 32 U.S. and European drug-makers listed above, 24 had data covering the period from 1984 to 1997.[2] All of the firms had complete—or near complete—data for the period from 1991 to 1997. Therefore, models will be estimated over both of these time horizons. The trend in *global* R&D intensity based upon the weighted-average R&D-to-sales ratio for the 24 U.S. and European firms with data from 1984-1997 is represented below in Figure 5.1.

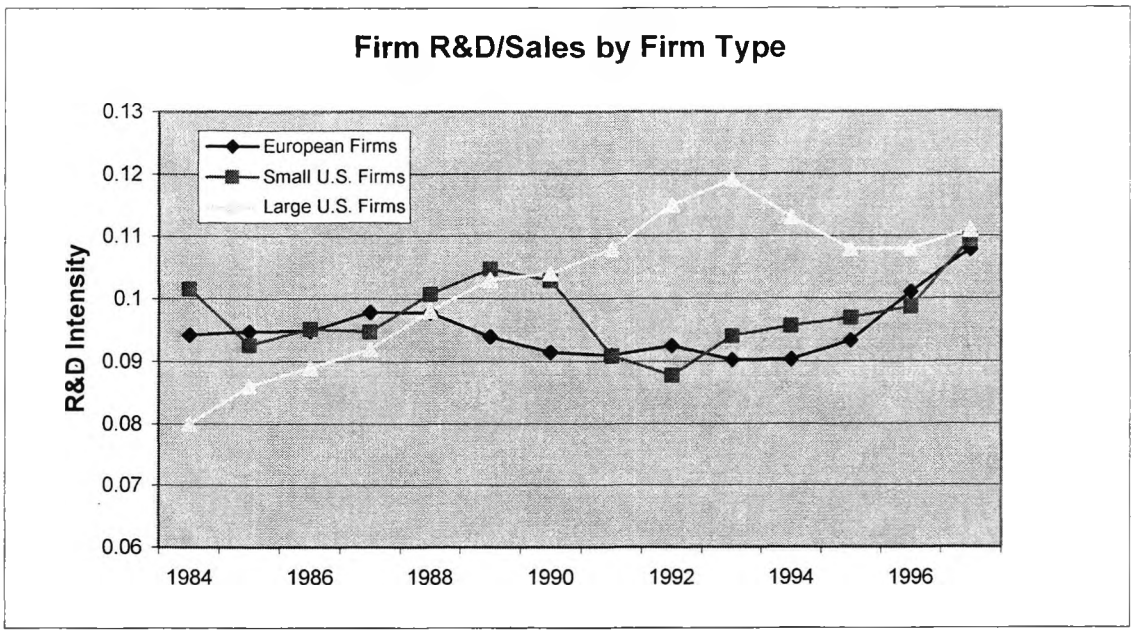
Figure 5.1

[2] The firms for which no data were available prior to 1991 were the following: Amgen, Bayer, E Merck, Forrest Labs, Roche, Mylan Labs, Pharmacia, Sandoz, and Zeneca.



An interesting observation to note from Figure 5.1 is that the R&D-to-sales ratio is lower than it was for the exclusively U.S.-firm sample over the same time period (11 large U.S. firms). To analyze why this was the case, R&D-to-sales ratios were examined separately for each type of firm. Figure 5.2 graphs the R&D-to-sales ratio for the European firms, the smaller-U.S. firms, and the large U.S. firms individually.

Figure 5.2



Section 2.3: *Model Specifications and Empirical Findings*

Having developed previously in Chapter Four what appear to be several highly robust model specifications for the determinants of pharmaceutical R&D, it makes sense to utilize similar specifications within the current sample of firms. The rationale being is that capital market imperfections are not likely to be specific to U.S. capital markets for pharmaceutical R&D, but rather to all capital markets for pharmaceutical R&D—U.S. and ex-U.S.[3] The first models estimated will be based on data from 24 firms over the time period 1984 to 1997.

Section 2.4.1: *The Determinants of Pharmaceutical R&D: A Study of 24 U.S. and European Drug Firms over the Time Period 1984-1997*

[3] It should be noted that by including non-U.S. firms in the sample, the previously developed capital-gains tax advantage associated with the U.S. tax system (refer to Chapter Three) does not necessarily apply. Indeed, the tax systems outside the U.S. vary considerably. However, the rationale for capital market imperfections based upon asymmetric information still holds. In fact, as was mentioned earlier in the thesis, it is highly plausible that asymmetric information—across borrowers and lenders in the capital markets for pharmaceutical R&D funds—is the *primary* cause of the higher cost of external finance relative to internal finance (i.e., cash flows).

To estimate the influence of a firm's internally generated cash flows on R&D investment, several models of the determinants of pharmaceutical R&D were estimated. Using the model specifications and variable definitions previously developed, linear regression analyses generated the findings in Table 5.1.[4]

Table 5.1

Linear Regression Results for 24 U.S. and European Firms Over the Period from 1984 -1997

Equation Model Specification	Intercept	PharMarg	CF	Pct	R^2/F
5.1.1 Classic OLS	-0.05 (-1.66)	0.21 (2.05)	0.20 (6.03)	0.07 (6.65)	0.50/92
5.1.2 Classic LSDV Fixed-Effects		0.22 (5.30)	0.09 (5.40)	.09 (6.93)	0.93/1672
5.1.3 FGLS (Common Intercept)	-0.01 (-0.33)	0.07 (1.97)	0.18 (11.66)	0.07 (15.29)	0.91/936
5.1.4 FGLS Fixed Effects		0.12 (5.56)	0.08 (4.86)	0.10 (12.08)	0.97/4385
5.1.5 Random Effects	-0.04 (-2.56)	0.22 (5.33)	0.09 (5.57)	0.09 (7.62)	0.93

Table 5.1 reports the statistical results from the five different model specifications estimated. Before discussing the empirical findings in detail, a brief discussion of the different specifications will be undertaken first.

Section 2.4.2: *Cross-sectional Heteroskedasticity and Feasible Generalized Least Squares*

As was the case with the Classic Ordinary Least Squares (OLS) and the Classic

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[4] An interesting feature of the present analyses, which will be discussed in full detail in a forthcoming section, was the fact that the previously statistically significant *NewRxs* variable lost its significance. Consequently, unlike the preceding chapter, which estimated models using both profit expectations variables, the current chapter only employees the *PharMarg* profit expectations variable.

Least Squares Dummy Variable (LSDV), models estimated in the previous chapter, diagnostic tests revealed the presence of cross-sectional heteroskedasticity. In both the classic OLS and classic LSDV models reported in Table 5.1, the previously discussed Bartlett, Levene, and Brown-Forsythe tests rejected the null hypothesis of no cross-sectional heteroskedasticity at the 1% level. These test statistics are summarized below in Table 5.2.[5]

Table 5.2

Diagnostic Tests for Cross-sectional Heteroskedasticity

Equation	Bartlett Test	Levene Test	Brown-Forsythe Test
5.1.1	156.12*	6.65*	4.47*
5.1.2	154.01*	6.75*	4.33*

* significant at the .0001 level

The presence of cross-sectional heteroskedasticity, while not biasing the OLS parameter estimates, does result in parameter estimates that are no longer asymptotically efficient (Greene 1993, Maddala 1992, and Kennedy 1994). That is, the OLS estimators will no longer have the minimum variance among all linear unbiased estimators. Therefore, models using the FGLS specification were also estimated.

In addition to testing for cross-sectional heteroskedasticity, the aforementioned models were also tested for cross-sectional correlation and within-group serial correlation. However, like the earlier Grabowski and Vernon studies (Grabowski 1968, Grabowski and Vernon 1981, Vernon 1995, and Grabowski and Vernon 1997) and the models estimated in Chapter Four, there was no evidence to suggest the presence of either. This was not surprising given that the two data samples had 11 firms in common—i.e., the 11 firms studied in Chapter Four.

[5] Because the *NewRxs* variable was statistically insignificant in all models estimated using the larger—and international—sample of firms, only two OLS specifications were tested for cross-sectional heteroskedasticity for the 1984-1997-time period.

Section 2.4.3: *Random- and Fixed-Effects Model Specifications Revisited*

Finally, a random-effects specification was estimated. For a full discussion of the theoretical considerations associated with this model (versus the fixed-effects model), the reader is referred to Chapter Four. Clearly, though, given the increase in sample size from 11 to 24 firms, the cost of estimating a fixed-effects model increased substantially. This was because of the additional degrees of freedom required to estimate the fixed-effects model. However, by expanding the sample size to include both European and smaller U.S. firms, the sample became less homogenous. Consequently, this increased the likelihood that a fixed-effects model would be required to control for systematic differences across firms (beyond that captured by the model's key regressors). Indeed, in the expanded international sample, many countries—with very different regulatory environments—were represented. Moreover, as a result of this expanded sample, there became considerable differences across firms based on their size, their involvement in biotechnology, and the extent to which they were involved in generic pharmaceutical manufacturing.[6]

Hence, the robust random-effects model specifications estimated in Chapter Four may not be appropriate for use with the more heterogeneous sample of firms in the present chapter. Recall that the random-effects model specification presumes the absence of systematic differences across firms. Therefore, to test the null hypothesis of no correlation between the random-effects and the model regressors, the Hausman test was conducted. (Refer to Equation 4.24 in the last chapter). Using the equations estimated from the current sample, the Hausman Wald statistic, which is distributed asymptotically as chi-squared with K degrees of freedom—where K is the number of regressors in the model, was calculated to be 9.77. This was significant at the 5% level. Therefore, it was believed that the fixed-effects model was the appropriate specification for the current

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[6] Several approaches were employed to detect the specific impact of these differences. For example, firm size was tried as an explanatory variable, as were country- and continent-specific dummy variables. When these attempts yielded no significant control variables, various other variables were tested. Specifically, firm involvement in biotechnology and generic drug manufacturing were tested, but did not yield any significant variables. Lastly, several interactive variables were entered into the model. Again, the empirical analyses yielded no significant variables.

sample. Consequently, it is this specification that should be used for drawing inferences around the role played by cash flows in R&D investment behavior.

Section 2.5.1: *Discussion of the Results Reported in Table 5.1*

Overwhelmingly, the results in Table 5.1 provide further evidence in support of the hypothesis that internal cash flows, because of their hypothesized lower cost of capital relative to external debt and equity, are an important determinant of R&D investment. This was the case regardless of the model specification employed. A notable artifact of the results in Table 5.1, as they pertain directly to the *CF* variable, is that—in addition to being highly significant—the estimated coefficients were very similar to those estimated in the last chapter using exclusively U.S.-firm data over a similar time period (1983-1996 versus 1984-1997). These comparisons are presented below in Table 5.3.

Table 5.3

A Comparison of the Estimated Coefficients for *CF*[7]

Equations Model Specification	Cash Flow Variable Coefficient 11 Largest U.S. Firms	Cash Flow Variable Coefficient 24 U.S. and European Firms
Equations: 4.4.4 and 5.1.1 Classic OLS	0.22 (6.38)	0.20 (6.03)
Equations: 4.5.4 and 5.1.2 Classic LSDV (Fixed Effects)	0.10 (2.90)	0.09 (5.40)

[7] A comparison of coefficients was deemed reasonable because of the similar time periods used in estimating the models—1984-1996 for the 11 U.S.-based firms and 1984-1997 for the present sample of international firms.

Equations: 4.7.4 and 5.1.3 FGLS (Common Intercept)	0.21 (8.61)	0.18 (11.66)
Equations: 4.8.4 and 5.1.4 FGLS (Fixed Effects)	0.09 (3.39)	0.08 (4.86)
Equations: 4.9.4 and 5.1.5 Random Effects	0.11 (3.53)	0.09 (5.57)

Consequently, Table 5.3 demonstrates what appears to be a fairly consistent role for cash flows in R&D investment spending. Alternatively expressed, for every additional cash flow dollar that becomes available to the firm, the marginal propensity to invest in pharmaceutical R&D appears to range between $0.08-$0.22, depending on the model specification and sample of firms considered. Conversely, as will be addressed later, for every $1 reduction in cash flows, a firm's reduction in R&D investment will be between $0.08-$0.22.[8]

In addition to affirming the importance of firm cash flows on R&D investment, the results in Table 5.1 also suggest that expected returns to R&D are an important determinant of pharmaceutical R&D expenditures. Interestingly, however, in contrast to the models estimated in Chapter Four, every model specification (and variable formulation) tested in the present analyses found the *NewRxs* variable to be statistically insignificant. In fact, in many of the specifications it carried the wrong algebraic sign.

The reasons why *NewRxs* lost significance when the sample was expanded to include more firms is not entirely clear. However, one plausible explanation may be the following. Several of the firms added to the sample had larger generic drug operations than did the eleven U.S. firms studied in Chapter Four. For firms developing a larger than average proportion of generic drugs, a more reasonable profit expectations variable may be *PharMarg*. This is because *NewRxs* strictly measures the returns to R&D based on *new* product introductions. Therefore, theoretically, *PharMarg* captures the expected

[8] Recall that the variables in the model are intensity measures. That is, both R&D investment and cash flows are divided by total firm sales. Therefore, multiplying the estimated regression equation through by total firms sales yields an equation that may be interpreted in the manner just presented. However, because cash flows are lagged one year, the interpretation must be viewed only as an approximation. In fact, the estimated coefficient on firm cash flows would need to be adjusted (multiplied) by the ratio of total firm sales in period (t) divided by total firms sales in period (t-1). Interestingly, therefore, for firms with growing real firm sales, the reported coefficient on cash flows would underestimate the impact on R&D investment of changes in firm cash flows. Similarly, for firms with decreasing real firm sales, this coefficient would overestimate the impact on R&D spending.

returns to both generic drugs and newly launched brand-name drugs. This hypothesis may be further supported by the fact that the time period over which these models were estimated, from 1984 to 1997, was after the 1984 Drug Price Competition and Patent Restoration Act—an Act that greatly facilitated the entry of generic drugs into the marketplace. (Refer to Chapter Two for more details). As a result, the volume of generic drugs developed and sold increased dramatically—making generic drug sales a larger component of the pharmaceutical industry's total revenues (PhRMA 1998).

Furthermore, while the estimated coefficient range for the cash flow variable (*CF*) was similar in the two samples, the coefficient range for the profit expectations variable (*PharMarg*) fell substantially—to approximately one-third that of the range estimated using the smaller, and exclusively U.S.-firm data sample. Specifically, when the sample was expanded to include smaller U.S. firms and European firms, the *PharMarg* variable's coefficient fell from a range of 0.34 to 0.65 to a range of 0.07 to 0.23. (Refer to Chapter Four and the model specifications that employed *PharMarg* as the sole profit expectations proxy variable).

Interactive dummy variables were also employed to allow for the possibility that the European firms had different profit expectations than did the U.S. firms. However, the European version of this variable was found to be statistically insignificant. This was somewhat expected given the relatively small number of European firms in the sample. The next section, which estimates models using a greater number of European firms, over a shorter time horizon, addresses this issue more closely.

Also, and of considerable empirical importance, was the fact that that the control variable, *Pct,* retained its high level of statistical significance (with t-statistics ranging from 6.65 to 15.29). Indeed, the estimated coefficients for *Pct* were also consistent with those reported in Chapter Four (ranging from 0.07 to 0.10). Therefore, in sum, these new results suggest that the general model specification, first tested in Chapter Four and extended to the current sample, is indeed quite robust—both cash flows and profit expectations are important determinants of pharmaceutical R&D.

Before turning our attention to models estimated using a larger sample of firms and data from the 1990's exclusively, an important question must first be addressed. Specifically, did structural change occur, insofar as investment in R&D is concerned, in

the global pharmaceutical industry in the 1990s? If so, then it may be inappropriate to compare results based on data from different time periods. Certainly there are a number of reasons to believe that structural change may have occurred.[9] For example, a number of regulatory changes were observed in the early 1990's, the political pressure surrounding the perceived high cost of prescription medication mounted, and many firms underwent major mergers, due, in part, to thinning R&D pipelines.

Section 2.5.2: *The Evidence of Structural Change in the Determinants of Pharmaceutical R&D Investment in the 1990's*

In order to test the appropriateness of making comparisons between the previously developed—and quite robust models—of R&D investment over the time period 1984 to 1997 to models estimated using firm data from the 1990's exclusively, the Chow-breakpoint test was employed.

Chow (1960) devised a test statistic to determine if a significant difference exists between a restricted model (one equation estimated over the entire sample) and an unrestricted model (the same equation estimated over two partitioned sub-samples of the data as specified by a breakpoint—i.e., a year). This Chow statistic is shown below:

$$F = \frac{(\tilde{u}'\tilde{u} - u_1'u_1 - u_2'u_2)/k}{(u_1'u_1 + u_2'u_2)/(T-2k)} \qquad (1)$$

The variables and terms in (1) are defined as follows:

$\tilde{u}'\tilde{u}$ = the restricted sum of squared residuals (SSR_R);

$u_1'u_1$ = the unrestricted sum of squared residuals for the first sub-sample (SSR_U^1);

$u_2'u_2$ = the unrestricted sum of squared residuals for the second sub-sample(SSR_U^2);

[9] Structural change in the 1990's was also examined in the previous chapter. However, because the current sample is larger, and contains as a subset, the same firms studied in the last chapter, formal analyses were deferred to this chapter for presentation.

T = the total number of observations;

k = the number of parameters in the model.[10]

Sub-sample *one* of the unrestricted model consists of firm data for the years 1984 to1990, and sub-sample *two* consists of data for the years 1991 to1997.

This Chow statistic, designed to detect the presence of structural change across the two sub-samples, has an exact finite sample F-distribution if and only if the error terms are identically distributed random variables (Chow 1960 and Greene 1993). That is, the Chow Breakpoint test is appropriate only when the regression error terms satisfy the following classical OLS assumption:

$$u_i \sim IN(0, \sigma^2) \qquad (2)$$

However, as was shown by Table 5.2, this is clearly not the case with the classic OLS models estimated here. Indeed, the Bartlett, Levene, and Brown-Forsythe tests all rejected the null hypothesis of error term homoskedasticity at the <0.0001 level. Under these circumstances, classic least squares estimates *should not* be used to calculate the Chow-statistic. Indeed, any attempt to do so will result in an overestimate of the significance level of the test statistic (Schmidt and Sickles 1977, Ohtani and Toyoda 1985, and Ohtani 1986). Stated slightly differently, it is probable that an F-statistic will be regarded as large, when it actually is less than the *appropriate* table value (Greene 1993). As a result, the appropriate technique for calculating the Chow-statistic is to use the residuals from the restricted and unrestricted models that have corrected the error term heteroskedasticity—models estimated using generalized least squares. In particular,

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[10] Given the determination that the appropriate model for this test was the Feasible-Generalized-LSDV specification, which consequently contained several "intercepts," or fixed effects, the approach followed was that suggested by Greene (1993). Specifically, Greene recommends not restricting the different intercepts, or fixed effects, and creating the restricted model by stacking only variable regressors. In essence, then, we are defining the restricted model to be one in which, under the null hypothesis, only the regressors are assumed to be equivalent across samples. For the present analyses this approach was deemed sufficient because our primary focus in these models is on the cash flow and profit expectations variables. In sum, then, the way that the restricted model, and hence the null hypothesis of no structural change, is defined in the present analysis is by assuming that U.S. and European firms have identical coefficient vectors with respect to the *CF, PharMarg,* and *Pct* variables. For a fuller explanation of this approach, and several examples, the reader is referred to Chapter 7 in Greene (1993).

for this specific Chow-test, it is necessary to use models that have homoskedastic error terms over time (not simply across cross-sectional units). Therefore, the residuals from a FGLS model—with homoskedastic error terms across years—was used to calculate the Chow F-statistic. These regression residuals, along with the Chow F-statistic calculation, are presented next.

The regression residuals generated by the Feasible Generalized LSDV specifications were estimated to be the following:

SSR_R (1984-1997 Model) = 0.0418

SSR_U^1 (1984-1990 Model) = 0.0122

SSR_U^2 (1991-1997 Model) = 0.0201

Consequently, the Chow F-statistic was calculated to be the following:

$$F = \frac{[(0.0517) - (0.0094) - (0.0198)]/[3]}{[(0.0094) + (0.0198)]/[259]} = 25.4$$

The critical 1% F-value for this test statistic was 3.78. This result clearly indicates that the null hypothesis of no structural change should be strongly rejected (i.e., $F=25.4 > F_{0.01} = 3.78$)[11]. Therefore, as we move into analyses based upon data for the shorter time period from 1991 to 1997, observed differences in the estimated parameter vector are likely to be the result of a different industrial climate for R&D investment.[12] We now turn our attention to estimates of our general model specification in a broader sample of firms over the shorter time horizon from 1991 to1997.

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[11] In addition to this Chow-test, a Wald-test was also performed (as suggested by Greene 1993). Not surprisingly, as was found using the Chow-test, the null hypothesis of no structural change was easily rejected ($p<0.00001$).

[12] It should not be overlooked that the addition of eight new—and mostly European—firms is also likely to affect the coefficient estimates of the determinants of R&D intensity.

Section 2.6.1: *The Determinants of Pharmaceutical R&D: A Study of 32 U.S. and European Drug Makers over the Time Period 1991-1997*

Models were also estimated over a much shorter time horizon—one from 1991 to 1997. This allowed for the inclusion of additional firms and allowed for estimates to be based exclusively on data from the 1990's. As was demonstrated in the last section, because of the dynamic nature of the global pharmaceutical industry over time, it is likely that models based on longer time series will obscure, and potentially bias, the coefficients of the explanatory variables for firm R&D investment. Therefore, the estimates provided in the forthcoming analyses may be a better reflection of the current economic climate and the influence of cash flows on pharmaceutical R&D investment behavior. Additionally, as was the case with the models estimated in the previous section, these analyses will be a reflection of the current *global* pharmaceutical environment and the influence of cash flows on *global* R&D investment.

Regression results obtained using the 32-firm sample are presented below in Table 5.4.

Table 5.4

Regression Results for 32 U.S. and European Firms over the Period from 1991-1997

(Values in parentheses are t-statistics)

Model Specification	Intercept	PharmMarg	CF	Pct	R^2/F
5.4.1	-0.06	0.27	0.16	0.08	0.57/82.7
Classic OLS	(-1.70)	(2.27)	(4.53)	(7.06)	
5.4.2		0.21	0.10	0.07	0.95/1408.8
Classic LSDV(Fixed Effects)		(4.44)	(5.12)	(3.16)	

5.4.3 FGLS (Common Intercept.)	-0.03 (-2.09)	0.16 (3.87)	0.15 (10.04)	0.08 (22.16)	0.95/1169.8
5.4.4 FGLS LSDV (Fixed Effects)		0.17 (6.95)	0.10 (6.92)	0.09 (7.12)	0.99/14159
5.4.5 Random Effects	-0.03 (-1.73)	0.22 (4.52)	0.10 (5.49)	0.08 (5.48)	0.94

The results reported in Table 5.4 largely replicate the findings presented in Table 5.1. Furthermore, regardless of the model specification estimated, lagged cash flows and profit expectations continued to be highly significant determinants of pharmaceutical R&D. As was the case with the models estimated in the last section, *NewRxs* was not found to be statistically significant—the hypothesized reasons for this finding have been discussed and apply equally to this firm sample.

As was the case with all previously estimated models, cross-sectional heteroskedasticity was detected in both of the OLS models (the classic OLS model and the LSDV model). These diagnostic results are summarized in Table 5.5

Table 5.5
Diagnostic Tests for Cross-sectional Heteroskedasticity

Equation	Bartlett Test	Levene Test	Brown-Forsythe Test
5.4.1	76.37***	2.70***	1.38*
5.4.2	102.72***	3.94***	2.26**

*** significant at the .0001 level
** significant at the .01 level
* significant at the .1 level

To correct for the cross-sectional heteroskedasticity, the method of generalized least squares was used to estimate asymptotically efficient parameter vectors. These results were reported in Table 5.4 as equations 5.4.3 and 5.4.4.

It is important to note that the FGLS-fixed-effects model (equation 5.4.4) did differ slightly from the same model estimated over the time period 1984 to 1997—equation 5.1.4. This may provide additional evidence to suggest that structural change did indeed occur in the pharmaceutical industry in the 1990's—at least as far as R&D investment behavior is concerned.[13] Interestingly, however, the only major structural difference between the two equations was the magnitude of the *PharMarg* coefficient (0.12 versus 0.17)—both the coefficient on the cash flow variable and the coefficient on the *Pct* variable were remarkably similar (0.08 versus 0.10 and 0.07 versus 0.08, respectively). This was true despite the shorter time series examined and the increased number of firms in the sample.

As Table 5.4.2 shows, a random-effects-model specification was also estimated. Here, too, the results largely replicated the findings reported in the last section. Indeed, the Hausman Test for random effects yielded a Wald-statistic of 12.04, easily rejecting the null hypothesis of orthogonality between the random effects and the model regressors. Consequently, the generalized-least-squares-fixed-effects-model specification was determined to be the appropriate model for the current sample.

An interesting question that arises from the present sample (in which the number of European firms now approximately equals the number of U.S. firms) is whether or not there exist structural differences in investment behaviors between U.S.- and European-based firms.

Section 2.6.2: *Structural Differences in the R&D Investment Model by Firm Type: U.S. and European Firms Compared*

Certainly there exist substantial industrial and economic differences between U.S. and European pharmaceutical firms. But do these differences substantially alter the firms' R&D investment behavior? It seems likely that they may. First of all, there are widely divergent tax systems in Europe, and these tax systems differ substantially from the U.S. tax system. As Chapter Three illustrated, for example, the tax system—and specifically the tax rate differential between capital gains and dividends—can play a very important role in a firm's internal-investment-decision-making process. Additionally, the

[13] Of course, this observation could be the result of the additional firms added to the sample.

regulatory and political environments, which also vary widely between U.S.- and European-based firms, may have an important and influential impact on the role that cash flows and profit expectations play in the firm R&D investment decision. It is also possible that cultural differences exist in management strategies and philosophies, depending on whether or not the firm is U.S.-based or European-based. These differences, or possible differences, it is plausible to think, may significantly impact the structure of our previously specified investment model. Therefore, a Chow-breakpoint test, similar to the one calculated in the last section, is used to test the null hypothesis of no structural differences between U.S.-based and European-based firms.

To do this, two new models were estimated using the previously specified, and econometrically sound, generalized-LSDV model: a U.S.-based model and a European-based model. These regression results are summarized below in Table 5.6.

Table 5.6
Feasible Generalized LSDV Model for U.S.-based and European-based Firms

Sample (Equation)	CF	PharMarg	Pct	R^2/F
U.S. Firms 5.6.1	0.09 (4.18)	0.18 (4.09)	0.09 (5.12)	0.98/2900
European Firms 5.6.2	0.06 (2.52)	0.10 (3.91)	0.09 (5.58)	0.99/6684

Next, to construct the Chow-test, regression results from these two new models were examined and compared to Equation 5.4.4. Equations 5.6.1 and 5.6.2 made up the unrestricted model, within which U.S.- and European-based firms were allowed to have separate coefficient vectors. Equation 5.4.4 was the restricted model, in which it was assumed that the two sub-samples (in this case U.S. firms and European firms) had the same model coefficient structure. In contrast to the Chow-statistic that was calculated in the last section, where the sample breakpoint was a year, in this application the "breakpoint" was by firm type—i.e., a U.S.-based firm or a European-based firm. From these three models, the sum of squared residuals were estimated to be the following:

SSR_R (Pooled Model) = 0.0282

SSR_U^1 (U.S.-firm Model) = 0.0217

SSR_U^2 (European-firm Model) = 0.0046

And the following Chow F-statistic was calculated:

$$F = \frac{[(0.0282) - (0.0217) - (0.0046)]/[3]}{[(0.0217) + (0.0046)]/[121]} = 2.91$$

This Chow F-statistic was significant at the 5% level, but insignificant at the 1% level. The critical F-statistics for these two significance levels were 2.6 and 3.78, respectively. Interestingly, and unlike the Chow-statistic estimated in the last section, where the F-ratio was extremely large (F = 66.65), the above F-ratio is relatively low. This raises some very important econometric issues that should be mentioned prior to making a decision as to whether or not to reject the null hypothesis of "no structural differences in R&D investment behavior between U.S.-based and European-based firms." Maddala (1992) makes the point that there exist a number of alternate critical F-ratios that may be used when deciding between a restricted and an unrestricted model specification.[14] Many of these require a much higher level of statistical significance than the conventional 5% level to reject the null hypothesis.

Furthermore, and on more general hypothesis-testing grounds, Maddala criticizes the conventional approach of using a constant significance level because, with sufficiently large samples, every null hypothesis can be rejected. Consequently, Maddala adds, conventional hypothesis testing increasingly distorts the interpretation of data against the null hypothesis as the sample size increases. Therefore, it is often argued, the significance level should be a decreasing function of the sample size (Maddala 1992 and Lindley 1957).

In any event, regarding our null hypothesis of no structural differences in R&D investment behavior between U.S.-based and European-based firms in the 1990's, it is

[14] The interested reader should refer directly to Sections 12.7-12.9 in Maddala (1990) for descriptions of these different F-statistic criteria.

clear that considerable caution should be taken when interpreting our marginally significant results against the null hypothesis. The evidence is not as compelling as that for the industry's structural change in the 1990's.

In sum, whatever the appropriate conclusion regarding structural differences, there is no ambiguity surrounding the hypothesis that cash flows, because of capital market imperfections, are an important determinant of R&D investment behavior. This result was found to be the case regardless of the model specification employed, the firms included in the sample, or the time period over which models were estimated.
We will now turn our attention to R&D investment models using data from the Japanese pharmaceutical industry over the period from 1994 to 1997.

Section 3.1: The Determinants of Pharmaceutical R&D: A Study of the Leading 28 Japanese Pharmaceutical Firms[15]

In an effort to further examine the relationship between internally generated funds and R&D expenditures, models were also estimated using Japanese firm data for the time period 1994-to-1997—the only years for which complete data could be obtained. While the Japanese pharmaceutical industry is different in many respects from the pharmaceutical industries previously studied, the arguments for a cost of capital differential between internal and external funds are still applicable. For this reason, data were gathered on the largest Japanese pharmaceutical firms to test this hypothesis. This section begins by presenting the firms in the sample and discussing the data characteristics and limitations. Following this, the model specifications are outlined and the empirical results reported.

In addition to estimating models based exclusively of Japanese firm data, this section will also estimate a model using a pooled sample of all 60 firms presented in this chapter—i.e., U.S., European, and Japanese firms—over the1994-to-1997 time period.

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[15] This section will also estimate a model that pools the sample of Japanese firms with the previously studied sample of U.S. and European firms.

Indeed, this last model will be global in nature and include a very diverse sample of firms.

Section 3.2: *Data Sample*

As was the case with the data in previous section, most of the data for these analyses were obtained from Scrip Company League Tables. The exception again was data on annual firm depreciation—a necessary variable required for the calculation of firm cash flows. This data had to be obtained from other sources. Unfortunately, however, data on this variable was severely limited for Japanese firms. In particular, values prior to 1993 were not obtainable. As a consequence, models were limited to the time period from 1994 to 1997.

The firms in this sample are listed below:

1) Asahi Chemical
2) Banyu Pharmaceuticals
3) Chugai Pharmaceuticals
4) Daiichi Seiyaku
5) Dainippon Pharmaceuticals
6) Eisai
7) Fujisawa
8) Fuso Pharmaceuticals
9) Green Cross
10) Hokuriku Seiyaku
11) Kaken Pharmaceuticals
12) Kyowa Hakko
13) Meiji Seika
14) Mochida Pharmaceuticals
15) Nikken Chemicals
16) Nippon Shinyaku
17) Ono
18) Sankyo
19) Shionogi
20) SS Pharmaceuticals
21) Taisho Pharmaceuticals
22) Takeda Chemical Industries
23) Tanabe Seiyaku
24) Tokyo Tanabe
25) Torii Pharmaceuticals
26) Toyama Chemical
27) Tsumura & Company
28) Yamanouchi

Section 3.3: *Model Specifications and Empirical Findings*

The models estimated in this section were the same as those estimated in the last two sections with the exception of the fixed-effects specification. The present panel data

contained too few time series relative to the number of cross-sectional units (i.e., firms). Thus, from a practical standpoint, the cost in terms of the number of degrees of freedom needed to estimate a LSDV model was considered to be too high (Greene 1993).[16] However, unlike the models in the last two sections—which contained a much more heterogenous sample of firms (with presumably systematic differences across firms not explained by the models three key regressors), diagnostic tests supported the use of a random-effects model specification.[17] More will be said on this latter in the section.

Furthermore, the short time series in the present sample also led to another complication; the firm-invariant profit expectation variable was no longer significant.[18] Consequently, time trend variables and year dummy variables were tested in the model to account for changing profit expectations over the 4-year period, but were not found to be statistically significant. (Refer to Appendix 2 for more details and regression results).[19] As a result, it was assumed that firm profit expectations remained constant over the period from 1994 to 1997. The following regression results were estimated using the Japanese-firm data:

Table 5.7

[16] In fact, attempts *were* made to estimate LSDV models; unfortunately, however, the loss in degrees of freedom was found to be too great to generate a robust model.

[17] Like the 11-U.S.-firm models, Hausman's Wald Statistic failed to reject the null-hypothesis of no correlation between the random effects and the model regressors. This is not surprising, because, unlike the pooled U.S.-based and European-based firm sample, which contained firms of all sizes, the 28-firm Japanese sample was fairly homogeneous—both in size, industrial climate, and type of R&D operations (large in generic manufacturing). This was much like the case with the 11-large-U.S. firm sample that also supported a random-effects specification.

[18] Due to the very limited number of time series observations in the Japanese-firm sample, *PharMarg* was not found to be statistically significant in these models. That is, because profit expectations were hypothesized to be uniform across all firms in any given year, such a short time series is not likely to provide a sufficient number of observations to detect the influence of changing profit expectations on R&D intensity. This is particularly true in this case, because there was very little variation in *PharMarg* over this time period. Moreover, because the formulation of *PharMarg* was based primarily on leading U.S. and European firms, this variable may not have been applicable as a proxy for the profit expectations of Japanese firms. Having said that, when a different *PharMarg* variable was tried—one that was constructed from the Japanese firms in this sample—the results were unaltered. The profit expectations variable was negative and insignificant. Consequently, this variable was dropped from the model.

[19] For the model that employed year dummy variables, all of the dummy variables were considered simultaneously for statistical significance.

Regression Results for 28 Japanese Pharmaceutical Firms over the Period from 1994-1997
(Values in parentheses are t-statistics)

Model Specification	Intercept	CF	Pct	R^2/F
Equation 5.7.1	0.01	0.33	0.05	0.47/36.3
Classic OLS	(0.92)	(5.90)	(3.18)	
Equation 5.7.2	0.01	0.27	0.06	0.96/1317.4
FGLS (Common Intercept)	(4.94)	(7.46)	(10.95)	
Equation 5.7.3	0.05	0.17	0.04	0.95
Random Effects	(2.10)	(2.83)	(1.51)	

As may be noted from Table 5.7, a FGLS model specification (Equation 5.7.2) was again estimated, thus indicating the detection of cross-sectional heteroskedasticty in the classic OLS model. Interestingly, while virtually none of the models estimated in this chapter tested positive for the presence of with-in group serial correlation or contemporaneous correlation, every OLS model suffered from cross-sectional heteroskedasticity. (See Appendix 2 for the diagnostic test results). This finding was particularly interesting given the fact that the model variables were specified as ratios (or size 'deflated' intensity measures)—a common remedy for heteroskedasticity.

Despite the fact that, for practical reasons, a fixed-effects model specification was deemed inappropriate for the current sample, diagnostic tests supported the use of a random-effects specification. Specifically, Hausman's Wald statistic—which tests the null hypothesis of no correlation between the random effects and the model regressors—was not found to be statistically significant (W= 3.71).[20] This finding, which was also the finding in the 11-U.S.-firm sample, may be due—in part—to the fact that the current sample of Japanese firms was relatively homogeneous. Consequently, systematic differences across firms may not have existed (aside from, of course, those differences explained by the key model regressors). Indeed, in the pooled U.S.-and European-based models, many countries—with very different regulatory environments —were represented. This, consequently, likely resulted in systematic differences across firms

[20] The critical values for this statistic (which are distributed asymptotically as Chi-squared) were: 4.61 and 5.99 for 10% and 5% levels of significance, respectively.

that could not be explained solely by the key model regressors.[21] The following exemplifies the counterpoint. In addition to operating in the same economic environment (i.e., country), the present sample of Japanese firms demonstrated considerably less variance in firm size, involvement in biotechnology, and the extent of their involvement in generic pharmaceutical production than did the firms in the U.S.- and European-based firms in this chapter.

The coefficient on the lagged cash flow variable was found to be highly significant in all of the above equations. Specifically, this coefficient ranged from 0.17 to 0.33. Interestingly, these coefficients were considerably larger than those estimated with the other, non-Japanese, firm data in this chapter. A summary of these estimated coefficients is presented below in Table 5.8. Coefficients are only reported for the models that were determined to be the econometrically appropriate specification for each particular sample.

Table 5.8

Estimated Lagged Cash Flow Variable Coefficients in Selected Model Specifications

(Values in parentheses are t-statistics)

Firm Sample and Selected Model Specification	Coefficient of Lagged Cash Flow Variable (CF)
Equation 5.8.1 24 U.S.-and European-based Firms (1984-1997) Feasible Generalized LSDV (i.e., Fixed Effects)	0.08 (4.86)
Equation 5.8.2 32 U.S.-and European-based Firms (1991-1997) Feasible Generalized LSDV (i.e., Fixed Effects)	0.10 (6.92)
Equation 5.8.3 28 Japanese Firms (1994-1997) Random Effects	0.17 (2.83)

[21] As was mentioned earlier, several variables were developed in an attempt to control for these differences. Unfortunately, however, these variables were found to either be insignificant or impossible to construct (due to limitations in the data).

The results from the models estimated in this section, which used exclusively Japanese-firm data, contribute to the growing body of empirical evidence supporting the hypothesis that cash flows are an important determinant of pharmaceutical R&D investment. Lastly, the final model estimated in this chapter is an expansion of the previous model and includes the 32 U.S. and European pharmaceutical firms studied above. This model will be estimated using a total of 60 firms with data covering the time period 1994 to1997.

Section 3.4: *The Determinants of Pharmaceutical R&D: A Study of 60 of the World's Leading Pharmaceutical Firms over the 1994-1997 Time Period*

As a final analysis for this chapter, data from all of the aforementioned U.S., European, and Japanese firms were pooled. However, given the limited time series available for the 28 Japanese firms, these models were constrained to data for the time period 1994 to 1997. As was the case with the models based on exclusively Japanese-firm data, the relatively short time series made the estimation of a fixed-effects model specification impractical.[22] Unfortunately, and *unlike* the Japanese-based-firm models, diagnostic tests revealed a statistically significant correlation between the model regressors and the random effects when a random-effects specification was estimated. Consequently, the results obtained from this model—whose specification was required for practical econometric reasons—likely suffers from inconsistency due to omitted variables.[23] This finding was expected given the heterogeneity of the 60 firms in the sample. The linear regressions results based on this 60-firm sample are presented below in Table 5.9.

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[22] As was the case with the Japanese-based models, because of the short time series and the time-invariant formulation of the profit expectations variable, all proxies that were employed to control for changing profit expectations were found to be statistically insignificant. These proxies included the *PharMarg* variable, year dummy variables, and several formulations of a time-trend variable. Consequently, as was believed to be the case with the exclusively Japanese-based models, profit expectations were assumed to be constant over this time period, and this variable was dropped from the equation. Regression details for the different specifications are reported in Appendix 2.

[23] Refer to Chapter Four for a fuller discussion on this point

Table 5.9

Linear Regression Results for 60 U.S., European, and Japanese Firms (1994 to 1997)
(Values in parentheses are t-statistics)

Model Specification	Intercept	CF	Pharm	R^2/F
Equation 5.9.1	0.01	0.25	0.07	0.53/85.5
Classic OLS	(0.68)	(8.64)	(6.89)	
Equation 5.9.2	0.01	0.23	0.07	0.98/3061.8
FGLS (Common Intercept)	(5.73)	(27.66)	(28.1)	
Equation 5.9.3	0.04	0.08	0.06	0.94
Random Effects	(3.37)	(2.67)	(3.84)	

The results in Table 5.9 provide still further compelling evidence to suggest that firm cash flows are an important determinant of pharmaceutical R&D investment. However, as was mentioned, these pooled results should be viewed with considerable caution. Because of the short time series, a fixed-effects-model specification was statistically impractical due to the high cost of estimating it—in terms of the required number of degrees of freedom. This turned out to be problematic because the random-effects-model specification, which used up only a few degrees of freedom and hence was econometrically practical for this data set, was determined *not* to be the "best" model for the data.[24] This was, however, of no surprise given the widely divergent firm characteristics present in this 60-firm sample.

Section 4: Conclusions and Discussion

The analyses undertaken in this chapter mark the first empirical study ever of the determinants of pharmaceutical R&D on a global scale—all previous studies have been limited to small samples of exclusively large U.S. firms. Hence, these empirical findings should be more representative of the role played by internal funds in the firm R&D

[24] Hausman's Wald statistic for the random-effects-model specification was calculated to be 12.27. This was statistically significant at the 1% level.

investment decision. Moreover, these analyses are based on a more contemporary data sample. Thus, these results are likely to be a better reflection of the current industrial climate for pharmaceutical R&D investment.

The results from the different models estimated in this chapter and the last are summarized below in Table 5.10. In addition to reporting the estimated coefficients for the cash flow variable, the elasticity of R&D intensity with respect to cash flows is also reported for each sample. In order to estimate this elasticity, sample means were calculated for both R&D intensity and the cash flow margin. Specifically, the elasticity of R&D intensity with respect to cash flows is defined to be the following:

$$E_{RD,CF} = \frac{\%\Delta RD}{\%\Delta CF} = \left(\frac{\partial RD}{\partial CF}\right) \times \left(\frac{\overline{CF}}{\overline{RD}}\right) \tag{3}$$

Table 5.10

Summary of Empirical Findings on the Role of Cash Flows in R&D Investment

Model (Time Period)	Cash Flow Coefficient	Mean RD/Sales for the Sample	Mean CF/Sales for the Sample	Cash Flow Elasticity
11 U.S. Firms (1976-1996)	0.11-0.25	0.085	0.213	0.275-0.625
11 U.S. Firms (1983-1996)	0.09-0.27	0.099	0.259	0.235-0.706
24 U.S. and European Firms (1984-1997)	0.08-0.20	0.097	0.215	0.177-0.443
32 U.S. and European Firms (1991-1997)	0.10-0.16	0.108	0.232	0.215-0.344
28 Japanese Firms (1994-1996)	0.17-0.33	0.100	0.139	0.236-0.459
60 U.S., European and Japanese Firms (1994-1997)	0.08-0.25	0.102	0.198	0.155-0.485

In sum, the regression results in this chapter provide substantial evidence to support the hypothesis that internally generated funds are an important determinant of pharmaceutical R&D. In fact, in every model estimated, a statistically significant and relatively stable positive relationship was found to exist between firm research and development intensity and lagged cash flow margins. This was the case both for models estimated over different time periods and for models estimated using different samples of firms. These findings are consistent with the theoretical model developed in Chapter Three.

Finally, as was shown earlier in the chapter, the lagged cash flow coefficient has a very interesting and useful policy interpretation. For every dollar reduction in a firm's cash flow, R&D investment will fall by approximately the value of the estimated cash flow coefficient. (Refer to footnote 7 for more details). For example, if the cash flow coefficient were estimated to be between 0.10 and 0.25 for a particular industry and industry cash flows fell by $10 billion, then R&D investment could be expected to fall by approximately $1 to $2.5 billion. This reduction in R&D investment would certainly exert a negative impact on long-term medical innovation—which depends so heavily on R&D investment.

Clearly, then, these types of R&D investment models may be used to gauge the relative impact of, for example, a new government policy that affects firm cash flows on R&D investment levels (Grabowski and Vernon 1997). This is indeed a useful, but somewhat limited application. The main shortcoming with this application is the lack of an explicit relationship between a given policy and firm cash flows. Consequently, all one can do is run "what if" scenarios. For example, if policy "X" impacts firm cash flows by "Y," the result will be a reduction in R&D investment by "Z." Of course, it goes without saying, seldom does a researcher have the ability to estimate an explicit statistical relationship between a particular government policy and a well-defined, quantifiable economic outcome. However, this is exactly what the next chapter will endeavor to do.

Chapter Six will build on the robust models estimated in this and the last chapter and estimate explicitly how a prescription-drug-price-control policy in the U.S. will affect global R&D investment. While the forthcoming empirical analyses in Chapter 6 will be severely hampered by data limitations, these analyses should nevertheless set forth an interesting and unique methodology to address, quantitatively, the question: "How, and to what degree, will pharmaceutical price controls in the United States affect global R&D investment?" This particular policy question was selected because it is, without a doubt, one of the most hotly debated political issues in United States at the present time. Therefore, having already established what has proven to be a highly robust investment model for pharmaceutical R&D, one that is based on capital market imperfections, it is both appropriate and very relevant to explore this application of our model. We turn to this now in Chapter Six.

Chapter Six

Price Controls and the Pharmaceutical Industry: Estimating the Effect of Pharmaceutical Price Controls on Pharmaceutical R&D Investment

Section 1: Introduction

There exists a great deal of debate in the United States over the potential economic implications of pharmaceutical price controls. Proponents for the regulation of prescription drug prices in the U.S. argue that pharmaceutical price controls—like those that are imposed in most foreign markets—are a necessary measure to ensure affordable health care for all Americans. However, on the other side of the debate, and equally compelling, are arguments against pharmaceutical price controls because of their likely impact on investment in pharmaceutical R&D. Supporters of this latter position contend that pharmaceutical price controls will have a negative effect on future drug innovation—i.e., the development of new life-saving medical advances in pharmaceuticals. This would result, the argument goes, because the incentives to invest in new R&D—which drive new drug innovation—would diminish considerably due to the expectations of lower returns (sales revenues) from drugs developed and marketed under regulated pricing.

Indeed, the last decade has seen this controversial debate grow all the more heated. This has been due in part to the rise in prescription drug prices relative to the prices of other goods and services in the United States (Grabowski 1994). However, at the same time, one must consider that there have been many innovative new drugs developed and brought to market in the past decade. These new medicines have greatly improved health care in a variety of disease areas. Examples include AIDS, cardiovascular disease, and mental illness, to mention only a few (PhRMA 1999). Furthermore, virtually half of all new drug introductions in the past two decades have been developed by U.S.-based firms—firms whose sales are predominantly U.S. sales (Grabowski 1994, Redwood 1993, PhRMA 1999). For this reason, several publicly funded studies by the Office of Technology Assessment and the Congressional Budget

Office have been undertaken to help us better understand the costs, risks, and rewards that are particular to pharmaceutical R&D. Importantly, however, there have been no studies that have empirically estimated the impact price controls will have on current and future levels of R&D investment. In fact, only a few studies have examined the empirical aspects of the incentives to invest in pharmaceutical R&D (Grabowski and Vernon 1981, Vernon 1995, and Grabowski and Vernon 1997). Consequently, this will be the first study ever to explicitly address the question of how price controls affect investment spending on pharmaceutical R&D.

Using data from twelve of the world's leading pharmaceutical firms over the period from 1994-1997, models of the determinants of pharmaceutical R&D investment will be estimated. These models will be similar to those estimated in Chapters Four and Five. However, the models estimated in this chapter will have one major distinction—they will be sufficiently modified to empirically estimate the influence of pharmaceutical price controls on R&D investment levels. Moreover, and of particular relevance from a public policy perspective, based on the models estimated in this chapter, it will be possible to estimate the impact *U.S. price controls* will have on current and *future* levels of R&D investment.

Section 2 of this chapter will begin by providing a brief background of the major differences between the U.S. pharmaceutical marketplace and non-U.S. pharmaceutical markets—with a particular focus on market launch pricing and the European pharmaceutical markets. Section 3 will describe and discuss the data used in this paper. Section 4 will describe the theoretical model and discuss its limitations and advantages, and Section 5 will present the statistical findings. Finally, Section 6 will discuss the empirical findings and the policy implications that result.

Section 2.1: Brief Background on Pharmaceutical Price Regulation

The United States is the only major industrialized country in the world that does not currently regulate prescription drug prices.[1] In the United States, prescription drug

[1] As will become apparent later in this chapter, a sharp distinction is drawn between the regulatory

prices are determined in a free market system. In direct contrast with this, practically every other country, either directly or indirectly, imposes one form of price controls or another on pharmaceuticals. To set the stage for the forthcoming analyses, it will be instructive to briefly describe the pricing and cost containment methods utilized by some of the major non-U.S. pharmaceutical markets. The 16 major ex-U.S. markets examined are the following:

1) Austria
2) Belgium
3) Denmark
4) Finland
5) France
6) Germany
7) Greece
8) Ireland
9) Italy
10) Netherlands
11) Norway
12) Portugal
13) Spain
14) Sweden
15) Switzerland
16) United Kingdom

Because the returns from pharmaceutical R&D come largely in the form of the revenues generated by recently launched, patented new drugs, the focus of this section will be on the pricing regulation of these newly-launch drugs. The regulations detailed in this section will be presented in a very succinct fashion—for more complete regulatory pricing details on each of the countries surveyed, the reader is referred to the 1998 PhRMA Pricing and Reimbursement Report.

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environment in U.S. market for prescription drugs and all other, ex-U.S. regulatory environments for prescription drugs. Specifically, the assertion that price regulation exists in one market (the "ex-U.S. market") but not the other (the U.S. market) is made. This is clearly an oversimplification. For one, the regulatory environments outside the U.S. are quite heterogeneous, and the degrees to which prescription drug prices are controlled vary greatly. Also, to say that in the U.S. there are *no* mechanisms by which prescription drug prices are regulated would be inaccurate. Nonetheless, it is a fact that there is far less regulation of prescription drug prices in the U.S. as compared to other countries. Therefore, this oversimplification—which imposes a binary-type classification for prescription drug price controls—still makes a good deal of sense from a modeling perspective. And as will be seen shortly, for interpretive purposes, this approach is quite valid—one only needs to modify the definition of regulated pricing.

To control public spending on newly introduced/launched pharmaceutical products in Europe, some governments opt to focus on the supply side of the market (the manufacturer and distributor) while others focus on the demand side of the market (the patient and the physician). In regulating pharmaceutical pricing on the supply side, the most common methods include controls over individual products, reference pricing (which is establishing a price based upon the price of the same or similar drugs in other countries), average pricing, constraints on wholesalers and pharmacists, and positive and negative product listings for reimbursement (which are lists of drugs that the government decides it will and will not pay for, respectively).

Alternatively, for countries that emphasize the regulation of pharmaceutical pricing on the demand side, frequently used methods include patient co-payments, advice, guidelines and/or budgets for physicians, parallel imports, and even the transfer of products from prescription-only to over-the-counter (OTC) status. However, no single country relies on a single method, but rather a combination of different methods.[2] Table 6.1 summarizes the different methods used by each of the aforementioned countries to regulate the prices of newly launched prescription pharmaceuticals.

[2] Again it should be emphasized that it is not implied that the U.S. does not employ any of these measures in regulating the prescription drug market. This clearly does occur. The main point being made is that there is, on average, a great deal more regulation in ex-U.S. pharmaceutical markets.

Table 6.1

Various Means of Regulating Prescription Drug Prices in Europe

Country	Control Prices at Launch	Control Reimbursement Prices	Reference Pricing	Profit Controls	Positive/ Negative Listings	Drug Budgets for Doctors	Patient Co-payments
Austria	√	√	-	-	√	-	√
Belgium	√	√	-	-	√	-	√
Denmark	-	-	√	-	√	-	√
Finland	-	√	-	-	√	-	√
France	-	√	-	-	√	√	√
Germany	-	-	√	-	√	√	√
Greece	√	√	-	-	√	-	√
Ireland	√	√	-	-	√	√	√
Italy	-	√	-	-	√	-	√
Netherlands	√	√	√	-	√	-	√
Norway	-	√	√	-	√	-	√
Portugal	√	√	-	-	√	-	√
Spain	√	√	-	√	√	-	√
Sweden	-	√	√	-	√	-	√
Switzerland	-	√	-	-	√	-	√
United Kingdom	-	-	-	√	√	√	√

Source: "Pricing and Reimbursement in Western Europe: A Concise Guide," A PhRMA Pricing Review Report (PPR Communications Ltd, 1998).

The above table demonstrates the vastly different types of health care systems that exist across Europe. However, all of the countries listed in Table 6.1 (indeed, practically *all* ex-U.S. markets, including Asia, Australia, Canada, South America, etc.) do have one thing in common: one form of pharmaceutical price controls or another. This, as was stated earlier, is not the case with the U.S. health care system. In the U.S., the government does not regulate prescription drug prices. This fact is germane to the following sections and the development of a variable that is capable of empirically estimating the impact pharmaceutical price controls have on R&D investment.

Section 2.2: *Implications of Price Controls for Pharmaceutical Innovation: Qualitative Considerations and Past Research*

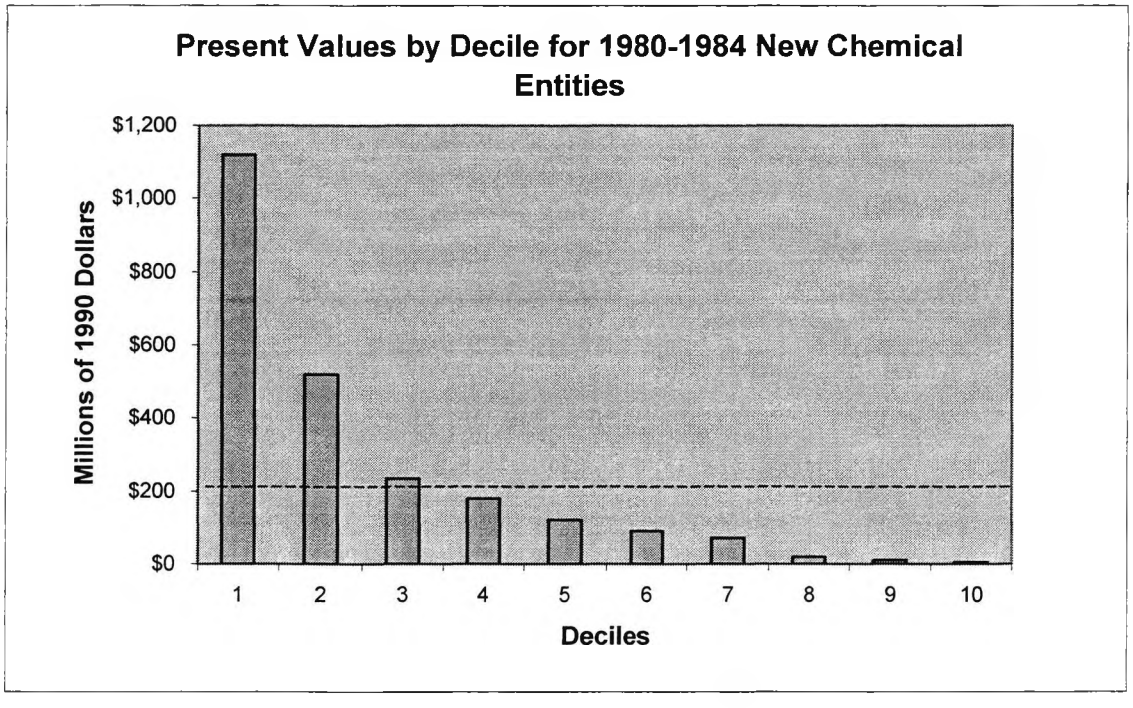
In his 1994 American Enterprise Institute (AEI) Study: Health Reform and Pharmaceutical Innovation, Grabowski outlined the key provisions and likely consequences of the Clinton Administration's previously introduced (November 1993) Health Security Act. While this Act was not passed by congress, the issues and essence of this Act are still being widely debated. Furthermore, the likelihood of a similar Act being introduced in the near future appears to be quite high. For this reason a brief overview of Grabowski's earlier research is provided before moving into the analyses undertaken in this chapter.

In his distillation of the Clinton Administration's Health Security Act and its likely impact on the pharmaceutical industry, Grabowski emphasized that the most important provisions of the act were the cost-control measures that would have impinged directly upon future drug returns. These provisions, which would have established negotiated rebates for newly launched drugs (and the related authority to exclude such drugs under Medicare), Grabowski argued, would have dramatically reduced the expected returns to pharmaceutical R&D—i.e., the sales revenues of new drugs. This in turn, he argued, would have dramatically diminished the incentive to invest in R&D and, hence, to innovate.

Along the same lines, the Health Security Act also contained provisions for imposing premium caps on the growth of health care expenditures and for the creation of the Advisory Council for Breakthrough Drugs. Indeed, provisions like these—as well as many others outlined in the act—would have established an incipient system of price controls over new drugs. The negotiated rebates on new drugs, for example, were to have been established by means of referencing drug prices in other countries. (See footnote 10 for more details.) As Grabowski notes, such a set of provisions would open up a Pandora's box of unintended and undesirable consequences, the greatest undesirable consequence being the impact such provisions would have on the incentives to invest in current and future research and development.

Drawing on some of his earlier work, Grabowski undertook a simple net present value (NPV) analysis to model the impact of various government price control scenarios on the returns to pharmaceutical R&D. While Grabowski's analysis did not address how such price controls would directly affect R&D investment, he did demonstrate the sensitivity of the NPV of R&D investments to price controls under various scenarios. Specifically, Grabowski considered four scenarios based on some of his earlier research —research in which he estimated the after-tax returns of new drugs by decile (based on a ranking of the drugs by their present value sales revenue) and the average R&D cost per new drug. (Refer to Chapter Two for a fuller discussion of these studies.) Figure 6.1 graphically summarizes these results (previously Figure 2.15).

Figure 6.1 (Previously 2.15)



Source: Grabowski and Vernon, "The Returns to R&D on New Drug Introductions in the 1980s," Journal of Health Economics, 1994.

As Figure 6.1 demonstrates, the returns to pharmaceutical R&D are highly skewed, with only the top three deciles of drugs generating present value sales revenues in excess of average R&D costs. Grabowski used these findings to create four hypothetical price control scenarios. The four scenarios were:

1) Base line (i.e., no price controls);
2) Top decile of new drugs constrained to break even;
3) Top two deciles of new drugs constrained to break even;
4) Top three deciles of new drugs constrained to break even.

These scenarios assumed that the government would impose variable rebates on the first, second, and third deciles of newly launched drugs such that those drugs would earn a return equivalent to the average cost required to bring a drug to market—$201 million in 1990 (Grabowski and Vernon 1994). Table 6.2 summarizes his findings.

Table 6.2

Government Price Constraints on Top Decile Drugs and Implications for the Mean New Chemical Entity Introduction
(millions of 1990 dollars)

Case	Present Value Cash Flow	R&D Costs	Net Present Value	Δ Net Present Value
Base line: no government price controls	224.1	201.9	22.2	-
Top decile constrained to break even	141.7	201.9	-60.2	-82.4
Top 2 deciles constrained to break even	110.8	201.9	-91.0	-113.2
Top 3 deciles constrained to break even	107.8	201.9	-94.0	-116.2

Source: Grabowski and Vernon, "The Returns to Pharmaceutical R&D: Prospects under Health Care Reform," in Robert B. Helms, Competitive Strategies in the Pharmaceutical Industry (AEI Press, 1994).

The NPV estimates illustrated in Table 6.2 clearly demonstrate how price controls could have a negative—and quite substantial—impact on the incentives to invest in R&D. Indeed, R&D is a very risky investment, especially in the early discovery phases of research. Such dramatic changes in the returns to R&D—and hence the expected

future returns to R&D—would likely reduce current and future R&D investment substantially. The exact quantitative impact on R&D investment is unclear, and has never been estimated empirically. This is due, of course, to the difficulty inherent in *quantifying* the effect U.S. price controls have on firm profit expectations.

Models of the determinants of pharmaceutical R&D investment have been estimated (Grabowski and Vernon 1981, Grabowski and Vernon 1997, Chapter Four, and Chapter Five) and found to be quite robust. However, these models did not explicitly account for the role price controls play in influencing the expected future returns to R&D investment. As will be seen in the forthcoming sections, using a newly developed variable—one that is defined to be the ratio of a firm's U.S. pharmaceutical sales to the firm's total pharmaceutical sales—it *is* possible to empirically estimate the role regulated prescription drug prices have on R&D investment. This new variable—which may be thought of as the proportion of a firm's pharmaceutical sales that are not subjected to price controls—and how it implicitly enters into the general model specifications developed in Chapters Four and Five, will be discussed in detail in the following sections.

Having outlined and discussed the major differences between the U.S. and ex-U.S. pharmaceutical markets and the economic consequences of these differences in terms of the incentives to invest R&D, it is now appropriate to present the data used in the forthcoming empirical analyses.

Section 3: Data

The data obtained for use in this chapter, as was the case for the previous two chapters, came predominantly from *Scrip Pharmaceutical Company League Tables and Scrip Pharmaceutical Company Annual Reports*. The exception to this was firm annual depreciation. This variable, which was necessary for the construction of one of the key variables in the model, was obtained from several different sources. These sources included annual reports, SEC fillings (i.e., 10K and 10Q fillings), and various online financial databases (i.e., Hoovers, Edgar Online, PRARS, and CAROL). Furthermore, as will be discussed more thoroughly in the next section, because the data were obtained

from different sources—or different tables in the *Scrip* Reports, they were rigorously validated by confirming that all available sources (or *Scrip* tables) reported the same estimate for each of the variables. The firms used in this study were selected based on the following criteria:

1) Data were available to estimate the percent of the firm's pharmaceutical sales that were ex-U.S. pharmaceutical sales.

2) Detailed financial data were available on the firm's pharmaceutical operations. Specifically, the following financial variables were available:

    i) Total firm sales
    ii) Total firm pharmaceutical sales
    iii) Net income for the firm's pharmaceutical operations
    iv) Total firm R&D expenditures
    v) Total firm depreciation expense

3) The firm had to be of sufficient size and market capitalization.

The first criterion was by far the most restrictive for this study. Data on the percentage of a firm's pharmaceutical sales that were ex-U.S. pharmaceutical sales were difficult to procure. In fact, these data were available for only one year—1996. Indeed, this restriction further limited the sample size by restricting the number of years included in the study—1994-1997. Moreover, these data were reported for only twenty firms. The second criterion—having a complete set of financial data—eliminated eight of the remaining twenty firms in the sample. The variable that was not available for these firms was pharmaceutical net income. Finally, the remaining twelve firms were all deemed to be sufficient in size and market capitalization to be included in the study.

Data were available to estimate investment models based upon the following sample of twelve firms over the period from 1994-1997:

1) Abbot Laboratories
2) American Home Products
3) Amgen
4) Bayer
5) Bristol Myers Squibb
6) Glaxo-Wellcome

7) Hoechst
8) Johnson & Johnson
9) Pfizer
10) Schering-Plough
11) SmithKline Beecham
12) Warner Lambert

Section 4.1: Methods and the Theoretical Model

The theoretical framework guiding the empirical analyses in Section 4 will be based upon the investment model rigorously developed in Chapter Three. The empirical analyses, however, will differ slightly from earlier studies of the determinants of pharmaceutical R&D (and the models estimated in Chapters Four and Five). As will be discussed shortly, this is because of a new formulation of the profit expectations variable —one that is capable of incorporating the influence of pharmaceutical price controls. Before delving into this new model specification, a brief overview of the theoretical model will be presented next.

Section 4.2: *The Theoretical Investment Model: A Brief Overview*

Classical economic theory states that the optimal level of investment by any firm is that level of investment whereby the marginal rate of return on the next dollar invested is equal to the marginal cost of capital of that dollar. Equivalently stated, the optimal level of firm investment is determined by solving simultaneously an expected marginal rate-of-return equation, *mrr*, and an expected marginal cost-of-capital equation, *mcc*. In the case of pharmaceutical R&D, this marginal rate of return may be thought of as the expected rate of return on the next R&D project. Specifically, the expected rate of return on the next project is assessed by the firm to be the expected present value revenues from the next project *less* the expected present value operating costs from the next project all *divided* by the present value R&D expenditures for that project. This is expressed algebraically by equation (1).

$$mrr_i = \frac{E(R_i) - E(C_i)}{RD_i} \qquad (1)$$

The subscript i denotes the ith R&D project in the firm's R&D project portfolio. Refer to Chapter Three for a more rigorous development of this expected marginal-rate-of–return concept. Projects are then arranged in the R&D project portfolio in decreasing order with respect to their risk-adjusted expected rate of return.

The *mcc* equation, on the other hand, reflects the opportunity cost of capital incurred through investing in R&D on the margin. This opportunity cost may be thought of as the expected rate of return on the next best alternative investment of similar risk. As discussed in Chapter Three, and confirmed empirically in Chapters Four and Five, there is both theoretical and empirical evidence to support the hypothesis that capital market imperfections exist and result in a lower cost of capital for internal funds relative to external funds (i.e., new debt and equity finance). The theoretical rationale for the hypothesis that internal finance is less costly than the issuance of new shares or debt has already been rigorously developed in this thesis.[3] The general form of this model may be expressed algebraically as follows:

$$mrr(RD^*, \mathbf{X}, \mathbf{Y}) = mcc(RD^*, \mathbf{Z}) \qquad (2)$$

The arguments of the *mrr* and *mcc* equations are defined as follows:

RD^*= the optimal level of pharmaceutical R&D investment
X =a vector of variables influencing expected returns to pharmaceutical R&D
Y =a vector of variables influencing the expected costs of pharmaceutical R&D
Z =a vector of variables influencing the firm's cost of capital

Hence, the optimal level of R&D is implicit within the above equation. The general solution to this model is thus a function of the vectors **X**, **Y**, and **Z**.

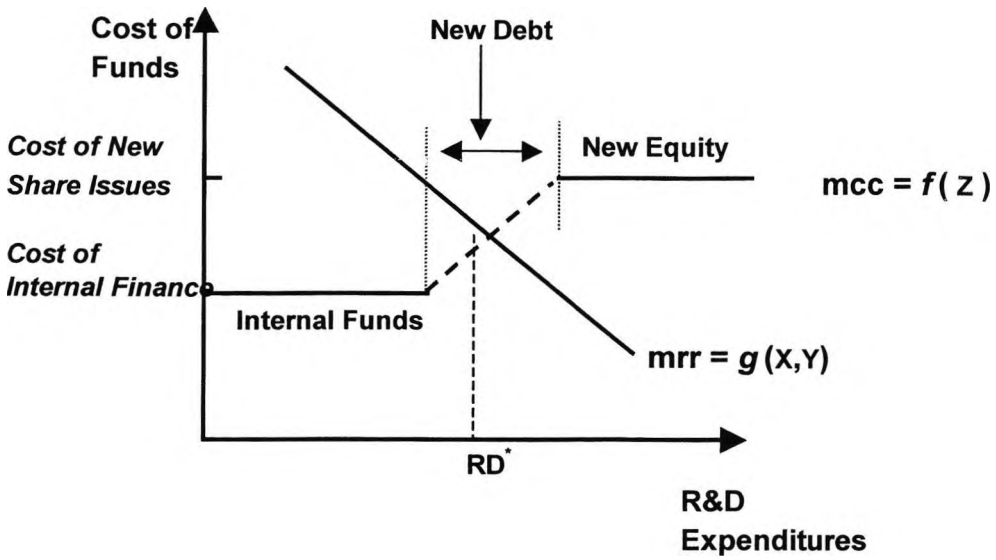
[3] The five principle arguments put forth in Chapter Three were based upon transaction costs, tax advantages, asymmetric information, agency problems, and the costs of financial distress. For a full theoretical development of this hypothesis refer to the aforementioned chapter.

$$RD^{*} = f(\mathbf{X}, \mathbf{Y}, \mathbf{Z}) \qquad (3)$$

Equation (3) clearly implies that any change in one or more of the variables contained in the **X**, **Y**, or **Z** vectors is likely to alter the optimal level of R&D. This equilibrium condition is depicted graphically in Figure 6.2.

Figure 6.2

The Optimal Level of R&D Expenditures with Financing Constraints



In the context of the above graph, it is easy to see how changes in the demand for R&D (shifts in the *mrr* curve) and changes in the level of internal funds affect the optimal level of R&D investment (refer to Figures 3.4 and 3.5 in Chapter Three).

Section 4.3: *Model Specifications & the Influence of Price Controls on Expected Returns from R&D*

Before presenting the model specifications used in this chapter to estimate the effect of pharmaceutical price controls on firm R&D investment, it will first be necessary to discuss how, theoretically, price controls are expected to influence the optimal level of R&D. As was presented first in Chapter Four, the general model specification for the determinants of pharmaceutical R&D intensity is the following:

$$RDS_{it} = f(E\pi_t, CF_{it-1}, Pct_{it}) \tag{4}$$

The dependent and independent variables are defined as follows:

RDS_{it} = research and development expenditures divided by total firm sales for the ith firm in year t.

$E\pi_t$ = an index of the expected profitability of *R&D* investments.

CF_{it-1} = cash flow for firm i in period t-1 divided by sales in period t-1.

Pct_{it} = the percentage of the ith firm's sales accounted for by pharmaceutical sales in year t.

This specification was demonstrated to be quite robust when estimating models using both U.S. firm data (Chapter Four) and international firm data (Chapter Five). The key issue to be addressed in this chapter, however, deals with the way in which pharmaceutical price controls will enter into the above specification. A reasonable assumption is that price controls will impact the aforementioned model—and hence the equilibrium level of R&D investment— via their influence on the expected rate of return from R&D on the margin. In the context of equation (1), the *mrr* for project i, this will be captured by the first term of the numerator—the expected discounted stream of future drug revenues. Formally, this assumption may be expressed as the following condition:[4]

[4] It should be noted that for condition (5) to hold, the expected elasticity of total revenues with respect to project i's future prescription sales volume must be—in absolute terms—less than unity, i.e. inelastic. Thus, if for example, a Medicare prescription drug benefit is passed into law, and is accompanied by mandated prescription drug price controls, the net impact would be a reduction in total sales revenues. In fact, in two recent and independent studies by Muse and Lewin VHI Inc. have concluded that this would indeed be the case. Specifically, they found that the revenue gains from universal prescription drug coverage would be outweighed by revenue losses resulting from Medicare rebates, increased use of generic substitutes, and increased price competition from managed-care options (Grabowski 1994). Thus, it is reasonable to expect condition (5) to hold in the event of U.S. price controls on pharmaceuticals.

$$E(R_i)_{PC} < E(R_i)_{\sim PC} \quad (5)$$

The variables in this inequality are defined as the following:

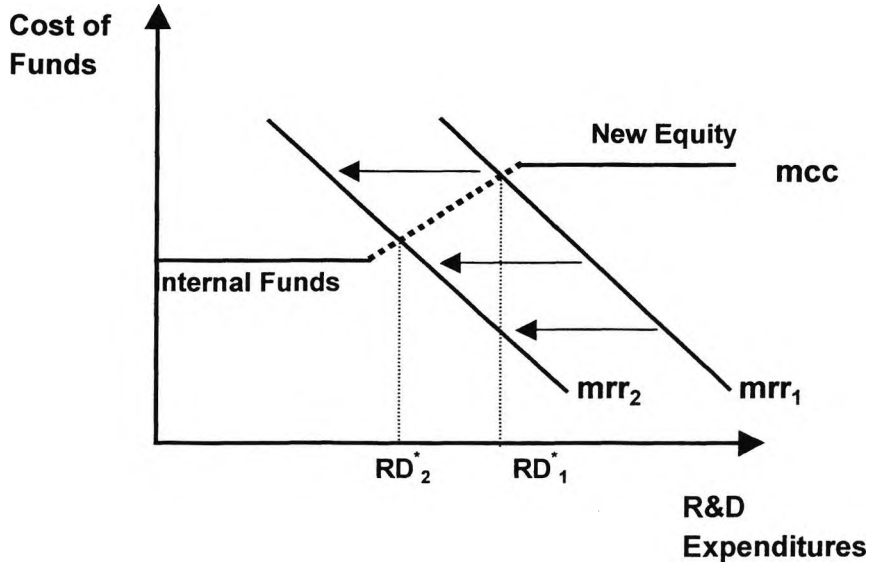
$E(R_i)_{PC}$ = the expected discounted stream of revenues generated by R&D project *i* when price controls are imposed on the pharmaceutical product(s) developed under project *i*.

$E(R_i)_{\sim PC}$ = the expected discounted stream of revenues generated by R&D project *i* when price controls *are not* imposed on the pharmaceutical product(s) developed under project *i*.

Clearly, if inequality (5) holds, the expected marginal rate of return on *all* R&D projects (the *mrr* schedule) will decrease. This may be graphically represented by an inward shift in the *mrr* schedule—the demand for R&D investment. This is shown below in Figure 6.3.

Figure 6.3

An Decrease in the Demand for R&D Resulting from a New U.S. Policy Imposing Price Controls on Pharmaceuticals

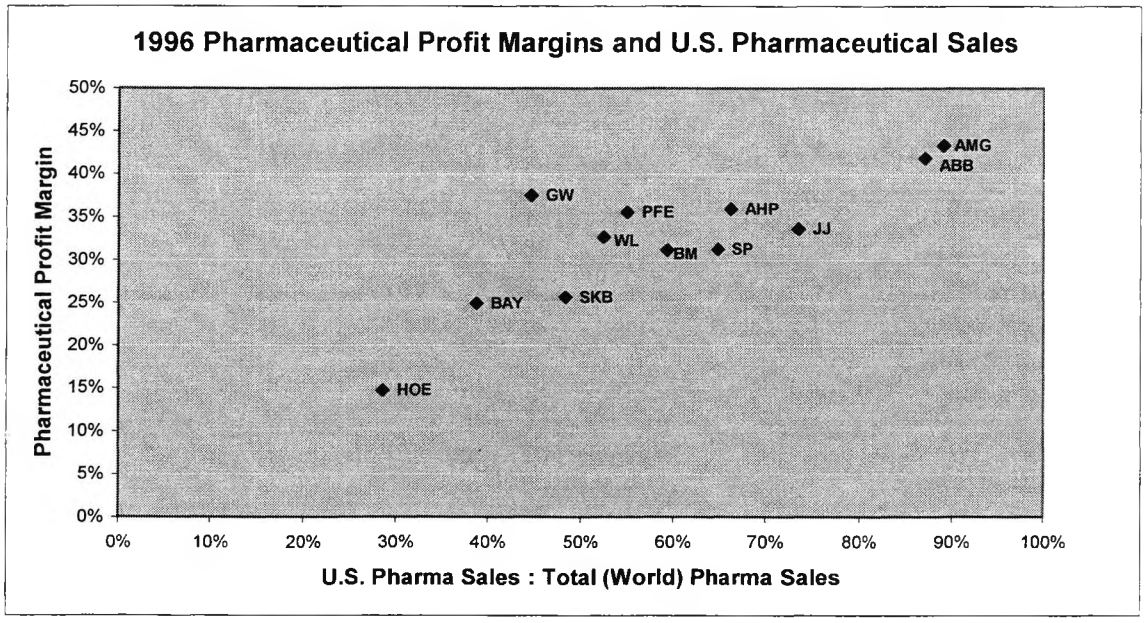


Thus, theoretically, it is expected that price controls will have a negative impact on firm R&D investment. To test this hypothesis empirically, it is first necessary to determine the extent to which pharmaceutical price controls affect the profitability of a firm's pharmaceutical operations. To measure this effect, the relationship between firm pharmaceutical profit margins and the percentage of total firm pharmaceutical sales accounted for by U.S. pharmaceutical sales was examined. As discussed previously, because the U.S. pharmaceutical market is the *only* major drug market with no form of regulated prices, the ratio of U.S. pharmaceutical sales to total firm pharmaceuticals sales is one measure of the extent to which price controls affect the firm's pharmaceutical business. In one extreme circumstance, firms whose pharmaceutical sales are entirely U.S. sales will not be affected by price controls. Conversely, in the other extreme circumstance, firms whose drug sales are entirely ex-U.S. sales will operate in an environment where all prescription drug prices are regulated. Clearly, it is to be expected that the larger the proportion of a firm's pharmaceutical sales that are U.S. sales, the higher the profit margin on the firm's pharmaceutical operations.

Using 1996 data, the only year data on the percent of pharmaceutical sales accounted for by U.S. pharmaceutical sales were available, a simple graph was developed. As Figure 6.4 shows, there exists a very strong linear relationship between pharmaceutical profit margins and the proportion of firm pharmaceutical sales that are U.S. sales. At this point it should be emphasized that, due to the small sample sizes used in this chapter, caution should be taken when considering the conclusions drawn from the forthcoming analyses. Indeed, the linear profit margin "function" depicted below (in Figures 6.4 and 6.5), and the regression analyses that appear later in the chapter, are based on sample sizes of $n = 12$ and $n = 48$, respectively.

Figure 6.4

The Relationship Between Firm Pharmaceutical Profit Margins and the Percent of Pharmaceutical Sales that are U.S. Sales



The observed positive relationship between pharmaceutical profit margins and the percent of pharmaceutical sales that are U.S. pharmaceutical sales—as seen in Figure 6.4—is central to the forthcoming empirical analyses that will estimate the impact price controls have on firm investment in R&D. First, however, a closer examination of these data will prove instructive.

Section 4.4: *The Profitability of Firm Pharmaceutical Operations*

To estimate the linear relationship observed in Figure 6.4, a classical ordinary least squares (OLS) univariate regression was run. The simple model had the following functional form:

$$PM_i = \beta_0 + \beta_1(\%US_i) + \varepsilon_i \qquad (6)$$

The variables in equation (5) are defined as follows:

PM_i = Firm *i's* pharmaceutical profit margin, and

$\%US_i$ = The percent of firm *i's* pharmaceutical sales that were U.S. sales

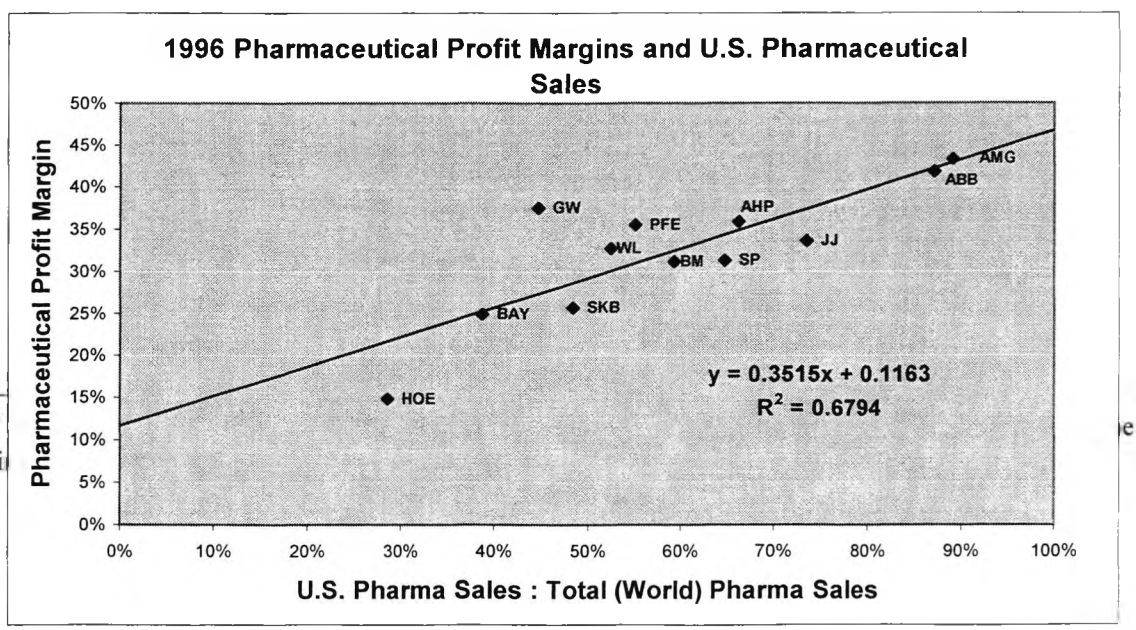
Regression results, which were estimated using Microsoft TSP E-Views, are summarized below in equation (7), and illustrated in Figure 6.5. The t-statistics appear underneath the estimated coefficients, and full regression results are reported in Appendix 1.

$$PM_i = \underset{(2.47)}{0.116} + \underset{(4.60)}{0.352(\%US_i)} \qquad R^2/F = 0.68/21.2 \qquad (7)$$

This equation is graphically displayed below with the data from the twelve firms in the sample.

Figure 6.5

The Relationship Between Firm Pharmaceutical Profit Margins and the Percent of Pharmaceutical Sales That Are U.S. Sales[5]



The regression model demonstrates that a fairly strong linear relationship exists between firm pharmaceutical profitability and the proportion of firm pharmaceutical sales that are U.S. pharmaceutical sales.[6] Both the intercept and the slope coefficient are statistically significant at the 5% level with t-statistics of 2.5 and 4.6, respectively. This estimated relationship between PM_i and $\%US_i$ (which is named PCT_US in the regression) may be used to make some interesting distinctions between the profitability of the prescription drug market in the U.S. and in other countries.

In particular, one may interpret the slope coefficient of $\%US$ (0.35) as an estimate of the difference between the profitability of the average firm's U.S. and ex-U.S. pharmaceutical operations. This may demonstrated in the following way. While not reported separately, firms may be thought of as having essentially two pharmaceutical profit margins: the profit margin on their U.S. pharmaceutical sales and the profit margins on their ex-U.S. pharmaceutical sales. The reported profit margin for all of a firm's pharmaceutical sales is consequently a weighted-average of these two components. This is expressed mathematically as follows:

$$PM_i = (\%US_i)(PMU_i) + (1 - \%US_i)(PMX_i) \qquad (8)$$

Specifically, the variables are defined as follows:

PMU_i = The profit margin on firm i's U.S. pharmaceutical sales, and

PMX_i = The profit margin on firm i's ex-U.S. pharmaceutical sales

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[6] Another variable that was hypothesized to affect firm pharmaceutical profit margins was firm size—specifically the size of a firm's pharmaceutical operations. It was believed that economies of scale would influence pharmaceutical margins such that larger firms—with lower average pharmaceutical manufacturing costs—would, all else being constant, have higher profit margins than smaller scale firms with higher average manufacturing costs. The variable used to proxy the size of a firm's pharmaceutical operations was total firm pharmaceutical sales. This variable was not found to be a statistically significant predictor of pharmaceutical profit margins (various formulations of this variable were tested). This is most likely due to the fact that the firms in the sample were some of the largest pharmaceutical firms in the industry. Hence, variations in firm size at such large scales may not substantially alter average manufacturing costs. That is, $\left.\frac{\partial^2 (TC/Q)}{\partial Q^2}\right|_{Q=Large\_Scale} \approx 0$.

Differentiating equation (8) with respect to *%US* yields:

$$\frac{\partial(PM_t)}{\partial(\%US_t)} = PMU_t - PMX_t \qquad (9)$$

While intuitively obvious, the above result allows for a direct empirical estimation of the average difference between U.S. and ex-U.S. pharmaceutical profit margins. Therefore, based on data reported by the twelve aforementioned pharmaceutical firms, over the period from 1994-1997, the following pharmaceutical profit margins were estimated:

Table 6.3: Estimated Pharmaceutical Profit Margins

Mean Pharmaceutical Profit Margin	Regression Estimate
U.S. Sales	46.8%
Ex-U.S. Sales	11.6%
Difference	35.2%

These results are easily seen in the context of Figure 6.4. The intercept of 11.6%, which is the predicted pharmaceutical profit margin for a firm with no U.S. pharmaceutical sales, may reasonably be interpreted as the pharmaceutical profit margin in an environment where all prescription drug prices are regulated. Similarly, extrapolating along the regression equation to a *%US* value of 100%, indicates a predicted pharmaceutical profit margin of 46.8%. This estimate may be interpreted as the profit margin in an environment without pharmaceutical price regulation.[7] While these estimates are based on a relatively small sample of firms—because of the limited availability of data—they do represent the first estimate to date of the relationship between firm pharmaceutical profitability and the extent to which a firm's pharmaceutical sales are subjected to price controls. The results from this simple analysis will now be used to empirically estimate the impact price controls have on pharmaceutical R&D investment—and, more interestingly, the impact a *new* U.S. policy, one imposing pharmaceutical price controls, will have on future R&D investment.

Section 4.5: *The Empirical Influence of Pharmaceutical Price Controls on R&D Investment*

We have estimated the statistical relationship between pharmaceutical price controls and pharmaceutical profitability as well as the role of pharmaceutical profitability—through profit expectations—in determining a firm's level of R&D investment. It is now appropriate to bring the two together to directly estimate the influence of price controls on R&D investment.

As was discussed earlier, it is the impact of pharmaceutical price controls on firm pharmaceutical profitability—and hence the expectation of future profitability—that will deterministically affect firm investment in pharmaceutical R&D. Mathematically, this implicit relationship between pharmaceutical price controls and pharmaceutical R&D investment is seen as follows:

$$RDS_{it} = f\left[E\pi(\%US), CFM_{it}, Pct_{it}\right] \tag{10}$$

where,

$$\frac{\partial(RDS)}{\partial(\%US)} = \frac{\partial(RDS)}{\partial(E\pi)} \cdot \frac{\partial(E\pi)}{\partial(\%US)} \tag{11}$$

and,

$$\frac{\partial(RDS)}{\partial(E\pi)} > 0 \tag{12}$$

$$\frac{\partial(E\pi)}{\partial(\%US)} > 0 \tag{13}$$

implying that,

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[7] The reader is referred to footnote 1 for a discussion of the appropriate interpretation of this statement.

$$\frac{\partial(RDS)}{\partial(\%US)} > 0 \qquad (14)$$

The implication of (14) is straightforward. The greater the proportion of a firm's pharmaceutical sales that are not regulated (i.e., not subject to price controls), the greater the level of firm investment in R&D. To test this hypothesis formally, a slightly modified model was estimated. However, before moving into the analyses, the differences between the forthcoming model(s) and the models from Chapters Four and Five are briefly reviewed.

Unlike the models that were estimated in Chapters Four and Five, the models estimated in this chapter were based on a much smaller sample size (n = 48). The reason for this was the limited availability of data on the percent of a firm's pharmaceutical sales accounted for by U.S. sales. In fact, these data were available for only one year—1996. Therefore, it was deemed inappropriate to include years that were more than 2 years removed from 1996 (complete data for 1998 were not available). This decision was made because the composition of firm pharmaceutical sales (i.e., U.S. and ex-U.S.) was believed to fluctuate over time. This fluctuation, it was assumed, would be minimal over short time horizons—i.e., two years. However, over many years it is likely that such fluctuations would grow more substantial.[8]

The other major difference between the models estimated in this chapter and those estimated in the previous two chapters is the formulation of the profit expectations variable. Because of the short time series, the highly significant industry-wide measure of firm profit expectations—used in the earlier models—was not found to be statistically significant. Therefore, individual firm pharmaceutical profit margins were used. This slightly different approach allowed for cross-sectional variations in firm pharmaceutical profit expectations.[9]

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[8] In fact, there were two firms (Johnson & Johnson and Abbott Laboratories) that did report this data over several years prior to 1996. Fluctuations were observed to be minor and within a few percentage points of one another over short periods of time (i.e., one to two years).

[9] This profit expectations variable was also tested in the earlier models. However, the statistical performance of this variable was marginal and not as robust as the industry-wide variables included in the final models. As was discussed in detail in the earlier chapters, different variable formulations for profit expectations performed very differently over the various time periods studied. Possibly, in the mid-to-late

Therefore, the model specification to be estimated is modified only slightly from equation (4):

$$RDS_{it} = f(E\pi_{it}, CF_{it-1}, Pct_{it}) \qquad (15)$$

Section 5.1: Statistical Findings

Using classical ordinary least squares, a linear model was estimated using data from the twelve firms in the sample over the period from 1994-1997. Full regression results and diagnostics are reported in Appendix 1.

Table 6.4: A Model of the Determinants of Pharmaceutical R&D (Specification 1)

Dependent Variable: RDS
Method: Least Squares

Sample: 1 48
Included observations: 48

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	0.004789	0.012190	0.392899	0.6963
CFM	0.119770	0.046799	2.559266	0.0140
PCT	0.075855	0.022323	3.398023	0.0015
PMARG	0.102963	0.042730	2.409640	0.0202
R-squared	0.758082	F-statistic		45.95995
Adjusted R-squared	0.741588	Prob(F-statistic)		0.000000

As is seen in Table 6.4, all three independent variables are significant at the .05 level. Interestingly, the control variable *Pct* is significant at the .01 level, and has virtually the same coefficient as the estimates reported in Chapters Four and Five. Furthermore, the

1990's, firms were more reliant on their own success in the pharmaceutical business when formulating their expected returns to R&D. This might be deemed reasonable in light of the fact that firms by this time were well acquainted with their R&D success with rational drug design and no longer focused as much externally to the industry-wide returns from this new R&D process. In any event, in order to estimate a model over the 1994-1997 time period—when fixed-effect specifications were impractical—it was clearly necessary to establish a profit expectation formulation that varied cross-sectionally by firm.

0.76 R-squared for this model is also in the range of the explained sum of squares from the earlier U.S. and international models (0.69-0.76). A notable difference, however, between the previously estimated models and the current model, is the noticeably smaller coefficient on the cash flow variable and the profit expectations variable, 0.12 and 0.10, respectively. In light of the vastly different time period and firms studied, this should not be too surprising. In fact, the results from this model provide considerable evidence in support of the *general* model specification employed. In both of the earlier Grabowski and Vernon studies and in the models estimated in this and previous chapters, the general model has demonstrated considerable stability under both different specifications and samples.

In addition to estimating a model that implicitly accounted for the impact of pharmaceutical price controls on R&D investment, two other specifications were estimated that allowed the price control proxy variable to enter explicitly into the regression equation. These models are presented and discussed next.

From theoretical standpoint, pharmaceutical price controls will influence R&D investment through the impact they have on the expected future returns from pharmaceutical R&D. As was demonstrated previously, the proxy price control variable *%US* and *Pmarg* are highly correlated ($\rho = 0.68$). However, in spite of this, it was considered a reasonable possibility that both variables captured different aspects of the expected returns to pharmaceutical R&D. To test this statistically, both variables were entered into the linear regression model as explanatory variables. Not surprisingly, because of their high degree of co-linearity, neither variable—when entered into the model simultaneously—was found to be statistically significant. The remaining variable's coefficient estimates and their respective t-statistics remained virtually unchanged from the model with *Pmarg* alone. The statistical results from this model are presented below in Table 6.5.

Table 6.5: A Model of the Determinants of Pharmaceutical R&D (Specification 2)

Dependent Variable: RDS Method: Least Squares				
Sample: 1 48 Included observations: 48				
Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.004086	0.013456	-0.303646	0.7629
CFM	0.119466	0.046190	2.586427	0.0132
PCT	0.075432	0.022034	3.423360	0.0014
PMARG	0.054006	0.053699	1.005708	0.3202
PCT_US	0.042046	0.028549	1.472768	0.1481
R-squared	0.769699	F-statistic		35.92807
Adjusted R-squared	0.748276	Prob(F-statistic)		0.000000

The second model specification that allowed $\%US$ to enter explicitly into the regression model used $\%US$ as the sole proxy variable for expected returns. From a theoretical perspective, however, this specification was viewed as marginally inferior to the model that used *Pmarg* alone. This was believed to be the case because of the theoretical formulation of $E\pi$. That is, $E\pi$ was theorized to be a composite function, one where $E\pi = Pm\arg(\%US)$. Nevertheless, this model was estimated to test the robustness of the general model specification. The results from this regression are reported below in Table 6.6.

Table 6.6: A Model of the Determinants of Pharmaceutical R&D (Specification 3)

Dependent Variable: RDS Method: Least Squares				
Sample: 1 48 Included observations: 48				
Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.001109	0.013128	-0.084481	0.9331
CFM	0.133384	0.044074	3.026389	0.0041
PCT	0.074951	0.022032	3.401901	0.0014
PCT_US	0.059820	0.022424	2.667655	0.0107
R-squared	0.764282	F-statistic		47.55457
Adjusted R-squared	0.748210	Prob(F-statistic)		0.000000

The statistical results from Specification 3 indicate that *%US* is a significant predictor of *RDS* when entered into the regression equation as the only proxy for expected returns. This model specification, however, likely overestimates the impact of pharmaceutical price controls. This is because %US, as a profit expectation variable, forces profit expectations to zero in an environment where all pharmaceutical sales are ex-US sales (or an environment where all prescription drug prices are regulated). This is clearly an erroneous assumption. In the composite variable formulation, a %US value of 0 corresponds to a pharmaceutical profit margin of 11.6% (the intercept in the OLS regression of *Pmarg* on %US). This bias would be analogous to using the composite variable formulation and forcing the intercept of the regression of *Pmarg* on US% to zero. In fact, this restriction was imposed in order to compare the two results. The findings confirmed that, if the theoretically correct formulation *is* a composite formulation, the use of %US as a proxy for expected returns does indeed bias the coefficient upward. These findings are summarized in Table 6.7 below.

Table 6.7

A Demonstration of Coefficient Bias under Mis-specification

Variable Formulation	Coefficient	Regression Estimate
$E\pi = Pm\arg(\alpha + \beta(\%US))$	$\frac{\partial(RDS)}{\partial(Pm\arg)} \cdot \frac{\partial(Pm\arg)}{\partial(\%US)}$	$0.103 \times 0.352 = 0.0363$
$E\pi = \%US$	$\frac{\partial(RDS)}{\partial(\%US)}$	0.0598
$E\pi = Pm\arg(\beta\%US)$	$\frac{\partial(RDS)}{\partial(Pm\arg)} \cdot \frac{\partial(Pm\arg)}{\partial(\%US)}$	$0.103 \times 0.533 = 0.0549$

Section 5.2: *Other Specifications: Non-Linear Profit Expectations*

In addition to the three main specifications just presented, other specifications were also tested. Specifically, models that allowed for interaction effects and non-linear profit expectations were also estimated. The findings from these regressions are summarized below in Table 6.8. Complete statistical results from these regressions are

reported in Appendix 1. An interesting observation common to all of these regressions was a higher level of statistical significance associated with the $E\pi$ variable when profit expectations were assumed to be non-linear. A theoretical explanation for these findings is not clear.[10] The policy implications associated with such profit expectations, however, are quite substantial as will be seen in the following section.

Table 6.8

Regression Equations Using Different Formulations For Expected Pharmaceutical Profitability

Type of Profit Expectations	Intercept	*Pmarg*	*CFM*	*Pct*	R^2/F	$\partial(RDS)/\partial(\%US)$ [11]
Linear	0.00 (0.39)	0.10 (2.41)	0.12 (2.56)	(0.08) (3.40)	0.76/46.0	0.036
Quadratic	0.02 (2.38)	0.19 (3.58)	0.09 (2.05)	0.08 (3.99)	0.79/54.5	(0.13)(*Pmarg*)
Cubic	0.03 (3.53)	0.29 (4.08)	0.09 (1.98)	0.09 (4.33)	0.80/59.2	(0.31)(*Pmarg*)^2
Interactive (with %US)	0.01 (1.58)	0.14 (4.10)	0.09 (2.12)	0.08 (4.08)	0.80/59.4	(.05)(*%US*) + (.14)(*Pmarg*)

[10] One possibility may be that there exists a strong association between a firm's pharmaceutical profit margin and the number of blockbuster drugs the firm currently has on the market (this seems intuitively quite obvious). Therefore, firms that have had phenomenal recent success developing blockbusters may have dramatically different (and disproportionate) expectations surrounding their ability to develop and bring to market such blockbusters.

[11] These derivatives have been simplified using regression estimates. The algebraic versions are shown below. First, however, for notation convenience the following conventions will be adopted: R= *RDS*, P=*Pmarg*, U=*%US*, β_P = coefficient estimate for Pmarg, and β_U = coefficient estimate for %US (in regression of Pmarg on %US). Therefore we have the following:

Linear: $$\frac{\partial R}{\partial U} = \frac{\partial R}{\partial P} \cdot \frac{\partial P}{\partial U} = \beta_P \cdot \beta_U$$

Quadratic: $$\frac{\partial R}{\partial U} = \frac{\partial R}{\partial P} \cdot \frac{\partial P}{\partial U} = 2\beta_P \cdot \beta_U \cdot P(U)$$

Cubic: $$\frac{\partial R}{\partial U} = \frac{\partial R}{\partial P} \cdot \frac{\partial P}{\partial U} = 3\beta_P \cdot \beta_U \cdot [P(U)]^2$$

Interaction: $$\frac{\partial R}{\partial U} = \beta_I \left[\frac{\partial P}{\partial U} \cdot U + P(U) \right]$$

Before proceeding to the next section, it should be mentioned that the classic OLS models estimated in this section were found to be econometrically sound. That is, tests for heteroskedasticity and within group serial correlation were not able to reject the null hypothesis of no heteroskedasticity and no serial correlation. For this reason, the OLS models were deemed a sufficient method of estimation. Moreover, given the relatively small sample size (n=48), fixed- and random-effects models specifications were not estimated. Indeed, a fixed-effects model specification would have been impractical given the short time series of data available on each firm (4 years).[12]

Section 6: Conclusions and Policy Implications

The past decade has witnessed a dramatic escalation in the political pressures to contain the growing cost of health care in the United States—with a particular focus being paid to the cost of prescription medications. This is not surprising, since prescription pharmaceuticals are the least insured element of basic health care in the United States and their prices have been increasing faster than inflation. Consequently, as was discussed earlier in the chapter, many efforts have been made to pass into law universal insurance coverage—with *price-regulated* pharmaceuticals as part of the basic benefit package. This was the case under the Health Security Act proposed earlier this decade by the Clinton Administration. Despite the fact that congress failed to pass this Act into law, the mounting pressures and growing health care costs are likely to result in new proposals in the near future. From a public policy perspective, it is not only necessary to consider the immediate cost savings associated with prescription drug price controls, but how those price controls will impact current and future levels of investment in pharmaceutical R&D—and hence innovation.

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[12] Random-effects models were estimated. However, the statistical results were not as good as those associated with the classical OLS model. For this reason the analysis focuses on the OLS specification.

In this chapter several models were estimated to empirically address the role prescription drug price controls play in a firm's decision to allocate funds to R&D. The analysis in this chapter represents the first effort to date that has sought to directly quantify this impact. Using robust and well-established models for the determinants of pharmaceutical R&D investment, slight modifications were made to the formulation of the firm profit expectations variable (which is a proxy for the expected returns to pharmaceutical R&D investment). These modifications—or more precisely the expanded data set and re-formulation of the profit expectations variable—were used to estimate several specifications. The results confirmed the hypothesis that regulated prescription drug prices stifle investment in pharmaceutical R&D. The magnitude of this effect varied depending on the model specification employed. Using the various specifications estimated in this chapter, elasticities of R&D investment with respect to price controls (i.e., the proportion of a firm's pharmaceutical sales that were not subjected to price controls) were calculated using industry mean values (see Table 6.9).[13] These elasticities are reported in Table 6.10 below.

Table 6.9

Industry Average Values (1994-1997)

Variable	Industry Average
RDS	11.51%
Pmarg	31.86%
%US	58.98%

[13] Recall that the elasticity is defined as follows: $E_{RD,PC} = \frac{\partial(RDS)}{\partial(\%US)} \cdot \frac{\%US_{Ave}}{RDS_{Ave}}$.

Table 6.10

Estimated Elasticities of R&D Investment with Respect to Price Controls

Model Specification	Estimated Elasticity
Specification 1 (Linear Profit Expectations)	(0.036)(5.13) = 0.19
Specification 3 (%US used as $E\pi$ proxy)	(0.059)(5.13) = 0.31
Quadratic Profit Expectations (Pmarg)	(0.13)(0.32)(5.13) = 0.22
Cubic Profit Expectations (Pmarg)	$(0.31)(0.32)^2(5.13) = 0.17$
Interaction Formulation (%US*Pmarg)	[(0.05)(0.59)+(0.14)(0.32)][5.13] = 0.38

The interpretation of these estimated elasticities deserves a brief explanation. Recall that the proxy variable for price controls was defined as the percentage of firm pharmaceutical sales that were U.S. pharmaceutical sales (i.e., non-price regulated pharmaceutical sales). Therefore, the appropriate interpretation for these elasticities is the following: the percentage increase (decrease) in R&D investment intensity that is associated with a one percentage point increase (decrease) in the proportion of firm pharmaceutical sales that are U.S. sales. However, in the context of a public policy perspective, point elasticities do not provide the best estimate of the consequences of a new U.S. policy mandating price controls on pharmaceuticals (in terms of the reduction in current and future R&D investment). Therefore, a more interesting application of the models estimated in this chapter would be to predict the *actual* impact on firm R&D investment resulting from such a policy —i.e., the passing of an Act similar to the previously proposed Health Security Act. These estimates could then be expressed in terms of the resulting percentage reduction in R&D investment intensity.

In order to simulate the impact of a new policy in the U.S. that imposes prescription drug price controls, it is first necessary to observe how such a policy would affect the variable *%US*. In the event of such a policy, the proportion of a firm's global pharmaceutical sales not price regulated would be zero. That is, the U.S. pharmaceutical market—the only non-regulated drug market in the world—would become regulated, and *all* prescription drug prices would be subject to price controls. In the context of the way the price control proxy variable was designed (to capture the proportion of non-price regulated drug sales to total worldwide drug sales), this would imply that *%US* would be

driven to zero. This is analogous to saying that the prices of prescription drugs in the U.S. would be subject to the same type of price controls found in most ex-U.S. markets.[14] Therefore, to estimate the impact that pharmaceutical price controls in the U.S. would have on R&D investment intensity, the models were evaluated at the independent variables' mean values. The models were first evaluated using the mean value for $\%US$ (58.98%) and then at $\%US = 0$.[15] The difference between the two forecasted R&D intensities is thus a measure of the impact that U.S. pharmaceutical price controls would have on R&D investment. These results are summarized in Table 6.11 below. Appendix A contains a complete set of calculations.

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[14] In fact, a major provision in the Health Security Act stipulated that negotiated Medicare rebates on new drugs in the U.S. would be referenced to the outcomes of regulatory processes in other countries. Specifically, for products introduced at a lower price in any one of 21 referenced countries, the Secretary of Health and Human Services could negotiate a rebate as high as the difference between the manufacturer's average retail price in the U.S. and any price at which the drugs were available to wholesalers in these countries. The 21 specified countries are: Australia, Austria, Belgium, Canada, Denmark, Germany, Finland, France, Iceland, Ireland, Italy, Japan, Luxembourg, the Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, and the United Kingdom.

[15] It should be noted that using the partial derivatives calculated earlier in the chapter is not appropriate for these estimations (with the exception of the linear model—i.e., specification 1). This is because of the functional form of these derivatives (i.e., they are non-constants). Consequently, the estimated *RDS* equations were simply evaluated at the mean %US value and zero. That is, the change in *RDS* was estimated in the following way: $\Delta RDS = RDS(\%US = .59) - RDS(\%US = 0)$. All other variables were left at their 1994-1997 mean values. The mean *CFM* and *PCT* were calculated to be 0.289 and 0.566, respectively. Finally, it should be pointed out that because $x_{Ave}^2 \neq \frac{1}{n}\sum_{i=1}^{n} x_i^2$ the following mean values were used when calculating the change in RDS for the non-linear profit expectations models:

1) $\frac{1}{48}\sum_{i=1}^{12}\sum_{t=1}^{4}(Pm\arg_{it})^2 = 0.1122$

2) $\frac{1}{48}\sum_{i=1}^{12}\sum_{t=1}^{4}(Pm\arg_{it})^3 = 0.0433$

3) $\frac{1}{48}\sum_{i=1}^{12}\sum_{t=1}^{4}(Pm\arg_{it})(\%US_{it}) = 0.2005$

Table 6.11

Estimating the Impact of U.S. Prescription Drug Price Controls on Pharmaceutical R&D Intensity (Based on 1994-1997 Mean Values)

Model Specification	RDS w/o U.S. Price Controls	RDS w/ U.S. Price Controls	Δ RDS	Percentage Decrease in RDS
Specification 1 (Linear $E\pi$)	0.1151	0.0942	0.0209	18.12%
Specification 3	0.1151	0.0798	0.0353	30.64%
Quadratic $E\pi$	0.1151	0.0964	0.0187	16.28%
Cubic $E\pi$	0.1151	0.1030	0.0120	10.47%
Interaction $E\pi$	0.1151	0.0864	0.0287	24.98%

As the results in Table 6.11 indicate, the impact of a new U.S. policy that regulates prescription drug prices will have a very substantial impact on R&D investment. Specifically, the results obtained in this chapter show that such a policy could reduce R&D investment intensity anywhere from approximately 10% to 30%. This would indeed have a substantial negative impact on future drug innovation.[16]

The expected returns from R&D investment have been demonstrated—both in this chapter and in earlier chapters—to have a significant role in the level of R&D investment undertaken by the firm. Furthermore, it has been shown that pharmaceutical price controls have a direct effect on the expected returns from pharmaceutical R&D. In this chapter this implicit relationship—between expected profitability and price controls

[16] These estimates of the reduction in R&D intensity that would result from U.S. pharmaceutical price controls may well be an underestimate. This is because price controls would also be expected to have a significant—and negative—effect on firm cash flows—another major determinant of firm R&D intensity (the primary thesis of this dissertation—refer to Chapters Two-Five). Hence, the estimated range of a 10%-30% reduction in R&D intensity resulting from U.S. price controls should probably be viewed as a conservative estimate. In fact, using a similar approach to that employed in the formulation of the profit expectations variable, the relationship between %*US* and lagged cash flow margins was examined. However, the presence of a statistical relationship was not observed. This may be due to the fact that pharmaceutical revenues are only one component of a firm's total revenues—recall the definition of the *Pct* variable. Hence, the impact of U.S. pharmaceutical price controls would not have as direct an impact on lagged firm cash flows as they would on pharmaceutical profitability.

—has been exploited to empirically estimate the impact a new U.S. policy (like the previously proposed Health Security Act) would have on R&D investment—and, consequently, on new drug innovation. The findings in this chapter suggest that, from a public policy perspective, these regulations would have a precipitous effect on the incentives for research and development in innovative new medicines. Over the long term, such a policy would be expected to have a negative net effect on patient and societal welfare.

Chapter Seven

Conclusions

General Discussion

In this thesis we investigated several hypotheses relating to the economics of pharmaceutical R&D investment. In particular, we endeavored to demonstrate that, contrary to the classical theory of investment, where external finance is considered a perfect substitute for internal finance, in the pharmaceutical industry, the source of investment finance *does* matter. Specifically, we hypothesized that internal finance, or a firm's cash flow, is an important determinant of pharmaceutical R&D investment.

We based our hypothesis on several theoretical underpinnings. These included, for example, transaction costs, tax advantages, and asymmetric information. Our research subsequently uncovered an abundance of empirical evidence suggesting that the classical theory is not appropriate for pharmaceutical R&D finance. Indeed, our findings suggest that internal finance is an *extremely* important determinant of pharmaceutical R&D investment.

In addition to testing this hypothesis in our research, we also considered, within the framework of our empirical models, the economic implications of pharmaceutical price controls in the United States—an extremely controversial political issue at the present. According to our research, such a policy would have a negative, and quite substantial, impact on future levels of R&D investment through decreased profit incentives to innovate.

Principle Research Findings and Conclusions

Chapter Two set the stage for our research by mapping out the landscape of the scientific, and economic, particulars of the pharmaceutical R&D process. The unique nature of pharmaceutical R&D, unlike other forms of industrial R&D, we argued, was one reason to expect capital market imperfections in the markets for external pharmaceutical R&D finance. Consequently, this chapter described the scientific process

by which new drugs are discovered, developed, and brought to market. In addition to formally presenting the clinical aspects of pharmaceutical R&D, the key economic characteristics were also introduced and discussed extensively. Specifically, issues relating to the costs, risks, and rewards of pharmaceutical R&D were reviewed in great detail. In essence, Chapter Two introduced many of the concepts and ideas that formed the basis from which our thesis was built.

In Chapter Three we integrated existing theoretical work on capital market imperfections into a specialized case for pharmaceutical R&D finance. The rationale for R&D financing constraints were developed around transaction costs, tax advantages, asymmetric information, financial distress, and agency problems. Indeed, much literature has been published on these topics over the years—some more so than others. However, in Chapter Three, we adapted, and slightly modified this research to the specific case for pharmaceutical R&D investment. For example, Tobin's well-known q-theory of investment was modified to specifically consider the pharmaceutical R&D investment decision in the presence of capital market imperfections. This modified q-theoretic framework was then employed to elucidate how, under certain circumstances—such as those argued to be present in the markets for pharmaceutical R&D finance, market imperfections can result in different acceptance criteria being used for potential investment projects, depending on how the project is financed—i.e., with internal or external finance.

A particular case was made for the existence of asymmetric information in the pharmaceutical industry. This was argued to be an especially relevant rationale for financing constraints because new information, which is obtained via R&D, is the primary means by which firms in the pharmaceutical industry compete. That is, the competitive intelligence obtained from pharmaceutical R&D plays a central role in the race to patent and develop new compounds. As such, much of this information is not publicly available. Consequently, we argued, there are likely to be significant information gaps between firm managers and potential investors. This information gap may be particularly large in light of the uncertainty and long development times associated with pharmaceutical R&D.

In sum, Chapter Three adapted existing, and quite general, theoretical work on capital market imperfections to the specific case of the pharmaceutical R&D investment decision. This theory—which was demonstrated to be well grounded in microeconomic principles—set the stage for the forthcoming empirical analyses in Chapters Four, Five, and Six.

In Chapter Four, we estimated several models of the determinants of pharmaceutical R&D investment using data from 11 large U.S. firms from 1976 to 1996. We began this chapter by first reviewing and critiquing the earlier empirical work conducted by ourselves and other authors. Several potential problems, both econometric and data-driven, were identified with these earlier studies, and various remedies were recommended. To address the data-driven problems, we employed the use of a more complete data set—one that is not generally available to the public. This new data set provided us with the necessary, and previously unavailable, financial data on firm pharmaceutical operations. Consequently, we were able to eliminate the data deficiencies that hampered the earlier studies. After constructing this more complete, and contemporary data set, we estimated several different models of the determinants of R&D investment. Indeed, extensive analyses were undertaken and multiple specifications and variable formulations were tested. Using the most theoretically grounded and statistically sound models, a series of regression results were reported. Specifically, we reported results over two different time periods: The 1976-to-1996-time period and the 1983-to-1996-time period. Our results strongly affirmed the hypothesis that cash flows positively influence R&D investment. In fact, in every model estimated, over both time periods, the cash flow variable was found to be highly statistically significant. Subsequent statistical diagnostics revealed that the 'best' model was the random-effects specification. Consequently, the results from this model were deemed the most appropriate for testing our hypothesis, and, in general, drawing inferences. In our models employing this specification, the estimated coefficient on the cash flow variable ranged between 0.14 and 0.24 and 0.11 to 0.23 for the 1976-to-1996 and 1983-to-1996-time periods, respectively.

These coefficient estimates, we showed, could be interpreted as an approximate dollar change in R&D investment corresponding to a $1 change in firm cash flows. Thus, a $1 dollar decrease in firm cash flows could, for example, result in a $0.11-$0.24

decrease in firm R&D investment. Therefore, for model based on large U.S. pharmaceutical firms, we concluded that firm cash flows were, indeed, an important determinant of firm R&D investment. This result, we argued, demonstrated that the classical model of firm investment was inappropriate for analyzing pharmaceutical R&D investment.

Finally, in closing, we emphasized that, despite the strong evidence in favor of the capital market imperfections hypothesis, it was important not to generalize these findings to the *global* pharmaceutical marketplace. Indeed, the analyses undertaken in Chapter Four were based on a relatively small sample of exclusively U.S.-based firms. Consequently, we stressed, it remained unclear what role, if any, cash flows played in the larger global pharmaceutical marketplace.

In Chapter Five we estimated R&D investment models based on a larger, and *international*, sample of firms. Specifically, we obtained financial data on 60 of the world's leading pharmaceutical firms. This we emphasized was, to our knowledge, the first empirical study to-date of pharmaceutical R&D investment that utilized international firm data. Consequently, we argued, models based on this larger—and more globally representative—sample of firms would provide a better test of our capital market imperfections hypothesis. Moreover, we hoped, this research would enable us to uncover some new, and previously unexamined, characteristics of the global pharmaceutical industry.

Our findings in Chapter Five contributed substantially to the body of evidence supporting the hypothesis that internally generated cash flows, because of their lower cost of capital relative to external debt and equity, are an important determinant of pharmaceutical R&D investment. Specifically, we found that cash flows exerted a statistically significant, and positive, influence on a firm's level of R&D investment.

In this chapter we estimated models using 3 subsets of the aforementioned 60-firm sample—2 U.S.- and European-firm models and a Japanese-firm model. Specifically, because of the limited availability of financial data for many of the international firms, we estimated a 24-firm model over the 1984-to-1997-time period, a 32-firm model over the 1991-to-1997-time period, and a 28-firm, exclusively Japanese model, over the 1994-to-1997-time period. Econometric analyses indicated that for both

the 24-firm and 32-firm samples, the Feasible-Generalized LSDV model was the 'best' model from which inferences should be drawn. This finding, we argued, resulted from the systematic differences across firms that could not be captured by other variables. The fact that systematic differences across firms remained, we contended, was not surprising given the heterogeneous nature of the firms in these samples. In contrast to this finding, however, for the Japanese-firm model, diagnostic tests revealed that a random-effects model was the most appropriate specification. This finding, as was the case with the U.S. models in Chapter Four, was presumably due to the relative homogeneity of the firms in then sample. A summary of these findings, as they relate to the cash flow variable, is provided below in Table 7.1.

Table 7.1

Estimated Lagged Cash Flow Variable Coefficients in Selected Model Specifications

(Values in parentheses are t-statistics)

Firm Sample and Selected Model Specification	Coefficient of Lagged Cash Flow Variable (CF)
24 U.S.-and European-based Firms (1984-1997)	0.08
Best Model: Feasible Generalized LSDV	(4.86)
32 U.S.-and European-based Firms (1991-1997)	0.10
Best Model: Feasible Generalized LSDV	(6.92)
28 Japanese Firms (1994-1997)	0.17
Best Model: Random Effects	(2.83)

In addition to further substantiating the important role of cash flows in the pharmaceutical R&D investment decision, several new facts were also uncovered. Specifically, we uncovered evidence suggesting that significant structural changes occurred in the pharmaceutical industry during the 1990's. This finding, we pointed out, would make models based on more recent data—i.e., data from the decade of the

1990's—the most appropriate models for answering questions relating to contemporary policy issues. Furthermore, we also investigated whether or not there were significant differences in R&D investment behaviors between U.S.- and European-based firms. The evidence suggested that there were differences, but these findings were only marginally statistically significant.

In Chapter Six we deviated slightly from our central line of inquiry to address a particularly relevant policy issue in the United States: Pharmaceutical price controls. Using the robust models developed in Chapters Four and Five, we attempted to estimate the impact pharmaceutical price controls in the U.S. would have on future investment in R&D.

We started our analysis by drawing a sharp distinction between pharmaceutical price regulation in the U.S. and other non-U.S. countries. Specifically, we argued that pharmaceutical prices are more regulated in markets outside the U.S. We then developed an empirical measure intended to proxy the extent to which a firm's pharmaceutical sales were subjected to price controls—the ratio of U.S.-to-total pharmaceutical sales. Hence, the lower this ratio, the more a firm's pharmaceutical business is affected by price regulation. We acknowledged that this type of binary classification for pharmaceutical price controls was indeed a simplification; however, we argued, it was a reasonable proxy due to the much greater degree of pharmaceutical price regulation in markets outside the U.S.

Using data from the mid 1990's—the only period for which data were available to construct our price control proxy variable—we were able to estimate the impact, in terms of reduced R&D investment, of a new U.S. price control policy on pharmaceuticals. We found that such a policy would result in a 10.47% to 30.64% decline in R&D investment spending. Consequently, from a public policy perspective, whilst reducing the burden on consumers in the short run, the long run impact of such a policy would be to reduce innovative activity in pharmaceutical research. This would, most likely, have a negative effect on future patient and societal welfare.

In this thesis, we have attempted to demonstrate that pharmaceutical R&D is unlike any other major form of industrial R&D, and, because of these unique characteristics (both scientific and economic), we argued, internal finance becomes an

important determinant of firm R&D investment. Our empirical findings supported this hypothesis overwhelmingly. In addition to this, we demonstrated how our investment models could be used to predict the economic implications of new public policies. Throughout the course of this research many new facts pertaining to the global pharmaceutical R&D industry were uncovered. As such, this represents advancement in the current knowledge in this field.

Appendix 1

Regression Equation 4.4.1: OLS Regression Results for 11 U.S. Firms (1976-1996)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1976 1996
Included observations: 21
Number of cross-sections used: 11
Total panel (unbalanced) observations: 228

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.136024	0.020914	-6.504133	0.0000
CFM?	0.223888	0.027778	8.059888	0.0000
PCT?	0.079668	0.009436	8.443163	0.0000
PMARG?	0.481827	0.085499	5.635442	0.0000
R-squared	0.734601	Mean dependent var		0.085100
Adjusted R-squared	0.731046	S.D. dependent var		0.036873
S.E. of regression	0.019123	Sum squared resid		0.081912
Log likelihood	580.6677	F-statistic		206.6705
Durbin-Watson stat	1.670063	Prob(F-statistic)		0.000000

Regression Equation 4.4.2: OLS Regression Results for 11 U.S. Firms (1976-1996)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1976 1996
Included observations: 21
Number of cross-sections used: 11
Total panel (unbalanced) observations: 228

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.056607	0.006804	-8.320025	0.0000
CFM?	0.245837	0.024443	10.05757	0.0000
PCT?	0.076458	0.009033	8.464254	0.0000
(NEWRX?)/1000	0.161765	0.023274	6.950412	0.0000
R-squared	0.750731	Mean dependent var		0.085100
Adjusted R-squared	0.747392	S.D. dependent var		0.036873
S.E. of regression	0.018533	Sum squared resid		0.076934
Log likelihood	587.8158	F-statistic		224.8757
Durbin-Watson stat	1.526896	Prob(F-statistic)		0.000000

Regression Equation 4.4.3: OLS Regression Results for 11 U.S. Firms (1976-1996)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1976 1996
Included observations: 21
Number of cross-sections used: 11
Total panel (unbalanced) observations: 228

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.112077	0.020565	-5.449766	0.0000
CFM?	0.213568	0.026589	8.032306	0.0000
PCT?	0.080486	0.009004	8.939095	0.0000
PMARG?	0.265719	0.093145	2.852749	0.0047
(NEWRX?)/1000	0.125732	0.026163	4.805730	0.0000

R-squared	0.759507	Mean dependent var	0.085100
Adjusted R-squared	0.755194	S.D. dependent var	0.036873
S.E. of regression	0.018244	Sum squared resid	0.074225
Log likelihood	591.9020	F-statistic	176.0659
Durbin-Watson stat	1.692615	Prob(F-statistic)	0.000000

Regression Equation 4.4.4: OLS Regression Results for 11 U.S. Firms (1983-1996)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1983 1996
Included observations: 14
Number of cross-sections used: 11
Total panel (balanced) observations: 151

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.104598	0.030141	-3.468248	0.0005
CFM?	0.215164	0.033723	6.380260	0.0000
PCT?	0.084160	0.011276	7.463412	0.0000
PMARG?	0.341065	0.110631	3.082889	0.0027

R-squared	0.701754	Mean dependent var	0.098640
Adjusted R-squared	0.675259	S.D. dependent var	0.035357
S.E. of regression	0.020149	Sum squared resid	0.059678
Log likelihood	377.3640	F-statistic	117.4687
Durbin-Watson stat	1.861995	Prob(F-statistic)	0.000000

Regression Equation 4.4.5: OLS Regression Results for 11 U.S. Firms (1983-1996)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1983 1996
Included observations: 14
Number of cross-sections used: 11
Total panel (balanced) observations: 151

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.051626	0.017247	-2.992441	0.0038
CFM?	0.245193	0.030446	8.053436	0.0000
PCT?	0.084318	0.011847	7.116973	0.0000
NEWRX?/1000	0.132926	0.055789	2.382211	0.0117

R-squared	0.703620	Mean dependent var	0.098640
Adjusted R-squared	0.667980	S.D. dependent var	0.035357
S.E. of regression	0.020373	Sum squared resid	0.061015
Log likelihood	375.6904	F-statistic	112.5932
Durbin-Watson stat	1.910575	Prob(F-statistic)	0.000000

Regression Equation 4.4.6: OLS Regression Results for 11 U.S. Firms (1983-1996)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1983 1996
Included observations: 14
Number of cross-sections used: 11
Total panel (balanced) observations: 151

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.103542	0.029239	-3.541230	0.0005
CFM?	0.215838	0.033650	6.414122	0.0000
PCT?	0.084857	0.011431	7.422979	0.0000
PMARG?	0.275776	0.125270	2.201443	0.0278
NEWRX?/1000	0.061453	0.057770	1.063751	0.2892

R-squared	0.682163	Mean dependent var	0.098640
Adjusted R-squared	0.673455	S.D. dependent var	0.035357
S.E. of regression	0.020205	Sum squared resid	0.059601
Log likelihood	377.4612	F-statistic	78.33879
Durbin-Watson stat	1.758344	Prob(F-statistic)	0.000000

Regression Equation 4.5.1: Least Squares Dummy Variable (Fixed Effects) Regression Results for 11 U.S. Firms (1976-1996)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1976 1996
Included observations: 21
Number of cross-sections used: 11
Total panel (unbalanced) observations: 228

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.169900	0.029450	5.769189	0.0000
PMARG?	0.620116	0.083625	7.415451	0.0000
PCT?	0.078786	0.011827	6.661467	0.0000
Fixed Effects				
_ABB--C	-0.167656			
_AHP--C	-0.191033			
_BMS--C	-0.165964			
_JJ--C	-0.147094			
_LIL--C	-0.147231			
_MRK--C	-0.173248			
_PFE--C	-0.159694			
_SP--C	-0.165451			
_SYN--C	-0.142154			
_UPJ--C	-0.137839			
_WL--C	-0.163880			

R-squared	0.887302	Mean dependent var	0.085100
Adjusted R-squared	0.880456	S.D. dependent var	0.036873
S.E. of regression	0.012749	Sum squared resid	0.034783
Log likelihood	678.3112	F-statistic	842.4380
Durbin-Watson stat	1.650269	Prob(F-statistic)	0.000000

Regression Equation 4.5.2: Least Squares Dummy Variable (Fixed Effects) Regression Results for 11 U.S. Firms (1976-1996)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1976 1996
Included observations: 21
Number of cross-sections used: 11
Total panel (unbalanced) observations: 228

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.241953	0.020779	11.64405	0.0000
NEWRX?/1000	0.158992	0.016994	9.355893	0.0000
PCT?	0.089529	0.010761	8.319872	0.0000
Fixed Effects				
_ABB--C	-0.069262			
_AHP--C	-0.090922			
_BMS--C	-0.063552			
_JJ--C	-0.042527			
_LIL--C	-0.054023			
_MRK--C	-0.082221			
_PFE--C	-0.059914			
_SP--C	-0.069661			
_SYN--C	-0.053611			
_UPJ--C	-0.042711			
_WL--C	-0.058164			

R-squared	0.899465	Mean dependent var	0.085100
Adjusted R-squared	0.893358	S.D. dependent var	0.036873
S.E. of regression	0.012041	Sum squared resid	0.031029
Log likelihood	691.3309	F-statistic	957.3065
Durbin-Watson stat	1.819286	Prob(F-statistic)	0.000000

Regression Equation 4.5.3: Least Squares Dummy Variable (Fixed Effects) Regression Results for 11 U.S. Firms (1976-1996)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1976 1996
Included observations: 21
Number of cross-sections used: 11
Total panel (unbalanced) observations: 228

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.132402	0.026049	5.082851	0.0000
PMARG?	0.466688	0.075154	6.209777	0.0000
NEWRX?/1000	0.134313	0.016170	8.306423	0.0000
PCT?	0.071520	0.010340	6.916837	0.0000
Fixed Effects				
_ABB--C	-0.152407			
_AHP--C	-0.176691			
_BMS--C	-0.152971			
_JJ--C	-0.135515			
_LIL--C	-0.129090			
_MRK--C	-0.153733			
_PFE--C	-0.145144			
_SP--C	-0.148640			
_SYN--C	-0.121804			
_UPJ--C	-0.120828			
_WL--C	-0.152578			

R-squared	0.914876	Mean dependent var	0.085100
Adjusted R-squared	0.909281	S.D. dependent var	0.036873
S.E. of regression	0.011106	Sum squared resid	0.026273
Log likelihood	710.2999	F-statistic	763.0759
Durbin-Watson stat	1.673057	Prob(F-statistic)	0.000000

Regression Equation 4.5.4: Least Squares Dummy Variable (Fixed Effects) Regression Results for 11 U.S. Firms (1983-1996)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1983 1996
Included observations: 14
Number of cross-sections used: 11
Total panel (balanced) observations: 151

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.090977	0.031397	2.897629	0.0044
PMARG?	0.581785	0.088755	6.554958	0.0000
PCT?	0.063268	0.011575	5.466043	0.0000
Fixed Effects				
_ABB--C	-0.127059			
_AHP--C	-0.154733			
_BMS--C	-0.132511			
_JJ--C	-0.116148			
_LIL--C	-0.098251			
_MRK--C	-0.127398			
_PFE--C	-0.117317			
_SP--C	-0.119696			
_SYN--C	-0.082937			
_UPJ--C	-0.087095			
_WL--C	-0.132578			

R-squared	0.914435	Mean dependent var	0.098640
Adjusted R-squared	0.906316	S.D. dependent var	0.035357
S.E. of regression	0.010822	Sum squared resid	0.016045
Log likelihood	476.5369	F-statistic	732.0602
Durbin-Watson stat	1.539503	Prob(F-statistic)	0.000000

Regression Equation 4.5.5: Least Squares Dummy Variable (Fixed Effects) Regression Results for 11 U.S. Firms (1983-1996)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1983 1996
Included observations: 14
Number of cross-sections used: 11
Total panel (balanced) observations: 151

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.233079	0.024789	9.402386	0.0000
NEWRX?/1000	0.082151	0.044594	1.842222	0.0676
PCT?	0.077745	0.012863	6.043888	0.0000
Fixed Effects				
_ABB--C	-0.037039			
_AHP--C	-0.060776			
_BMS--C	-0.035274			
_JJ--C	-0.013481			
_LIL--C	-0.016816			
_MRK--C	-0.048284			
_PFE--C	-0.023371			
_SP--C	-0.030755			
_SYN--C	-0.011631			
_UPJ--C	-0.000752			
_WL--C	-0.026307			

R-squared	0.890316	Mean dependent var	0.098640
Adjusted R-squared	0.879908	S.D. dependent var	0.035357
S.E. of regression	0.012253	Sum squared resid	0.020568
Log likelihood	457.7884	F-statistic	556.0221
Durbin-Watson stat	1.839098	Prob(F-statistic)	0.000000

Regression Equation 4.5.6: Least Squares Dummy Variable (Fixed Effects) Regression Results for 11 U.S. Firms (1983-1996)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1983 1996
Included observations: 14
Number of cross-sections used: 11
Total panel (balanced) observations: 151

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.091886	0.031458	2.920947	0.0041
PMARG?	0.567352	0.090653	6.258486	0.0000
NEWRX?/1000	0.032438	0.040229	0.806336	0.4215
PCT?	0.062428	0.011636	5.364953	0.0000
Fixed Effects				
_ABB--C	-0.133046			
_AHP--C	-0.160668			
_BMS--C	-0.138492			
_JJ--C	-0.122281			
_LIL--C	-0.104139			
_MRK--C	-0.133186			
_PFE--C	-0.123247			
_SP--C	-0.125499			
_SYN--C	-0.088761			
_UPJ--C	-0.092871			
_WL--C	-0.138474			

R-squared	0.914842	Mean dependent var	0.098640
Adjusted R-squared	0.906076	S.D. dependent var	0.035357
S.E. of regression	0.010836	Sum squared resid	0.015969
Log likelihood	476.8970	F-statistic	487.0107
Durbin-Watson stat	1.725061	Prob(F-statistic)	0.000000

Regression Equation 4.7.1: Feasible Generalized Least Squares Regression Results (Common Intercept) for 11 U.S. Firms (1976-1996)

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1976 1996
Included observations: 21
Number of cross-sections used: 11
Total panel (unbalanced) observations: 228

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.139363	0.015914	-8.757088	0.0000
CFM?	0.215850	0.020899	10.32801	0.0000
PMARG?	0.505096	0.065544	7.706161	0.0000
PCT?	0.075692	0.007801	9.702510	0.0000

Weighted Statistics			
R-squared	0.841187	Mean dependent var	0.101327
Adjusted R-squared	0.839060	S.D. dependent var	0.047472
S.E. of regression	0.019044	Sum squared resid	0.081242
Log likelihood	615.1322	F-statistic	395.4891
Durbin-Watson stat	1.788595	Prob(F-statistic)	0.000000

Unweighted Statistics			
R-squared	0.732661	Mean dependent var	0.085100
Adjusted R-squared	0.729080	S.D. dependent var	0.036873
S.E. of regression	0.019193	Sum squared resid	0.082511
Durbin-Watson stat	1.639231		

Regression Equation 4.7.2: Feasible Generalized Least Squares Regression Results (Common Intercept) for 11 U.S. Firms (1976-1996)

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1976 1996
Included observations: 21
Number of cross-sections used: 11
Total panel (unbalanced) observations: 228

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.052141	0.005126	-10.17116	0.0000
CFM?	0.249410	0.019297	12.92501	0.0000
NEWRX?/1000	0.146702	0.017865	8.211746	0.0000
PCT?	0.074396	0.007819	9.514320	0.0000

Weighted Statistics			
R-squared	0.862342	Mean dependent var	0.101234
Adjusted R-squared	0.860498	S.D. dependent var	0.049522
S.E. of regression	0.018496	Sum squared resid	0.076634
Log likelihood	618.8084	F-statistic	467.7398
Durbin-Watson stat	1.644914	Prob(F-statistic)	0.000000

Unweighted Statistics			
R-squared	0.750155	Mean dependent var	0.085100
Adjusted R-squared	0.746809	S.D. dependent var	0.036873
S.E. of regression	0.018554	Sum squared resid	0.077111
Durbin-Watson stat	1.476860		

Regression Equation 4.7.3: Feasible Generalized Least Squares Regression Results (Common Intercept) for 11 U.S. Firms (1976-1996)

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1976 1996
Included observations: 21
Number of cross-sections used: 11
Total panel (unbalanced) observations: 228

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.119831	0.015367	-7.797744	0.0000
CFM?	0.203352	0.020024	10.15521	0.0000
PMARG?	0.323587	0.070037	4.620233	0.0000
NEWRX?/1000	0.109124	0.019531	5.587181	0.0000
PCT?	0.077800	0.007418	10.48736	0.0000

Weighted Statistics			
R-squared	0.863734	Mean dependent var	0.102764
Adjusted R-squared	0.861290	S.D. dependent var	0.048743
S.E. of regression	0.018154	Sum squared resid	0.073491
Log likelihood	628.3223	F-statistic	353.3755
Durbin-Watson stat	1.761365	Prob(F-statistic)	0.000000

Unweighted Statistics			
R-squared	0.757782	Mean dependent var	0.085100
Adjusted R-squared	0.753437	S.D. dependent var	0.036873
S.E. of regression	0.018309	Sum squared resid	0.074758
Durbin-Watson stat	1.622439		

Regression Equation 4.7.4: Feasible Generalized Least Squares Regression Results (Common Intercept) for 11 U.S. Firms (1983-1996)

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1983 1996
Included observations: 14
Number of cross-sections used: 11
Total panel (balanced) observations: 151

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.102168	0.019462	-5.249483	0.0000
CFM?	0.204239	0.024961	8.610861	0.0000
PMARG?	0.362144	0.077859	4.651403	0.0000
PCT?	0.077228	0.008505	9.082313	0.0000

Weighted Statistics			
R-squared	0.911402	Mean dependent var	0.127727
Adjusted R-squared	0.909594	S.D. dependent var	0.066237
S.E. of regression	0.019916	Sum squared resid	0.058306
Log likelihood	408.5948	F-statistic	495.0617
Durbin-Watson stat	1.940501	Prob(F-statistic)	0.000000

Unweighted Statistics			
R-squared	0.677718	Mean dependent var	0.098640
Adjusted R-squared	0.671141	S.D. dependent var	0.035357
S.E. of regression	0.020276	Sum squared resid	0.060434
Durbin-Watson stat	1.772519		

Regression Equation 4.7.5: Feasible Generalized Least Squares Regression Results (Common Intercept) for 11 U.S. Firms (1983-1996)

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1983 1996
Included observations: 14
Number of cross-sections used: 11
Total panel (balanced) observations: 151

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.051691	0.011264	-4.589816	0.0000
CFM?	0.268282	0.022653	11.84192	0.0000
PCT?	0.075318	0.008294	9.083764	0.0000
NEWRX?/1000	0.123560	0.036373	3.396938	0.0006

Weighted Statistics			
R-squared	0.934561	Mean dependent var	0.131147
Adjusted R-squared	0.933225	S.D. dependent var	0.078137
S.E. of regression	0.020191	Sum squared resid	0.059930
Log likelihood	405.8385	F-statistic	675.7833
Durbin-Watson stat	2.095036	Prob(F-statistic)	0.000000

Unweighted Statistics			
R-squared	0.672173	Mean dependent var	0.098640
Adjusted R-squared	0.665483	S.D. dependent var	0.035357
S.E. of regression	0.020450	Sum squared resid	0.061474
Durbin-Watson stat	1.840279		

Regression Equation 4.7.6: Feasible Generalized Least Squares Regression Results (Common Intercept) for 11 U.S. Firms (1983-1996)

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1983 1996
Included observations: 14
Number of cross-sections used: 11
Total panel (balanced) observations: 151

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.100675	0.019207	-5.241351	0.0000
CFM?	0.219921	0.025072	8.771544	0.0000
PCT?	0.076997	0.008113	9.490287	0.0000
PMARG?	0.293826	0.090954	3.230422	0.0017
NEWRX?/1000	0.063221	0.040751	1.551409	0.1276

Weighted Statistics			
R-squared	0.916328	Mean dependent var	0.127915
Adjusted R-squared	0.909926	S.D. dependent var	0.066563
S.E. of regression	0.019977	Sum squared resid	0.058266
Log likelihood	408.6412	F-statistic	413.8247
Durbin-Watson stat	1.842075	Prob(F-statistic)	0.000000

Unweighted Statistics			
R-squared	0.678320	Mean dependent var	0.098640
Adjusted R-squared	0.669507	S.D. dependent var	0.035357
S.E. of regression	0.020326	Sum squared resid	0.060322
Durbin-Watson stat	1.701175		

Regression Equation 4.8.1: Feasible Generalized Least Squares Regression Results (Fixed Effects Specification) for 11 U.S. Firms (1976-1996)

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)
Date: 06/22/00 Time: 14:52
Sample: 1976 1996
Included observations: 21
Number of cross-sections used: 11
Total panel (unbalanced) observations: 228

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.167495	0.025288	6.623439	0.0000
PCT?	0.057411	0.009883	5.808869	0.0000
PMARG?	0.654494	0.072788	8.991733	0.0000
Fixed Effects				
_ABB--C	-0.164775			
_AHP--C	-0.188379			
_BMS--C	-0.165276			
_JJ--C	-0.150156			
_LIL--C	-0.141740			
_MRK--C	-0.164692			
_PFE--C	-0.156586			
_SP--C	-0.159879			
_SYN--C	-0.134321			
_UPJ--C	-0.129697			
_WL--C	-0.162941			

Weighted Statistics			
R-squared	0.873616	Mean dependent var	0.089756
Adjusted R-squared	0.865939	S.D. dependent var	0.034436
S.E. of regression	0.012608	Sum squared resid	0.034020
Log likelihood	699.5550	F-statistic	739.6279
Durbin-Watson stat	1.761006	Prob(F-statistic)	0.000000

Unweighted Statistics			
R-squared	0.885458	Mean dependent var	0.085100
Adjusted R-squared	0.878500	S.D. dependent var	0.036873
S.E. of regression	0.012853	Sum squared resid	0.035352
Durbin-Watson stat	1.618195		

Regression Equation 4.8.2: Feasible Generalized Least Squares Regression Results (Fixed Effects Specification) for 11 U.S. Firms (1976-1996)

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1976 1996
Included observations: 21
Number of cross-sections used: 11
Total panel (unbalanced) observations: 228

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.231869	0.019580	11.84242	0.0000
PCT?	0.089420	0.010477	8.535257	0.0000
NEWRX?/1000	0.150942	0.014826	10.18069	0.0000
Fixed Effects				
_ABB--C	-0.064810			
_AHP--C	-0.086699			
_BMS--C	-0.059526			
_JJ--C	-0.038559			
_LIL--C	-0.049006			
_MRK--C	-0.077099			
_PFE--C	-0.055674			
_SP--C	-0.065018			
_SYN--C	-0.048270			
_UPJ--C	-0.038248			
_WL--C	-0.054624			

Weighted Statistics			
R-squared	0.912055	Mean dependent var	0.090632
Adjusted R-squared	0.906713	S.D. dependent var	0.039294
S.E. of regression	0.012002	Sum squared resid	0.030824
Log likelihood	705.7573	F-statistic	1109.671
Durbin-Watson stat	2.021322	Prob(F-statistic)	0.000000

Unweighted Statistics			
R-squared	0.898942	Mean dependent var	0.085100
Adjusted R-squared	0.892803	S.D. dependent var	0.036873
S.E. of regression	0.012073	Sum squared resid	0.031190
Durbin-Watson stat	1.799019		

Regression Equation 4.8.3: Feasible Generalized Least Squares Regression Results (Fixed Effects Specification) for 11 U.S. Firms (1976-1996)

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1976 1996
Included observations: 21
Number of cross-sections used: 11
Total panel (unbalanced) observations: 228

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.107352	0.021845	4.914339	0.0000
PCT?	0.058271	0.008744	6.664457	0.0000
PMARG?	0.552791	0.065155	8.484255	0.0000
NEWRX?/1000	0.126126	0.013827	9.121759	0.0000
Fixed Effects				
_ABB--C	-0.160392			
_AHP--C	-0.185350			
_BMS--C	-0.163284			
_JJ--C	-0.148243			
_LIL--C	-0.134169			
_MRK--C	-0.156698			
_PFE--C	-0.153487			
_SP--C	-0.154540			
_SYN--C	-0.124460			
_UPJ--C	-0.125473			
_WL--C	-0.163877			

Weighted Statistics			
R-squared	0.928725	Mean dependent var	0.091898
Adjusted R-squared	0.924040	S.D. dependent var	0.039863
S.E. of regression	0.010986	Sum squared resid	0.025710
Log likelihood	731.6619	F-statistic	925.1359
Durbin-Watson stat	1.785358	Prob(F-statistic)	0.000000

Unweighted Statistics			
R-squared	0.913519	Mean dependent var	0.085100
Adjusted R-squared	0.907835	S.D. dependent var	0.036873
S.E. of regression	0.011194	Sum squared resid	0.026691
Durbin-Watson stat	1.637524		

Regression Equation 4.8.4: Feasible Generalized Least Squares Regression Results (Fixed Effects Specification) for 11 U.S. Firms (1983-1996)

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1983 1996
Included observations: 14
Number of cross-sections used: 11

Total panel (balanced) observations: 151

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.080322	0.023703	3.388732	0.0009
PCT?	0.050348	0.008879	5.670235	0.0000
PMARG?	0.646760	0.070850	9.128638	0.0000
Fixed Effects				
_ABB--C	-0.135461			
_AHP--C	-0.163103			
_BMS--C	-0.141963			
_JJ--C	-0.128385			
_LIL--C	-0.104062			
_MRK--C	-0.131579			
_PFE--C	-0.125600			
_SP--C	-0.125589			
_SYN--C	-0.086405			
_UPJ--C	-0.091957			
_WL--C	-0.142365			

Weighted Statistics			
R-squared	0.969539	Mean dependent var	0.120189
Adjusted R-squared	0.966649	S.D. dependent var	0.058681
S.E. of regression	0.010716	Sum squared resid	0.015733
Log likelihood	500.3468	F-statistic	2180.295
Durbin-Watson stat	1.734576	Prob(F-statistic)	0.000000

Unweighted Statistics			
R-squared	0.913494	Mean dependent var	0.098640
Adjusted R-squared	0.905285	S.D. dependent var	0.035357
S.E. of regression	0.010881	Sum squared resid	0.016222
Durbin-Watson stat	1.498395		

Regression Equation 4.8.5: Feasible Generalized Least Squares Regression Results (Fixed Effects Specification) for 11 U.S. Firms (1983-1996)

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1983 1996
Included observations: 14
Number of cross-sections used: 11
Total panel (balanced) observations: 151

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.236495	0.022931	10.31349	0.0000
PCT?	0.069727	0.011925	5.847154	0.0000
NEWRX?/1000	0.080762	0.033145	2.436635	0.0161
Fixed Effects				
_ABB--C	-0.033334			
_AHP--C	-0.056746			
_BMS--C	-0.031756			
_JJ--C	-0.011513			
_LIL--C	-0.011941			
_MRK--C	-0.042435			
_PFE--C	-0.019280			
_SP--C	-0.025360			
_SYN--C	-0.005894			
_UPJ--C	0.005170			
_WL--C	-0.022330			

Weighted Statistics			
R-squared	0.961201	Mean dependent var	0.119881
Adjusted R-squared	0.957520	S.D. dependent var	0.059303
S.E. of regression	0.012223	Sum squared resid	0.020467
Log likelihood	478.1268	F-statistic	1697.029
Durbin-Watson stat	2.094878	Prob(F-statistic)	0.000000

Unweighted Statistics			
R-squared	0.889974	Mean dependent var	0.098640
Adjusted R-squared	0.879534	S.D. dependent var	0.035357
S.E. of regression	0.012272	Sum squared resid	0.020632
Durbin-Watson stat	1.810365		

Regression Equation 4.8.6: Feasible Generalized Least Squares Regression Results (Fixed Effects Specification) for 11 U.S. Firms (1983-1996)

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1983 1996
Included observations: 14
Number of cross-sections used: 11

Total panel (balanced) observations: 151

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.084696	0.023797	3.475048	0.0007
PCT?	0.049461	0.008967	5.516035	0.0000
PMARG?	0.629294	0.072977	8.623206	0.0000
NEWRX?/1000	0.039672	0.030552	1.298532	0.1963
Fixed Effects				
_ABB--C	-0.143217			
_AHP--C	-0.170763			
_BMS--C	-0.149647			
_JJ--C	-0.136206			
_LIL--C	-0.111776			
_MRK--C	-0.139193			
_PFE--C	-0.133252			
_SP--C	-0.133133			
_SYN--C	-0.094116			
_UPJ--C	-0.099483			
_WL--C	-0.149866			

Weighted Statistics			
R-squared	0.970450	Mean dependent var	0.120990
Adjusted R-squared	0.967408	S.D. dependent var	0.059453
S.E. of regression	0.010733	Sum squared resid	0.015667
Log likelihood	501.1860	F-statistic	1488.786
Durbin-Watson stat	1.849175	Prob(F-statistic)	0.000000

Unweighted Statistics			
R-squared	0.913906	Mean dependent var	0.098640
Adjusted R-squared	0.905043	S.D. dependent var	0.035357
S.E. of regression	0.010895	Sum squared resid	0.016144
Durbin-Watson stat	1.685502		

Regression Equation 4.9.1: Random Effects Model Specification for 11 U.S. Firms (1976-1996)

Dependent Variable: RDS?
Method: GLS (Variance Components)

Sample: 1976 1996
Included observations: 21
Number of cross-sections used: 11
Total panel (unbalanced) observations: 228

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.157633	0.016591	-9.501372	0.0000
CFM?	0.176710	0.028169	6.273180	0.0000
PCT?	0.080650	0.011025	7.314868	0.0000
PMARG?	0.600093	0.079093	7.587223	0.0000
Random Effects				
_ABB--C	-0.006944			
_AHP--C	-0.029332			
_BMS--C	-0.004866			
_JJ--C	0.013676			
_LIL--C	0.012190			
_MRK--C	-0.013222			
_PFE--C	0.000852			
_SP--C	-0.005157			
_SYN--C	0.016621			
_UPJ--C	0.021352			
_WL--C	-0.002569			

GLS Transformed Regression			
R-squared	0.881672	Mean dependent var	0.085100
Adjusted R-squared	0.880087	S.D. dependent var	0.036873
S.E. of regression	0.012769	Sum squared resid	0.036521
Durbin-Watson stat	1.604458		

Unweighted Statistics including Random Effects			
R-squared	0.887061	Mean dependent var	0.085100
Adjusted R-squared	0.885549	S.D. dependent var	0.036873
S.E. of regression	0.012474	Sum squared resid	0.034857
Durbin-Watson stat	1.639964		

Regression Equation 4.9.3: Random Effects Model Specification for 11 U.S. Firms (1976-1996)

Dependent Variable: RDS?
Method: GLS (Variance Components)

Sample: 1976 1996
Included observations: 21
Number of cross-sections used: 11
Total panel (unbalanced) observations: 228

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.061866	0.007379	-8.384283	0.0000
CFM?	0.241650	0.020505	11.78468	0.0000
PCT?	0.087980	0.010271	8.565829	0.0000
NEWRX?/1000	0.159893	0.016775	9.531687	0.0000
Random Effects				
_ABB--C	-0.006556			
_AHP--C	-0.027607			
_BMS--C	-0.001171			
_JJ--C	0.018980			
_LIL--C	0.008432			
_MRK--C	-0.018733			
_PFE--C	0.002534			
_SP--C	-0.006752			
_SYN--C	0.008998			
_UPJ--C	0.019593			
_WL--C	0.004073			

GLS Transformed Regression			
R-squared	0.895069	Mean dependent var	0.085100
Adjusted R-squared	0.893664	S.D. dependent var	0.036873
S.E. of regression	0.012024	Sum squared resid	0.032386
Durbin-Watson stat	1.812615		

Unweighted Statistics including Random Effects			
R-squared	0.899327	Mean dependent var	0.085100
Adjusted R-squared	0.897978	S.D. dependent var	0.036873
S.E. of regression	0.011778	Sum squared resid	0.031072
Durbin-Watson stat	1.845713		

Regression Equation 4.9.3: Random Effects Model Specification for 11 U.S. Firms (1976-1996)

Dependent Variable: RDS?
Method: GLS (Variance Components)

Sample: 1976 1996

Included observations: 21

Number of cross-sections used: 11
Total panel (unbalanced) observations: 228

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.140517	0.014767	-9.515629	0.0000
CFM?	0.144230	0.025124	5.740791	0.0000
PCT?	0.075574	0.009734	7.763644	0.0000
PMARG?	0.433779	0.072623	5.973058	0.0000
NEWRX?/1000	0.132534	0.016305	8.128391	0.0000
Random Effects				
_ABB--C	-0.007167			
_AHP--C	-0.030323			
_BMS--C	-0.006858			
_JJ--C	0.010723			
_LIL--C	0.014266			
_MRK--C	-0.010186			
_PFE--C	3.55E-05			
_SP--C	-0.004217			
_SYN--C	0.020408			
_UPJ--C	0.022319			
_WL--C	-0.005993			

GLS Transformed Regression			
R-squared	0.908819	Mean dependent var	0.085100
Adjusted R-squared	0.907184	S.D. dependent var	0.036873
S.E. of regression	0.011234	Sum squared resid	0.028142
Durbin-Watson stat	1.725628		

Unweighted Statistics including Random Effects			
R-squared	0.914525	Mean dependent var	0.085100
Adjusted R-squared	0.912992	S.D. dependent var	0.036873
S.E. of regression	0.010877	Sum squared resid	0.026381
Durbin-Watson stat	1.798726		

Regression Equation 4.9.4: Random Effects Model Specification for 11 U.S. Firms (1983-1996)

Dependent Variable: RDS?
Method: GLS (Variance Components)

Sample: 1983 1996
Included observations: 14
Number of cross-sections used: 11
Total panel (balanced) observations: 151

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.111548	0.018993	-5.873181	0.0000
CFM?	0.108087	0.030581	3.534420	0.0005
PCT?	0.069178	0.011156	6.200868	0.0000
PMARG?	0.528543	0.086248	6.128201	0.0000
Random Effects				
_ABB--C	-0.008046			
_AHP--C	-0.034540			
_BMS--C	-0.012317			
_JJ--C	0.005001			
_LIL--C	0.018230			
_MRK--C	-0.010811			
_PFE--C	0.001721			
_SP--C	-0.001859			
_SYN--C	0.031427			
_UPJ--C	0.029215			
_WL--C	-0.011444			

GLS Transformed Regression			
R-squared	0.905320	Mean dependent var	0.098640
Adjusted R-squared	0.903388	S.D. dependent var	0.035357
S.E. of regression	0.010990	Sum squared resid	0.017754
Durbin-Watson stat	1.649943		

Unweighted Statistics including Random Effects			
R-squared	0.913776	Mean dependent var	0.098640
Adjusted R-squared	0.912017	S.D. dependent var	0.035357
S.E. of regression	0.010488	Sum squared resid	0.016169
Durbin-Watson stat	1.701917		

Regression Equation 4.9.5: Random Effects Model Specification for 11 U.S. Firms (1983-1996)

Dependent Variable: RDS?
Method: GLS (Variance Components)

Sample: 1983 1996
Included observations: 14
Number of cross-sections used: 11
Total panel (balanced) observations: 151

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.028329	0.015045	-1.882887	0.0617
CFM?	0.233271	0.024303	9.598623	0.0000
PCT?	0.078525	0.012266	6.401963	0.0000
NEWRX?/1000	0.081333	0.044095	1.844506	0.0671
Random Effects				
_ABB--C	-0.008656			
_AHP--C	-0.031750			
_BMS--C	-0.006899			
_JJ--C	0.014445			
_LIL--C	0.010873			
_MRK--C	-0.019816			
_PFE--C	0.004612			
_SP--C	-0.002700			
_SYN--C	0.015808			
_UPJ--C	0.026419			
_WL--C	0.001810			
GLS Transformed Regression				
R-squared	0.884297	Mean dependent var		0.098640
Adjusted R-squared	0.881936	S.D. dependent var		0.035357
S.E. of regression	0.012149	Sum squared resid		0.021697
Durbin-Watson stat	1.907758			
Unweighted Statistics including Random Effects				
R-squared	0.890145	Mean dependent var		0.098640
Adjusted R-squared	0.887903	S.D. dependent var		0.035357
S.E. of regression	0.011838	Sum squared resid		0.020600
Durbin-Watson stat	1.940225			

Regression Equation 4.9.6: Random Effects Model Specification for 11 U.S. Firms (1983-1996)

Dependent Variable: RDS?
Method: GLS (Variance Components)

Sample: 1983 1996
Included observations: 14
Number of cross-sections used: 11
Total panel (balanced) observations: 151

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.116837	0.020413	-5.723608	0.0000
CFM?	0.109956	0.030665	3.585739	0.0005
PCT?	0.068746	0.011213	6.130799	0.0000
PMARG?	0.511439	0.088393	5.785937	0.0000
NEWRX?/1000	0.031280	0.040968	0.763540	0.4464
Random Effects				
_ABB--C	-0.008085			
_AHP--C	-0.034460			
_BMS--C	-0.012282			
_JJ--C	0.004950			
_LIL--C	0.018128			
_MRK--C	-0.010810			
_PFE--C	0.001733			
_SP--C	-0.001801			
_SYN--C	0.031258			
_UPJ--C	0.029202			
_WL--C	-0.011278			
GLS Transformed Regression				
R-squared	0.905139	Mean dependent var		0.098640
Adjusted R-squared	0.902540	S.D. dependent var		0.035357
S.E. of regression	0.011038	Sum squared resid		0.017788
Durbin-Watson stat	1.686845			
Unweighted Statistics including Random Effects				
R-squared	0.914099	Mean dependent var		0.098640
Adjusted R-squared	0.911745	S.D. dependent var		0.035357
S.E. of regression	0.010504	Sum squared resid		0.016108
Durbin-Watson stat	1.710756			

Grunfeld and Griliches (G&G) Profit Expectations Variable: Models Based on Lagged Firm Market Capitalization as Proxy for Profit Expectations (1987-1996)

G&G Equation 1: Classic Ordinary Least Squares

Dependent Variable: RD?
Method: Pooled Least Squares

Sample(adjusted): 1987 1996
Included observations: 10 after adjusting endpoints
Number of cross-sections used: 12
Total panel (balanced) observations: 120

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	40.60827	46.16422	0.879648	0.3809
CF?	0.373087	0.025159	14.82943	0.0000
V1?	-0.000535	0.001737	-0.308150	0.7585
PC?	82.14475	67.45980	1.217685	0.2258

R-squared	0.893327	Mean dependent var	742.9404
Adjusted R-squared	0.890568	S.D. dependent var	533.9026
S.E. of regression	176.6176	Sum squared resid	3618478.
F-statistic	323.8115	Durbin-Watson stat	1.636227
Prob(F-statistic)	0.000000		

G&G Equation 2: Classic Ordinary Least Squares with Interactive Profit Expectations Variable

Dependent Variable: RD?
Method: Pooled Least Squares

Sample(adjusted): 1987 1996
Included observations: 10 after adjusting endpoints
Number of cross-sections used: 12
Total panel (balanced) observations: 120

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	86.73179	26.62794	3.257173	0.0015
CF?	0.369488	0.018270	20.22327	0.0000
V1?*PC?	-0.000352	0.001897	-0.185429	0.8532

R-squared	0.891966	Mean dependent var	742.9404
Adjusted R-squared	0.890119	S.D. dependent var	533.9026
S.E. of regression	176.9798	Sum squared resid	3664656.
F-statistic	482.9941	Durbin-Watson stat	1.632644
Prob(F-statistic)	0.000000		

G&G Equation 3: Classic Ordinary Least Squares with Interactive Profit Expectations Variable

Dependent Variable: RD?
Method: Pooled Least Squares

Sample(adjusted): 1988 1997
Included observations: 10 after adjusting endpoints
Number of cross-sections used: 12
Total panel (balanced) observations: 120

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	25.91917	49.50522	0.523564	0.6016
CF?	0.379361	0.019410	19.54471	0.0000
V1?*PC?	-0.001819	0.002140	-0.849865	0.3972
PC?	110.3126	75.84965	1.454359	0.1485

R-squared	0.893900	Mean dependent var	742.9404
Adjusted R-squared	0.891156	S.D. dependent var	533.9026
S.E. of regression	176.1424	Sum squared resid	3599031.
F-statistic	325.7702	Durbin-Watson stat	1.553167
Prob(F-statistic)	0.000000		

G&G Equation 4: Fixed-Effects Model (Least Squares Dummy Variable Model)

Dependent Variable: RD?
Method: Pooled Least Squares

Sample(adjusted): 1987 1996
Included observations: 10 after adjusting endpoints
Number of cross-sections used: 12
Total panel (balanced) observations: 120

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CF?	0.320758	0.022867	14.02682	0.0000
V1?	0.002024	0.001610	1.257179	0.2115
PC?	628.7858	155.2805	4.049356	0.0001
Fixed Effects				
_ABB--C	-191.4178			
_ALZ--C	-585.9912			
_AHP--C	-312.6695			
_BLK--C	-96.07187			
_BMS--C	-218.8296			
_CW--C	-260.3619			
_JJ--C	70.76483			
_LIL--C	-252.0097			
_MRK--C	-533.9928			
_PFE--C	2.537738			
_SP--C	-362.8895			
_WL--C	-142.0675			
R-squared	0.948894	Mean dependent var		742.9404
Adjusted R-squared	0.942080	S.D. dependent var		533.9026
S.E. of regression	128.4923	Sum squared resid		1733579.
F-statistic	974.7749	Durbin-Watson stat		1.991545
Prob(F-statistic)	0.000000			

G&G Equation 5: Fixed-Effects Model using "Interactive" Profit Expectations Variable

Dependent Variable: RD?
Method: Pooled Least Squares

Sample(adjusted): 1987 1996
Included observations: 10 after adjusting endpoints
Number of cross-sections used: 12
Total panel (balanced) observations: 120

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CF?	0.308871	0.021536	14.34210	0.0000
V1?*PC?	0.007091	0.002467	2.874924	0.0049
Fixed Effects				
_ABB--C	98.93838			
_ALZ--C	30.40426			
_AHP--C	13.32253			
_BLK--C	-4.828566			
_BMS--C	76.56717			
_CW--C	19.08927			
_JJ--C	294.9348			
_LIL--C	181.4832			
_MRK--C	-205.4605			
_PFE--C	341.2054			
_SP--C	115.3982			
_WL--C	141.3716			
R-squared	0.944647	Mean dependent var		742.9404
Adjusted R-squared	0.937859	S.D. dependent var		533.9026
S.E. of regression	133.0919	Sum squared resid		1877627.
F-statistic	1808.995	Durbin-Watson stat		1.940379
Prob(F-statistic)	0.000000			

G&G Equation 6: Fixed-Effects Model using "Interactive" Profit Expectations Variable

Dependent Variable: RD?
Method: Pooled Least Squares

Sample(adjusted): 1987 1996
Included observations: 10 after adjusting endpoints
Number of cross-sections used: 12
Total panel (balanced) observations: 120

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CF?	0.322942	0.021285	15.17198	0.0000
V1?*PC?	0.003613	0.002645	1.365896	0.1749
PC?	517.8131	172.3268	3.004833	0.0033
Fixed Effects				
_ABB--C	-135.3024			
_ALZ--C	-479.4555			
_AHP--C	-256.2496			
_BLK--C	-79.21030			
_BMS--C	-161.1723			
_CW--C	-210.7664			
_JJ--C	130.8769			
_LIL--C	-189.8997			
_MRK--C	-497.4826			
_PFE--C	57.91743			
_SP--C	-288.2351			
_WL--C	-88.98184			

R-squared	0.949030	Mean dependent var	742.9404
Adjusted R-squared	0.942234	S.D. dependent var	533.9026
S.E. of regression	128.3208	Sum squared resid	1728953.
F-statistic	977.5236	Durbin-Watson stat	2.001754
Prob(F-statistic)	0.000000		

G&G Equation 7: Generalized Least Squares Model

Dependent Variable: RD?
Method: GLS (Cross Section Weights)

Sample: 1987 1996
Included observations: 10
Number of cross-sections used: 12
Total panel (balanced) observations: 120

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-24.39008	16.90509	-1.442765	0.1518
CF?	0.361921	0.017323	20.89197	0.0000
V1?	0.002091	0.001438	1.454477	0.1485
PC?	128.3068	24.15652	5.311476	0.0000

Weighted Statistics			
R-squared	0.976323	Mean dependent var	1085.286
Adjusted R-squared	0.975710	S.D. dependent var	1035.805
S.E. of regression	161.4321	Sum squared resid	3022997.
F-statistic	1594.394	Durbin-Watson stat	1.812011
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	0.887049	Mean dependent var	742.9404
Adjusted R-squared	0.884128	S.D. dependent var	533.9026
S.E. of regression	181.7404	Sum squared resid	3831429.
Durbin-Watson stat	1.59235		

G&G Equation 8: Generalized Least Squares Model with "Interactive" Profit Expectations Variable

Dependent Variable: RD?
Method: GLS (Cross Section Weights)

Sample: 1987 1996
Included observations: 10
Number of cross-sections used: 12
Total panel (balanced) observations: 120

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	44.68074	10.56444	4.229351	0.0000
CF?	0.366397	0.010591	34.59424	0.0000
V1?*PC?	0.003404	0.001570	2.167949	0.0322

Weighted Statistics			
R-squared	0.964369	Mean dependent var	1017.746
Adjusted R-squared	0.963760	S.D. dependent var	866.3578
S.E. of regression	164.9278	Sum squared resid	3182539.
F-statistic	1583.313	Durbin-Watson stat	1.777037
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	0.884287	Mean dependent var	742.9404
Adjusted R-squared	0.882309	S.D. dependent var	533.9026
S.E. of regression	183.1616	Sum squared resid	3925137.
Durbin-Watson stat	1.589364		

G&G Equation 9: Generalized Least Squares Model with "Interactive" Profit Expectations Variable

Dependent Variable: RD?
Method: GLS (Cross Section Weights)

Sample: 1987 1996
Included observations: 10
Number of cross-sections used: 12
Total panel (balanced) observations: 120

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-20.16001	16.25430	-1.240288	0.2174
CF?	0.377139	0.011208	33.64933	0.0000
V1?*PC?	0.001648	0.001703	0.967671	0.3352
PC?	116.4564	28.56931	4.076276	0.0001

Weighted Statistics			
R-squared	0.974153	Mean dependent var	1064.651
Adjusted R-squared	0.973485	S.D. dependent var	985.0240
S.E. of regression	160.3970	Sum squared resid	2984355.
F-statistic	1457.317	Durbin-Watson stat	1.814803
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	0.887049	Mean dependent var	742.9404
Adjusted R-squared	0.884128	S.D. dependent var	533.9026
S.E. of regression	181.7405	Sum squared resid	3831433.
Durbin-Watson stat	1.553455		

G&G Equation 10: Generalized Least Squares Model with Fixed-Effects Specification

Dependent Variable: RD?
Method: GLS (Cross Section Weights)

Sample: 1987 1996
Included observations: 10
Number of cross-sections used: 12
Total panel (balanced) observations: 120

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CF?	0.297438	0.018605	15.98691	0.0000
V1?	0.004263	0.001243	3.430071	0.0009
PC?	454.1826	92.46106	4.912150	0.0000
Fixed Effects				
_ABB--C	-111.0769			
_ALZ--C	-415.1775			
_AHP--C	-220.8489			
_BLK--C	-71.14009			
_BMS--C	-156.5461			
_CW--C	-183.0859			
_JJ--C	115.8084			
_LIL--C	-116.1316			
_MRK--C	-449.3730			
_PFE--C	91.67895			
_SP--C	-220.6010			
_WL--C	-66.89610			

Weighted Statistics			
R-squared	0.984966	Mean dependent var	1081.547
Adjusted R-squared	0.982962	S.D. dependent var	954.2904
S.E. of regression	124.5642	Sum squared resid	1629206.
F-statistic	3439.637	Durbin-Watson stat	2.113366
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	0.947246	Mean dependent var	742.9404
Adjusted R-squared	0.940212	S.D. dependent var	533.9026
S.E. of regression	130.5473	Sum squared resid	1789472.
Durbin-Watson stat	1.999850		

G&G Equation 11: Generalized Least Squares Model with Fixed-Effects Specification and "Interactive" Profit Expectations Variable

Dependent Variable: RD?
Method: GLS (Cross Section Weights)

Sample: 1987 1996
Included observations: 10
Number of cross-sections used: 12
Total panel (balanced) observations: 120

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CF?	0.321695	0.016213	19.84153	0.0000
V1?*PC?	0.007448	0.001643	4.532563	0.0000
Fixed Effects				
_ABB--C	63.83971			
_ALZ--C	28.25585			
_AHP--C	-22.14661			
_BLK--C	-5.981739			
_BMS--C	30.98665			
_CW--C	17.90011			
_JJ--C	249.3164			
_LIL--C	146.2703			
_MRK--C	-268.8525			
_PFE--C	307.1794			
_SP--C	94.74217			
_WL--C	126.0966			

Weighted Statistics			
R-squared	0.981133	Mean dependent var	1170.189
Adjusted R-squared	0.978819	S.D. dependent var	908.5257
S.E. of regression	132.2249	Sum squared resid	1853244.
F-statistic	5512.168	Durbin-Watson stat	2.172234
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	0.944327	Mean dependent var	742.9404
Adjusted R-squared	0.937500	S.D. dependent var	533.9026
S.E. of regression	133.4760	Sum squared resid	1888480.
Durbin-Watson stat	1.951629		

G&G Equation 12: Generalized Least Squares Model with Fixed-Effects Specification and "Interactive" Profit Expectations Variable

Dependent Variable: RD?
Method: GLS (Cross Section Weights)

Sample: 1987 1996
Included observations: 10
Number of cross-sections used: 12
Total panel (balanced) observations: 120

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CF?	0.304146	0.015592	19.50667	0.0000
V1?*PC?	0.006511	0.001577	4.127827	0.0001
PC?	279.5509	96.11861	2.908395	0.0044
Fixed Effects				
_ABB--C	-12.72373			
_ALZ--C	-247.1603			
_AHP--C	-123.2172			
_BLK--C	-44.07396			
_BMS--C	-46.99167			
_CW--C	-104.5895			
_JJ--C	230.5174			
_LIL--C	-15.74288			
_MRK--C	-376.0569			
_PFE--C	188.7269			
_SP--C	-101.8622			
_WL--C	22.17925			

Weighted Statistics			
R-squared	0.986465	Mean dependent var	1102.162
Adjusted R-squared	0.984660	S.D. dependent var	1002.255
S.E. of regression	124.1337	Sum squared resid	1617965.
F-statistic	3826.268	Durbin-Watson stat	2.157650
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	1.947891	Mean dependent var	742.9404
Adjusted R-squared	0.940943	S.D. dependent var	533.9026
S.E. of regression	129.7472	Sum squared resid	1767604.
Durbin-Watson stat	1.970072		

G&G Equation 13: Random-Effects Model Specification

Dependent Variable: RD?
Method: GLS (Variance Components)

Sample: 1987 1996
Included observations: 10
Number of cross-sections used: 12
Total panel (balanced) observations: 120

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-85.52219	82.93266	-1.031225	0.3046
CF?	0.330720	0.022546	14.66836	0.0000
V1?	0.001609	0.001576	1.021194	0.3093
PC?	345.9213	117.0245	2.955974	0.0038
Random Effects				
_ABB--C	10.79893			
_ALZ--C	-197.1236			
_AHP--C	-73.37895			
_BLK--C	26.41364			
_BMS--C	8.260585			
_CW--C	-44.81798			
_JJ--C	206.1705			
_LIL--C	38.26385			
_MRK--C	-220.7736			
_PFE--C	231.7837			
_SP--C	-46.69502			
_WL--C	61.09790			

GLS Transformed Regression			
R-squared	0.940531	Mean dependent var	742.9404
Adjusted R-squared	0.938993	S.D. dependent var	533.9026
S.E. of regression	131.8722	Sum squared resid	2017273.
Durbin-Watson stat	1.842028		

Unweighted Statistics including Random Effects			
R-squared	0.946588	Mean dependent var	742.9404
Adjusted R-squared	0.945207	S.D. dependent var	533.9026
S.E. of regression	124.9754	Sum squared resid	1811787.
Durbin-Watson stat	1.937527		

G&G Equation 14: Random Effects Model Specification with "Interactive" Profit Expectations Variable

Dependent Variable: RD?
Method: GLS (Variance Components)

Sample: 1987 1996
Included observations: 10
Number of cross-sections used: 12
Total panel (balanced) observations: 120

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	95.95198	47.60135	2.015741	0.0461
CF?	0.321122	0.020039	16.02465	0.0000
V1?*PC?	0.005218	0.002211	2.360092	0.0199
Random Effects				
_ABB--C	-4.446474			
_ALZ--C	-54.82443			
_AHP--C	-73.45010			
_BLK--C	-90.29124			
_BMS--C	-9.147085			
_CW--C	-68.43115			
_JJ--C	161.6790			
_LIL--C	82.75215			
_MRK--C	-233.0823			
_PFE--C	227.6853			
_SP--C	22.76403			
_WL--C	38.79227			

GLS Transformed Regression			
R-squared	0.937558	Mean dependent var	742.9404
Adjusted R-squared	0.936490	S.D. dependent var	533.9026
S.E. of regression	134.5494	Sum squared resid	2118116.
Durbin-Watson stat	1.834676		

Unweighted Statistics including Random Effects			
R-squared	1.943567	Mean dependent var	742.9404
Adjusted R-squared	0.942602	S.D. dependent var	533.9026
S.E. of regression	127.9113	Sum squared resid	1914272.
Durbin-Watson stat	0.912492		

G&G Equation 15: Random Effects Model Specification with "Interactive" Profit Expectations Variable

Dependent Variable: RD?
Method: GLS (Variance Components)

Sample: 1987 1996
Included observations: 10
Number of cross-sections used: 12
Total panel (balanced) observations: 120

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-45.83372	83.81641	-0.546835	0.5855
CF?	0.330185	0.020426	16.16528	0.0000
V1?*PC?	0.003247	0.002424	1.339126	0.1831
PC?	265.6198	127.7999	2.078403	0.0399
Random Effects				
_ABB--C	12.91399			
_ALZ--C	-163.2859			
_AHP--C	-72.67398			
_BLK--C	1.692074			
_BMS--C	7.797991			
_CW--C	-47.96060			
_JJ--C	212.6476			
_LIL--C	39.47280			
_MRK--C	-242.2454			
_PFE--C	227.6273			
_SP--C	-35.90312			
_WL--C	59.91720			

GLS Transformed Regression			
R-squared	0.940560	Mean dependent var	742.9404
Adjusted R-squared	0.939023	S.D. dependent var	533.9026
S.E. of regression	131.8394	Sum squared resid	2016269.
Durbin-Watson stat	1.848480		

Unweighted Statistics including Random Effects			
R-squared	1.946894	Mean dependent var	742.9404
Adjusted R-squared	0.945521	S.D. dependent var	533.9026
S.E. of regression	124.6168	Sum squared resid	1801405.
Durbin-Watson stat	0.949683		

G&G Equation 16: Ordinary Least Squares (Expanded Firm Sample)

Dependent Variable: RD
Method: Least Squares

Sample(adjusted): 2 162
Included observations: 148
Excluded observations: 13 after adjusting endpoints

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	65.78074	53.53314	1.228785	0.2212
CASHFL	0.302866	0.024924	12.15150	0.0000
MKTCAP1	0.004049	0.001539	2.631617	0.0094
PCT	54.36582	71.34918	0.761968	0.4473

R-squared	0.867128	Mean dependent var	737.4347
Adjusted R-squared	0.864360	S.D. dependent var	573.3732
S.E. of regression	211.1699	Akaike info criterion	13.56986
Sum squared resid	6421352.	Schwarz criterion	13.65086
Log likelihood	-1000.169	F-statistic	313.2492
Durbin-Watson stat	1.456610	Prob(F-statistic)	0.000000

G&G Equation 17: Ordinary Least Squares Using MKTCAP1*PCT

Dependent Variable: RD
Method: Least Squares

Sample(adjusted): 2 162
Included observations: 148
Excluded observations: 13 after adjusting endpoints

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	95.11533	26.80240	3.548762	0.0005
CASHFL	0.314190	0.017448	18.00699	0.0000
MKTCAP1*PCT	0.005675	0.001659	3.421421	0.0008

R-squared	0.870010	Mean dependent var	737.4347
Adjusted R-squared	0.868217	S.D. dependent var	573.3732
S.E. of regression	208.1455	Akaike info criterion	13.53441
Sum squared resid	6282057.	Schwarz criterion	13.59517
Log likelihood	-998.5466	F-statistic	485.2354
Durbin-Watson stat	1.418916	Prob(F-statistic)	0.000000

G&G Equation 18: Ordinary Least Squares Using MKTCAP1*PCT

Dependent Variable: RD
Method: Least Squares

Sample(adjusted): 2 162
Included observations: 148
Excluded observations: 13 after adjusting endpoints

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	107.7351	55.70593	1.933997	0.0551
CASHFL	0.312242	0.019057	16.38504	0.0000
MKTCAP1*PCT	0.005868	0.001825	3.216153	0.0016
PCT	-19.80716	76.57212	-0.258673	0.7963

R-squared	0.870070	Mean dependent var	737.4347
Adjusted R-squared	0.867364	S.D. dependent var	573.3732
S.E. of regression	208.8184	Akaike info criterion	13.54746
Sum squared resid	6279139.	Schwarz criterion	13.62847
Log likelihood	-998.5122	F-statistic	321.4309
Durbin-Watson stat	1.416557	Prob(F-statistic)	0.000000

Diagnostic Test 1: Based Upon Residuals from Equation 4.4.1

Test for Equality of Variances Between Series

Sample: 1976 1996
Included observations: 21

Method	df	Value	Probability
Bartlett	10	33.83590	0.0002
Levene	(10, 217)	3.633829	0.0002
Brown-Forsythe	(10, 217)	3.019148	0.0014

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	21	0.007087	0.004694	0.004607
RESID_AHP	21	0.008429	0.006300	0.006168
RESID_BMS	21	0.007683	0.005794	0.005788
RESID_JJ	21	0.010250	0.008409	0.008267
RESID_LIL	21	0.013647	0.012052	0.011957
RESID_MRK	21	0.018466	0.013933	0.013850
RESID_PFE	21	0.013795	0.011320	0.011115
RESID_SP	21	0.013179	0.010662	0.010632
RESID_SYN	19	0.015297	0.011576	0.011000
RESID_UPJ	20	0.015202	0.012724	0.012565
RESID_WL	21	0.012698	0.010342	0.010143
All	228	0.018996	0.009772	0.009620

Bartlett weighted standard deviation: 0.012765

Diagnostic Test 2: Based Upon Residuals from Equation 4.4.2

Test for Equality of Variances Between Series

Sample: 1976 1996
Included observations: 21

Method	df	Value	Probability
Bartlett	10	26.04743	0.0037
Levene	(10, 217)	1.996279	0.0350
Brown-Forsythe	(10, 217)	1.471235	0.1516

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	21	0.010526	0.008865	0.008779
RESID_AHP	21	0.010964	0.008189	0.008037
RESID_BMS	21	0.007459	0.005939	0.005903
RESID_JJ	21	0.006541	0.005294	0.005268
RESID_LIL	21	0.011661	0.008528	0.008506
RESID_MRK	21	0.015254	0.011626	0.011620
RESID_PFE	21	0.015832	0.012927	0.011685
RESID_SP	21	0.010617	0.007934	0.007867
RESID_SYN	19	0.012131	0.009933	0.009864
RESID_UPJ	20	0.013617	0.009573	0.009515
RESID_WL	21	0.013874	0.010541	0.010536
All	228	0.018410	0.009022	0.008859

Bartlett weighted standard deviation: 0.012001

Diagnostic Test 3: Based Upon Residuals from Equation 4.4.3

Test for Equality of Variances Between Series

Sample: 1976 1996
Included observations: 21

Method	df	Value	Probability
Bartlett	10	25.32593	0.0048
Levene	(10, 217)	1.973977	0.0374
Brown-Forsythe	(10, 217)	1.723630	0.0769

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	21	0.008502	0.006601	0.006520
RESID_AHP	21	0.009653	0.007590	0.007478
RESID_BMS	21	0.007379	0.006070	0.005935
RESID_JJ	21	0.007682	0.006144	0.006061
RESID_LIL	21	0.010592	0.008038	0.007941
RESID_MRK	21	0.017044	0.012915	0.012883
RESID_PFE	21	0.013200	0.010785	0.010090
RESID_SP	21	0.009796	0.007237	0.007130
RESID_SYN	19	0.011715	0.009039	0.008979
RESID_UPJ	20	0.012543	0.009437	0.009381
RESID_WL	21	0.012464	0.009508	0.009385
All	228	0.018083	0.008479	0.008334

Bartlett weighted standard deviation: 0.011279

Diagnostic Test 4: Based Upon Residuals from Equation 4.4.4

Test for Equality of Variances Between Series

Sample: 1976 1996
Included observations: 21

Method	df	Value	Probability
Bartlett	10	27.18764	0.0024
Levene	(10, 140)	3.033125	0.0017
Brown-Forsythe	(10, 140)	2.765135	0.0038

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	14	0.010335	0.007011	0.007011
RESID_AHP	14	0.011225	0.007887	0.006965
RESID_BMS	14	0.006360	0.004338	0.004056
RESID_JJ	14	0.007673	0.006599	0.006599
RESID_LIL	14	0.011963	0.009072	0.009043
RESID_MRK	14	0.018314	0.014224	0.014224
RESID_PFE	14	0.014618	0.012669	0.012526
RESID_SP	14	0.006707	0.005149	0.005149
RESID_SYN	12	0.009183	0.007832	0.007832
RESID_UPJ	13	0.009469	0.007172	0.006887
RESID_WL	14	0.013950	0.011391	0.011292
All	151	0.019946	0.008503	0.008342

Bartlett weighted standard deviation: 0.011475

Diagnostic Test 5: Based Upon Residuals from Equation 4.4.5

Test for Equality of Variances Between Series

Sample: 1976 1996
Included observations: 21

Method	df	Value	Probability
Bartlett	10	34.41564	0.0002
Levene	(10, 140)	3.878144	0.0001
Brown-Forsythe	(10, 140)	3.191875	0.0010

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	14	0.011524	0.008705	0.008625
RESID_AHP	14	0.012598	0.008950	0.007707
RESID_BMS	14	0.006228	0.004133	0.004032
RESID_JJ	14	0.006213	0.005031	0.005031
RESID_LIL	14	0.012598	0.009823	0.009823
RESID_MRK	14	0.016489	0.012345	0.012345
RESID_PFE	14	0.017576	0.015552	0.015087
RESID_SP	14	0.005902	0.004669	0.004669
RESID_SYN	12	0.010268	0.008985	0.008985
RESID_UPJ	13	0.010567	0.008225	0.007881
RESID_WL	14	0.015839	0.012876	0.012876
All	151	0.020169	0.009033	0.008828

Bartlett weighted standard deviation: 0.012137

Diagnostic Test 6: Based Upon Residuals from Equation 4.4.6

Test for Equality of Variances Between Series

Sample: 1976 1996
Included observations: 21

Method	df	Value	Probability
Bartlett	10	28.56556	0.0015
Levene	(10, 140)	3.162493	0.0011
Brown-Forsythe	(10, 140)	2.819377	0.0032

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	14	0.010208	0.007067	0.007067
RESID_AHP	14	0.011225	0.007904	0.006951
RESID_BMS	14	0.006195	0.004281	0.003949
RESID_JJ	14	0.007596	0.006495	0.006495
RESID_LIL	14	0.011686	0.008835	0.008835
RESID_MRK	14	0.018375	0.014196	0.014196
RESID_PFE	14	0.014692	0.012862	0.012580
RESID_SP	14	0.006717	0.005164	0.005164
RESID_SYN	12	0.008979	0.007857	0.007857
RESID_UPJ	13	0.009353	0.007218	0.006942
RESID_WL	14	0.014262	0.011535	0.011392
All	151	0.019933	0.008509	0.008327

Bartlett weighted standard deviation: 0.011458

Diagnostic Test 7: Based Upon Residuals from Equation 4.5.1

Test for Equality of Variances Between Series

Sample: 1976 1996
Included observations: 21

Method	df	Value	Probability
Bartlett	10	33.33063	0.0002
Levene	(10, 217)	3.448766	0.0003
Brown-Forsythe	(10, 217)	2.851681	0.0024

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	21	0.007640	0.005196	0.005097
RESID_AHP	21	0.008683	0.006637	0.006399
RESID_BMS	21	0.007669	0.005804	0.005735
RESID_JJ	21	0.010841	0.008765	0.008549
RESID_LIL	21	0.012509	0.011056	0.010964
RESID_MRK	21	0.018914	0.014171	0.014098
RESID_PFE	21	0.013535	0.011085	0.010989
RESID_SP	21	0.011903	0.009504	0.009424
RESID_SYN	19	0.016283	0.012706	0.012253
RESID_UPJ	20	0.015340	0.012800	0.012512
RESID_WL	21	0.011304	0.009470	0.009325
All	228	0.012379	0.009705	0.009541

Bartlett weighted standard deviation: 0.012661

Diagnostic Test 8: Based Upon Residuals from Equation 4.5.2

Test for Equality of Variances Between Series
Date: 06/22/00 Time: 11:58
Sample: 1976 1996
Included observations: 21

Method	df	Value	Probability
Bartlett	10	24.96153	0.0054
Levene	(10, 217)	1.945881	0.0406
Brown-Forsythe	(10, 217)	1.469074	0.1524

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	21	0.011062	0.009058	0.008945
RESID_AHP	21	0.010926	0.008136	0.007951
RESID_BMS	21	0.007580	0.006038	0.006030
RESID_JJ	21	0.006668	0.005410	0.005394
RESID_LIL	21	0.011512	0.008353	0.008349
RESID_MRK	21	0.015330	0.011630	0.011615
RESID_PFE	21	0.015233	0.012489	0.011370
RESID_SP	21	0.010272	0.007416	0.007344
RESID_SYN	19	0.011425	0.009239	0.009205
RESID_UPJ	20	0.013569	0.009722	0.009684
RESID_WL	21	0.014502	0.011194	0.011143
All	228	0.011691	0.008966	0.008814

Bartlett weighted standard deviation: 0.011958

Diagnostic Test 9: Based Upon Residuals from Equation 4.5.3

Test for Equality of Variances Between Series
Date: 06/22/00 Time: 12:06
Sample: 1976 1996
Included observations: 21

Method	df	Value	Probability
Bartlett	10	33.73045	0.0002
Levene	(10, 217)	2.663403	0.0044
Brown-Forsythe	(10, 217)	2.378149	0.0108

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	21	0.007955	0.005938	0.005777
RESID_AHP	21	0.009671	0.007781	0.007516
RESID_BMS	21	0.006798	0.005774	0.005520
RESID_JJ	21	0.008552	0.007066	0.007006
RESID_LIL	21	0.008422	0.006493	0.006330
RESID_MRK	21	0.017709	0.013335	0.013212
RESID_PFE	21	0.012680	0.010211	0.009963
RESID_SP	21	0.008364	0.006622	0.006313
RESID_SYN	19	0.013669	0.010784	0.010691
RESID_UPJ	20	0.012380	0.009163	0.009114
RESID_WL	21	0.010412	0.008340	0.008087
All	228	0.010758	0.008293	0.008112

Bartlett weighted standard deviation: 0.011003

Diagnostic Test 10: Based Upon Residuals from Equation 4.5.4

Test for Equality of Variances Between Series

Sample: 1976 1996
Included observations: 21

Method	df	Value	Probability
Bartlett	10	39.38338	0.0000
Levene	(10, 140)	3.992293	0.0001
Brown-Forsythe	(10, 140)	3.327757	0.0007

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	14	0.008494	0.006090	0.006090
RESID_AHP	14	0.010720	0.008111	0.007002
RESID_BMS	14	0.005768	0.004531	0.004531
RESID_JJ	14	0.008778	0.007343	0.007343
RESID_LIL	14	0.007331	0.005923	0.005579
RESID_MRK	14	0.019674	0.014982	0.014880
RESID_PFE	14	0.013728	0.011493	0.011286
RESID_SP	14	0.005002	0.004283	0.004228
RESID_SYN	12	0.012374	0.010713	0.010713
RESID_UPJ	13	0.009061	0.006428	0.005940
RESID_WL	14	0.008789	0.007593	0.007402
All	151	0.010343	0.007927	0.007699

Bartlett weighted standard deviation: 0.010706

Diagnostic Test 11: Based Upon Residuals from Equation 4.5.5

Test for Equality of Variances Between Series

Sample: 1976 1996
Included observations: 21

Method	df	Value	Probability
Bartlett	10	35.75083	0.0001
Levene	(10, 140)	4.020024	0.0001
Brown-Forsythe	(10, 140)	3.187865	0.0010

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	14	0.011124	0.008583	0.008474
RESID_AHP	14	0.012678	0.009070	0.007820
RESID_BMS	14	0.006288	0.004241	0.004204
RESID_JJ	14	0.006061	0.004908	0.004908
RESID_LIL	14	0.012490	0.009687	0.009687
RESID_MRK	14	0.016385	0.012273	0.012273
RESID_PFE	14	0.018087	0.016027	0.015460
RESID_SP	14	0.005592	0.004628	0.004628
RESID_SYN	12	0.010701	0.009366	0.009366
RESID_UPJ	13	0.010732	0.008333	0.007826
RESID_WL	14	0.015341	0.012351	0.012351
All	151	0.011710	0.009043	0.008817

Bartlett weighted standard deviation: 0.012121

Diagnostic Test 12: Based Upon Residuals from Equation 4.5.6

Test for Equality of Variances Between Series
Date: 06/22/00 Time: 12:20
Sample: 1976 1996
Included observations: 21

Method	df	Value	Probability
Bartlett	10	40.31072	0.0000
Levene	(10, 140)	4.090025	0.0001
Brown-Forsythe	(10, 140)	3.448991	0.0005

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	14	0.008275	0.005969	0.005969
RESID_AHP	14	0.010730	0.008151	0.006902
RESID_BMS	14	0.005660	0.004627	0.004627
RESID_JJ	14	0.008731	0.007289	0.007289
RESID_LIL	14	0.007008	0.005565	0.005410
RESID_MRK	14	0.019736	0.014865	0.014865
RESID_PFE	14	0.013812	0.011710	0.011467
RESID_SP	14	0.005091	0.004385	0.004232
RESID_SYN	12	0.012146	0.010742	0.010742
RESID_UPJ	13	0.008915	0.006389	0.005852
RESID_WL	14	0.009109	0.007763	0.007512
All	151	0.010318	0.007924	0.007687

Bartlett weighted standard deviation: 0.010680

Diagnostic Test 13: Based Upon Residuals from G&G Equation 1

Test for Equality of Variances Between Series

Sample: 1986 1996
Included observations: 11

Method	df	Value	Probability
Bartlett	11	158.5885	0.0000
Levene	(11, 108)	9.583201	0.0000
Brown-Forsythe	(11, 108)	4.662194	0.0000

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	10	36.86549	27.82828	26.12824
RESID_ALZ	10	27.40828	23.71184	23.71184
RESID_AHP	10	247.9823	204.0072	185.3211
RESID_BLK	10	6.743461	4.246858	4.087620
RESID_BMS	10	196.8206	147.6931	135.6631
RESID_CW	10	8.658646	6.013074	5.657811
RESID_JJ	10	98.08688	77.74425	77.74425
RESID_LIL	10	155.0314	115.3767	111.7329
RESID_MRK	10	194.7929	162.0217	138.8444
RESID_PFE	10	207.1293	171.5681	171.5681
RESID_SP	10	32.62367	28.97624	28.97624
RESID_WL	10	76.70938	56.86417	51.91203
All	120	174.3771	85.50429	80.11231

Bartlett weighted standard deviation: 136.6002

Diagnostic Test 14: Based Upon Residuals from G&G Equation 2

Test for Equality of Variances Between Series

Sample: 1986 1996
Included observations: 11

Method	df	Value	Probability
Bartlett	11	162.5959	0.0000
Levene	(11, 108)	10.34623	0.0000
Brown-Forsythe	(11, 108)	4.789224	0.0000

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	10	33.46385	25.66778	25.66778
RESID_ALZ	10	27.48447	23.77158	23.77158
RESID_AHP	10	250.1775	206.0484	187.7160
RESID_BLK	10	6.602541	4.011878	3.912846
RESID_BMS	10	192.0646	146.5110	131.9039
RESID_CW	10	8.321833	5.483643	5.430347
RESID_JJ	10	97.12740	77.10793	77.10793
RESID_LIL	10	153.8050	115.3341	114.5905
RESID_MRK	10	205.8682	172.6345	145.2446
RESID_PFE	10	217.7118	180.8148	180.8148
RESID_SP	10	35.15000	31.41990	31.41990
RESID_WL	10	74.10757	53.37760	50.71357
All	120	175.4863	86.84860	81.52448

Bartlett weighted standard deviation: 138.7633

Diagnostic Test 15: Based Upon Residuals from G&G Equation 3

Test for Equality of Variances Between Series

Sample: 1986 1996
Included observations: 11

Method	df	Value	Probability
Bartlett	11	158.2806	0.0000
Levene	(11, 108)	9.589192	0.0000
Brown-Forsythe	(11, 108)	4.620506	0.0000

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	10	35.72417	27.10404	25.24165
RESID_ALZ	10	27.40894	23.73601	23.73601
RESID_AHP	10	245.9423	202.0171	183.2099
RESID_BLK	10	6.871114	4.359502	4.222836
RESID_BMS	10	199.6448	148.9950	138.1578
RESID_CW	10	8.972234	6.419863	6.006936
RESID_JJ	10	96.28461	75.07708	75.07708
RESID_LIL	10	155.8963	117.1717	112.5623
RESID_MRK	10	205.7004	170.7455	146.0167
RESID_PFE	10	209.8799	174.5494	174.5494
RESID_SP	10	35.15870	30.85929	30.85929
RESID_WL	10	77.68356	57.66597	52.27546
All	120	173.9079	86.55837	80.99295

Bartlett weighted standard deviation: 138.3559

Diagnostic Test 16: Based Upon Residuals from G&G Equation 4

Test for Equality of Variances Between Series

Sample: 1986 1996
Included observations: 11

Method	df	Value	Probability
Bartlett	11	134.3801	0.0000
Levene	(11, 108)	8.199954	0.0000
Brown-Forsythe	(11, 108)	4.289463	0.0000

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	10	90.77303	73.25809	68.80053
RESID_ALZ	10	28.98805	24.59479	24.59479
RESID_AHP	10	265.5209	219.9070	199.9095
RESID_BLK	10	7.491098	5.438841	5.382986
RESID_BMS	10	176.1182	135.5502	126.5022
RESID_CW	10	14.14663	11.07114	11.07114
RESID_JJ	10	88.10255	73.93003	73.53043
RESID_LIL	10	145.9285	98.97440	98.24962
RESID_MRK	10	99.31217	83.79169	77.47596
RESID_PFE	10	166.6948	132.5412	130.0662
RESID_SP	10	21.64905	17.34035	16.61794
RESID_WL	10	120.7839	92.07363	86.64517
All	120	120.6975	80.70596	76.57054

Bartlett weighted standard deviation: 126.6951

Diagnostic Test 17: Based Upon Residuals from G&G Equation 5

Test for Equality of Variances Between Series

Sample: 1986 1996
Included observations: 11

Method	df	Value	Probability
Bartlett	11	162.2911	0.0000
Levene	(11, 108)	10.26493	0.0000
Brown-Forsythe	(11, 108)	5.642338	0.0000

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	10	53.86714	46.24482	46.24482
RESID_ALZ	10	30.61208	24.19827	24.19827
RESID_AHP	10	272.4960	226.2871	208.5247
RESID_BLK	10	5.578025	3.683657	3.446540
RESID_BMS	10	169.7434	132.6820	126.8531
RESID_CW	10	7.105301	4.971535	4.922257
RESID_JJ	10	100.7411	86.07345	84.47181
RESID_LIL	10	142.1916	102.7251	102.7251
RESID_MRK	10	150.8119	129.9580	120.5024
RESID_PFE	10	206.7809	162.9427	162.9427
RESID_SP	10	23.99906	20.12859	19.93968
RESID_WL	10	72.05681	50.59740	47.95394
All	120	125.6120	82.54106	79.39379

Bartlett weighted standard deviation: 131.8538

Diagnostic Test 18: Based Upon Residuals from G&G Equation 6

Test for Equality of Variances Between Series

Sample: 1986 1996
Included observations: 11

Method	df	Value	Probability
Bartlett	11	138.3580	0.0000
Levene	(11, 108)	8.065629	0.0000
Brown-Forsythe	(11, 108)	4.318867	0.0000

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	10	90.00815	72.95825	68.46004
RESID_ALZ	10	29.14314	24.33223	24.33223
RESID_AHP	10	264.4866	218.9499	199.1656
RESID_BLK	10	7.143467	5.140724	5.026569
RESID_BMS	10	178.8425	136.4363	127.1389
RESID_CW	10	12.41216	9.926949	9.588326
RESID_JJ	10	96.35640	82.21098	80.84047
RESID_LIL	10	148.7977	99.29260	99.29260
RESID_MRK	10	96.36101	83.39876	76.85160
RESID_PFE	10	164.5406	128.9312	127.3756
RESID_SP	10	20.03716	15.36303	15.36303
RESID_WL	10	113.2535	85.70945	82.09974
All	120	120.5364	80.22087	76.29456

Bartlett weighted standard deviation: 126.5260

Diagnostic Test Summary: Significance Levels of Breusch and Pagan Lagrange Multiplier Test Statistic for Cross-sectional Heteroskedasticity

Equation # (for generating residuals)	Significance of λ_{LM}
7.1	0.127
7.2	0.301
7.3	0.154
7.4	0.322
7.5	0.099
7.6	0.195
8.1	0.341
8.2	0.411
8.3	0.246
8.4	0.444
8.5	0.132
8.6	0.267

Regression Equation 5.1.1: OLS Regression Results for 23 U.S. and European Firms

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1984 1997
Included observations: 14
Number of cross-sections used: 23
Total panel (unbalanced) observations: 286

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.047363	0.028457	-1.664395	0.0971
CFM?	0.197946	0.032811	6.032910	0.0000
PHARMARG?	0.205278	0.099672	2.059544	0.0404
PCT?	0.068871	0.010356	6.650290	0.0000

R-squared	0.495507	Mean dependent var	0.097076
Adjusted R-squared	0.490140	S.D. dependent var	0.052337
S.E. of regression	0.037371	Sum squared resid	0.393832
F-statistic	92.32564	Durbin-Watson stat	1.677734
Prob(F-statistic)	0.000000		

Regression Equation 5.1.2: LSDV Regression Results for 23 U.S. and European Firms

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1984 1997
Included observations: 14
Number of cross-sections used: 23
Total panel (unbalanced) observations: 286

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.086289	0.016009	5.390031	0.0000
PHARMARG?	0.218650	0.041290	5.295498	0.0000
PCT?	0.090894	0.013121	6.927235	0.0000

Fixed Effects	
_ABB--C	-0.036174
_AKZ--C	-0.038230
_ALZ--C	0.095723
_AMC--C	-0.028263
_AHP--C	-0.064010
_AST--C	-0.007845
_BLK--C	-0.055662
_BMS--C	-0.047475
_CW--C	-0.048417
_DOW--C	-0.038006
_FL--C	-0.093176
_HST--C	-0.029730
_JJ--C	-0.025930
_LIL--C	-0.017075
_MRK--C	-0.055627
_MON--C	-0.019323
_MYL--C	-0.112713
_PFE--C	-0.027349
_SP--C	-0.041369
_SKB--C	-0.043350
_SYN--C	-0.001810
_UPJ--C	-0.007899
_WL--C	-0.046608

R-squared	0.927856	Mean dependent var	0.097076
Adjusted R-squared	0.920919	S.D. dependent var	0.052337
S.E. of regression	0.014718	Sum squared resid	0.056319
F-statistic	1671.951	Durbin-Watson stat	1.764673
Prob(F-statistic)	0.000000		

Regression Equation 5.1.3: Feasible Generalized Least Squares Regression Results (Common Intercept) 23 U.S. and European Firms

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1984 1997
Included observations: 14
Number of cross-sections used: 23
Total panel (unbalanced) observations: 286

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.003200	0.009827	-0.325618	0.7450
CFM?	0.177493	0.015220	11.66204	0.0000
PHARMARG?	0.068099	0.034609	1.967668	0.0501
PCT?	0.067546	0.004416	15.29473	0.0000

Weighted Statistics			
R-squared	0.908798	Mean dependent var	0.197379
Adjusted R-squared	0.907828	S.D. dependent var	0.118118
S.E. of regression	0.035860	Sum squared resid	0.362645
F-statistic	936.6833	Durbin-Watson stat	1.692686
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	0.489462	Mean dependent var	0.097076
Adjusted R-squared	0.484031	S.D. dependent var	0.052337
S.E. of regression	0.037594	Sum squared resid	0.398550
Durbin-Watson stat	1.556710		

Regression Equation 5.1.4: Feasible Generalized Least Squares Regression Results (Fixed Effects) 23 U.S. and European Firms

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1984 1997
Included observations: 14
Number of cross-sections used: 23
Total panel (unbalanced) observations: 286

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.075029	0.014496	4.865330	0.0000
PHARMARG?	0.122411	0.021994	5.565656	0.0000
PCT?	0.102692	0.008496	12.08744	0.0000
Fixed Effects				
_ABB--C	-0.010268			
_AKZ--C	-0.010101			
_ALZ--C	0.118502			
_AMC--C	-0.004385			
_AHP--C	-0.039823			
_AST--C	0.013047			
_BLK--C	-0.027785			
_BMS--C	-0.022479			
_CW--C	-0.024488			
_DOW--C	-0.008786			
_FL--C	-0.072949			
_HST--C	-0.001620			
_JJ--C	0.001200			
_LIL--C	0.006971			
_MRK--C	-0.032571			
_MON--C	0.009866			
_MYL--C	-0.091848			
_PFE--C	-0.003041			
_SP--C	-0.018930			
_SKB--C	-0.017084			
_SYN--C	0.020343			
_UPJ--C	0.013074			
WL--C	-0.022606			

Weighted Statistics			
R-squared	0.971203	Mean dependent var	0.136945
Adjusted R-squared	0.968434	S.D. dependent var	0.079373
S.E. of regression	0.014102	Sum squared resid	0.051704
F-statistic	4384.413	Durbin-Watson stat	1.865640
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	0.925645	Mean dependent var	0.097076
Adjusted R-squared	0.918495	S.D. dependent var	0.052337
S.E. of regression	0.014942	Sum squared resid	0.058045
Durbin-Watson stat	1.715759		

Regression Equation 5.1.5: Random Effects Model Specification for 23 U.S. and European Firms

Dependent Variable: RDS?
Method: GLS (Variance Components)

Sample: 1984 1997
Included observations: 14
Number of cross-sections used: 23
Total panel (unbalanced) observations: 286

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.037914	0.014826	-2.557295	0.0111
CFM?	0.088228	0.015837	5.571055	0.0000
PHARMARG?	0.217921	0.040858	5.333593	0.0000
PCT?	0.091029	0.011940	7.624037	0.0000
Random Effects				
_ABB--C	0.001353			
_AKZ--C	-0.000374			
_ALZ--C	0.131496			
_AMC--C	0.009374			
_AHP--C	-0.026118			
_AST--C	0.029182			
_BLK--C	-0.017626			
_BMS--C	-0.009732			
_CW--C	-0.010462			
_DOW--C	-0.000217			
_FL--C	-0.055133			
_HST--C	0.008019			
_JJ--C	0.011647			
_LIL--C	0.020095			
_MRK--C	-0.017993			
_MON--C	0.018229			
_MYL--C	-0.074531			
_PFE--C	0.010124			
_SP--C	-0.003800			
_SKB--C	-0.005743			
_SYN--C	0.035115			
_UPJ--C	0.029295			
_WL--C	-0.008745			

GLS Transformed Regression			
R-squared	0.922837	Mean dependent var	0.097076
Adjusted R-squared	0.922016	S.D. dependent var	0.052337
S.E. of regression	0.014615	Sum squared resid	0.060237
Durbin-Watson stat	1.872381		

Unweighted Statistics including Random Effects			
R-squared	0.927796	Mean dependent var	0.097076
Adjusted R-squared	0.927028	S.D. dependent var	0.052337
S.E. of regression	0.014138	Sum squared resid	0.056366
Durbin-Watson stat	1.718560		

Regression 5.4.1: Classic OLS Model with 32 U.S. and European Firms over the Period from 1991-1997

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1991 1997
Included observations: 7
Number of cross-sections used: 32
Total panel (unbalanced) observations: 191

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.061184	0.036097	-1.694998	0.0917
CFM?	0.157199	0.034711	4.528748	0.0000
PC?	0.084120	0.011909	7.063306	0.0000
PMARG?	0.269909	0.119025	2.267661	0.0245

R-squared	0.570319	Mean dependent var	0.107578
Adjusted R-squared	0.563426	S.D. dependent var	0.054125
S.E. of regression	0.035762	Sum squared resid	0.239163
F-statistic	82.73553	Durbin-Watson stat	1.982527
Prob(F-statistic)	0.000000		

Regression 5.4.2: Classic LSDV Model (Fixed Effects) with 32 U.S. and European Firms over the Period from 1991-1997

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1991 1997
Included observations: 7
Number of cross-sections used: 32
Total panel (unbalanced) observations: 191

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.096959	0.018941	5.118917	0.0000
PC?	0.069472	0.021962	3.163227	0.0019
PMARG?	0.214267	0.048292	4.436895	0.0000
Fixed Effects				
_ABB--C	-0.017688			
_AKZ--C	-0.036474			
_ALZ--C	0.105741			
_AMC--C	-0.014849			
_AHP--C	-0.041300			
_AMG--C	0.040448			
_AST--C	-0.008425			
_BAY--C	-0.017230			
_BLK--C	-0.054023			
_BMS--C	-0.038786			
_CW--C	-0.043997			
_DOW--C	-0.042333			
_EMK--C	-0.021937			
_FOR--C	-0.074355			
_HOE--C	-0.023980			
_JJ--C	-0.022691			
_LIL--C	-0.004389			
_GLX--C	-0.023741			
_MRK--C	-0.053606			
_MON--C	-0.014265			
_MYL--C	-0.088709			
_PFE--C	-0.001569			
_PHR--C	0.027081			
_RHO--C	-0.018827			
_ROC--C	0.012891			
_SAN--C	-0.010441			
_SHP--C	-0.024934			
_SKB--C	-0.032667			
_SOL--C	-0.043308			
_SYT--C	0.022415			
_UPJ--C	0.018027			
_WLA--C	-0.028591			
_ZEN--C	-0.005984			

R-squared	0.947856	Mean dependent var	0.107578
Adjusted R-squared	0.936081	S.D. dependent var	0.054125
S.E. of regression	0.013684	Sum squared resid	0.029024
F-statistic	1408.767	Durbin-Watson stat	1.897265
Prob(F-statistic)	0.000000		

Regression 5.4.3: FGLS Model Specification (Common Intercept) with 32 U.S. and European Firms over the Period from 1991-1997

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1991 1997
Included observations: 7
Number of cross-sections used: 32
Total panel (unbalanced) observations: 191

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.026395	0.012638	-2.088515	0.0381
CFM?	0.150636	0.014998	10.04357	0.0000
PC?	0.082458	0.003721	22.16177	0.0000
PMARG?	0.162559	0.042012	3.869305	0.0002

Weighted Statistics			
R-squared	0.949409	Mean dependent var	0.225942
Adjusted R-squared	0.948598	S.D. dependent var	0.154427
S.E. of regression	0.035012	Sum squared resid	0.229230
F-statistic	1169.775	Durbin-Watson stat	1.620832
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	0.567901	Mean dependent var	0.107578
Adjusted R-squared	0.560969	S.D. dependent var	0.054125
S.E. of regression	0.035863	Sum squared resid	0.240508
Durbin-Watson stat	1.575319		

Regression 5.4.4: FGLS Model Specification (LSDV) with 32 U.S.& European Firms

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1991 1997
Included observations: 7
Number of cross-sections used: 32
Total panel (unbalanced) observations: 191

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.098512	0.014236	6.920109	0.0000
PC?	0.090667	0.012739	7.117520	0.0000
PMARG?	0.173960	0.025024	6.951632	0.0000
Fixed Effects				
_ABB--C	-0.014933			
_AKZ--C	-0.028168			
_ALZ--C	0.096321			
_AMC--C	-0.015063			
_AHP--C	-0.041690			
_AMG--C	0.030881			
_AST--C	-0.017833			
_BAY--C	-0.008781			
_BLK--C	-0.044871			
_BMS--C	-0.039099			
_CW--C	-0.041177			
_DOW--C	-0.032302			
_EMK--C	-0.020561			
_FOR--C	-0.084180			
_HOE--C	-0.016909			
_JJ--C	-0.017738			
_LIL--C	-0.010185			
_GLX--C	-0.034058			
_MRK--C	-0.057576			
_MON--C	-0.006423			
_MYL--C	-0.098322			
_PFE--C	-0.004235			
_PHR--C	0.023468			
_RHO--C	-0.028115			
_ROC--C	0.012024			
_SAN--C	-0.009022			
_SHP--C	-0.031224			
_SKB--C	-0.032929			
_SOL--C	-0.034566			
_SYT--C	0.015005			
_UPJ--C	0.011438			
_WLA--C	-0.024619			
ZEN--C	-0.002844			

Weighted Statistics			
R-squared	0.999453	Mean dependent var	0.220922
Adjusted R-squared	0.999329	S.D. dependent var	0.520871
S.E. of regression	0.013490	Sum squared resid	0.028206
F-statistic	141559.3	Durbin-Watson stat	1.991852
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	0.947290	Mean dependent var	0.107578
Adjusted R-squared	0.935387	S.D. dependent var	0.054125
S.E. of regression	0.013758	Sum squared resid	0.029339
Durbin-Watson stat	1.846823		

Regression 5.4.5: Random Effects Model Specification with 32 U.S.& European Firms

Dependent Variable: RDS?
Method: GLS (Variance Components)

Sample: 1991 1997
Included observations: 7
Number of cross-sections used: 32
Total panel (unbalanced) observations: 191

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.030851	0.017873	-1.726146	0.0860
CFM?	0.101171	0.018420	5.492426	0.0000
PC?	0.084310	0.015360	5.488793	0.0000
PMARG?	0.215062	0.047606	4.517565	0.0000
Random Effects				
_ABB--C	0.005207			
_AKZ--C	-0.008764			
_ALZ--C	0.117319			
_AMC--C	0.006778			
_AHP--C	-0.019801			
_AMG--C	0.053142			
_AST--C	0.005738			
_BAY--C	0.010066			
_BLK--C	-0.025425			
_BMS--C	-0.017300			
_CW--C	-0.019757			
_DOW--C	-0.013158			
_EMK--C	0.000490			
_FOR--C	-0.058516			
_HOE--C	0.002810			
_JJ--C	0.002163			
_LIL--C	0.012227			
_GLX--C	-0.009494			
_MRK--C	-0.034459			
_MON--C	0.012485			
_MYL--C	-0.072789			
_PFE--C	0.017466			
_PHR--C	0.043779			
_RHO--C	-0.003836			
_ROC--C	0.032393			
_SAN--C	0.011986			
_SHP--C	-0.007989			
_SKB--C	-0.011311			
_SOL--C	-0.015159			
_SYT--C	0.037655			
_UPJ--C	0.034228			
_WLA--C	-0.004146			
_ZEN--C	0.016308			

GLS Transformed Regression			
R-squared	0.938672	Mean dependent var	0.107578
Adjusted R-squared	0.937688	S.D. dependent var	0.054125
S.E. of regression	0.013511	Sum squared resid	0.034136
Durbin-Watson stat	1.977140		

Unweighted Statistics including Random Effects			
R-squared	0.947466	Mean dependent var	0.107578
Adjusted R-squared	0.946623	S.D. dependent var	0.054125
S.E. of regression	0.012505	Sum squared resid	0.029241
Durbin-Watson stat	1.840716		

Diagnostic Test 1: Based Upon Residuals from Equation 5.1.1

Test for Equality of Variances Between Series

Sample: 1983 1997
Included observations: 15

Method	df	Value	Probability
Bartlett	22	156.1287	0.0000
Levene	(22, 263)	6.646134	0.0000
Brown-Forsythe	(22, 263)	4.472236	0.0000

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	14	0.009299	0.006570	0.006570
RESID_AKZ	11	0.005208	0.004035	0.003432
RESID_ALZ	9	0.039291	0.029482	0.029296
RESID_AMC	9	0.004699	0.003418	0.002994
RESID_AHP	14	0.014752	0.012618	0.010989
RESID_AST	14	0.031182	0.026131	0.025683
RESID_BLK	14	0.004914	0.002875	0.002855
RESID_BMS	14	0.010477	0.006464	0.006424
RESID_CW	14	0.011996	0.008410	0.007318
RESID_DOW	14	0.012283	0.008726	0.008716
RESID_FL	14	0.027556	0.021232	0.017249
RESID_HST	9	0.003912	0.002412	0.002291
RESID_JJ	14	0.007203	0.005815	0.005815
RESID_LIL	14	0.015603	0.011745	0.011698
RESID_MRK	14	0.018390	0.014300	0.014244
RESID_MON	9	0.018404	0.013691	0.011927
RESID_MYL	14	0.014864	0.011859	0.011764
RESID_PFE	14	0.015857	0.013555	0.013227
RESID_SP	14	0.008177	0.006115	0.006096
RESID_SKB	8	0.007258	0.005516	0.005516
RESID_SYN	10	0.009263	0.007795	0.007795
RESID_UPJ	11	0.010734	0.008239	0.007214
RESID_WL	14	0.012514	0.009906	0.009794
All	286	0.037173	0.010583	0.010056

Bartlett weighted standard deviation: 0.015990

Diagnostic Test 2: Based Upon Residuals from Equation 5.1.2

Test for Equality of Variances Between Series

Sample: 1983 1997
Included observations: 15

Method	df	Value	Probability
Bartlett	22	154.0098	0.0000
Levene	(22, 263)	6.754248	0.0000
Brown-Forsythe	(22, 263)	4.326423	0.0000

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	14	0.013729	0.009666	0.009666
RESID_AKZ	11	0.004579	0.003527	0.003044
RESID_ALZ	9	0.038479	0.030564	0.029930
RESID_AMC	9	0.004301	0.003180	0.002993
RESID_AHP	14	0.016374	0.014027	0.012695
RESID_AST	14	0.023406	0.019517	0.019483
RESID_BLK	14	0.004537	0.002923	0.002923
RESID_BMS	14	0.009418	0.006707	0.006707
RESID_CW	14	0.014299	0.010931	0.009642
RESID_DOW	14	0.010743	0.008667	0.008291
RESID_FL	14	0.023867	0.018077	0.014938
RESID_HST	9	0.003375	0.002013	0.001979
RESID_JJ	14	0.004996	0.004179	0.004079
RESID_LIL	14	0.008816	0.007072	0.007007
RESID_MRK	14	0.016367	0.012427	0.011956
RESID_MON	9	0.016243	0.011382	0.010082
RESID_MYL	14	0.012733	0.010211	0.010137
RESID_PFE	14	0.015297	0.012855	0.012544
RESID_SP	14	0.007112	0.005848	0.005848
RESID_SKB	8	0.004584	0.003314	0.003241
RESID_SYN	10	0.013227	0.011335	0.010852
RESID_UPJ	11	0.011377	0.008915	0.007571
RESID_WL	14	0.013103	0.011047	0.010882
All	286	0.014057	0.009997	0.009480

Bartlett weighted standard deviation: 0.014634

Diagnostic Test 3: Based Upon Residuals from Equation 5.4.1

Test for Equality of Variances Between Series

Sample: 1990 1997
Included observations: 8

Method	df	Value	Probability
Bartlett	32	76.36585	0.0000
Levene	(32, 158)	2.696310	0.0000
Brown-Forsythe	(32, 158)	1.381476	0.1008

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	6	0.010409	0.007679	0.007064
RESID_AKZ	7	0.006717	0.005370	0.004953
RESID_ALZ	6	0.032398	0.022348	0.019619
RESID_AMC	2	0.004369	0.003089	0.003089
RESID_AHP	7	0.013796	0.011687	0.010612
RESID_AMG	6	0.026660	0.022991	0.022991
RESID_AST	7	0.013434	0.010733	0.009427
RESID_BAY	7	0.006783	0.005126	0.003918
RESID_BLK	6	0.007790	0.005692	0.005518
RESID_BMS	7	0.012644	0.009171	0.008366
RESID_CW	7	0.018352	0.015046	0.013368
RESID_DOW	6	0.010895	0.006106	0.006086
RESID_EMK	6	0.006540	0.005295	0.004408
RESID_FOR	6	0.023634	0.015813	0.012232
RESID_HOE	6	0.002469	0.001797	0.001634
RESID_JJ	7	0.006376	0.004832	0.004763
RESID_LIL	7	0.017694	0.013990	0.013820
RESID_GLX	2	0.003389	0.002396	0.002396
RESID_MRK	7	0.014314	0.012191	0.011683
RESID_MON	7	0.018945	0.014343	0.013499
RESID_MYL	7	0.016350	0.013430	0.012697
RESID_PFE	7	0.006701	0.005076	0.004879
RESID_PHR	2	0.007955	0.005625	0.005625
RESID_RHO	7	0.006900	0.005809	0.005337
RESID_ROC	6	0.018104	0.014650	0.014561
RESID_SAN	3	0.008496	0.006498	0.005195
RESID_SHP	7	0.011014	0.008565	0.008348
RESID_SKB	7	0.006549	0.004976	0.004816
RESID_SOL	7	0.010357	0.007468	0.006970
RESID_SYT	3	0.006335	0.004625	0.004138
RESID_UPJ	4	0.014539	0.011196	0.011196
RESID_WLA	7	0.010749	0.008243	0.007985
RESID_ZEN	2	0.003165	0.002238	0.002238
All	191	0.035479	0.009484	0.008808

Bartlett weighted standard deviation: 0.014146

Diagnostic Test 4: Based Upon Residuals from Equation 5.4.2

Test for Equality of Variances Between Series
Date: 07/21/00 Time: 13:01
Sample: 1990 1997
Included observations: 8

Method	df	Value	Probability
Bartlett	32	102.7217	0.0000
Levene	(32, 158)	3.938794	0.0000
Brown-Forsythe	(32, 158)	2.263612	0.0005

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ABB	6	0.008839	0.006620	0.005867
RESID_AKZ	7	0.005314	0.004190	0.003990
RESID_ALZ	6	0.032351	0.023483	0.023483
RESID_AMC	2	0.004489	0.003174	0.003174
RESID_AHP	7	0.014510	0.012355	0.011301
RESID_AMG	6	0.029270	0.025518	0.025518
RESID_AST	7	0.014139	0.010717	0.009981
RESID_BAY	7	0.005442	0.004043	0.003273
RESID_BLK	6	0.006489	0.005049	0.004841
RESID_BMS	7	0.011046	0.008168	0.007709
RESID_CW	7	0.018368	0.015979	0.014553
RESID_DOW	6	0.007996	0.004746	0.004746
RESID_EMK	6	0.005511	0.004489	0.004282
RESID_FOR	6	0.024503	0.016504	0.012432
RESID_HOE	6	0.001886	0.001392	0.001253
RESID_JJ	7	0.003738	0.002868	0.002807
RESID_LIL	7	0.011048	0.009301	0.008615
RESID_GLX	2	0.003008	0.002127	0.002127
RESID_MRK	7	0.015312	0.012902	0.012883
RESID_MON	7	0.018677	0.013617	0.012797
RESID_MYL	7	0.015233	0.012508	0.011660
RESID_PFE	7	0.006258	0.004986	0.004907
RESID_PHR	2	0.006962	0.004923	0.004923
RESID_RHO	7	0.009204	0.007600	0.007339
RESID_ROC	6	0.013255	0.010761	0.010587
RESID_SAN	3	0.008086	0.006160	0.005007
RESID_SHP	7	0.008954	0.006918	0.006769
RESID_SKB	7	0.005241	0.004004	0.003965
RESID_SOL	7	0.008891	0.006485	0.005992
RESID_SYT	3	0.006890	0.004948	0.004538
RESID_UPJ	4	0.015113	0.011684	0.011684
RESID_WLA	7	0.008263	0.006496	0.006264
RESID_ZEN	2	0.000406	0.000287	0.000287
All	191	0.012359	0.008871	0.008367

Bartlett weighted standard deviation: 0.013553

Regression Equation 5.5.1: Generalized LSDV European Firms 1991-1997

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1991 1997
Included observations: 7
Number of cross-sections used: 13
Total panel (unbalanced) observations: 76

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.061674	0.024520	2.515233	0.0146
PC?	0.095803	0.017171	5.579393	0.0000
PMARG?	0.101920	0.026034	3.914840	0.0002
Fixed Effects				
_AST--C	0.013131			
_BAY--C	0.017759			
_BLK--C	-0.018814			
_EMK--C	0.004995			
_HOE--C	0.008013			
_RHO--C	-0.003774			
_ROC--C	0.044207			
_SKB--C	-0.004374			
_GLX--C	-0.003177			
_AKZ--C	-0.002488			
_BLK--C	-0.018814			
_SOL--C	-0.028029			
_ZEN--C	0.026569			

Weighted Statistics			
R-squared	0.995532	Mean dependent var	0.149212
Adjusted R-squared	0.994415	S.D. dependent var	0.116771
S.E. of regression	0.008726	Sum squared resid	0.004569
F-statistic	6684.733	Durbin-Watson stat	1.881306
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	0.965966	Mean dependent var	0.093874
Adjusted R-squared	0.957457	S.D. dependent var	0.043825
S.E. of regression	0.009039	Sum squared resid	0.004902
Durbin-Watson stat	1.747015		

Regression Equation 5.5.2: Generalized LSDV U.S. Firms 1991-1997

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1991 1997
Included observations: 7
Number of cross-sections used: 19
Total panel (unbalanced) observations: 116

Variable	Coefficient	Std. Error	t-Statistic	Prob.
CFM?	0.056384	0.025910	2.176103	0.0321
PC?	0.085433	0.018374	4.649627	0.0000
PMARG?	0.142329	0.046324	3.072494	0.0028
Fixed Effects				
_ABB--C	0.009220			
_ALZ--C	0.125453			
_AMC--C	0.005120			
_AHP--C	-0.018463			
_AMG--C	0.063989			
_BMS--C	-0.015772			
_CW--C	-0.025344			
_DOW--C	-0.016205			
_FOR--C	-0.056431			
_JJ--C	0.002405			
_LIL--C	0.018965			
_MRK--C	-0.030901			
_MON--C	0.011456			
_MYL--C	-0.067835			
_PFE--C	0.019449			
_SHP--C	-0.004600			
_SYT--C	0.045145			
_UPJ--C	0.037059			
_WLA--C	-0.005949			

Weighted Statistics			
R-squared	0.984053	Mean dependent var	0.159596
Adjusted R-squared	0.980490	S.D. dependent var	0.108712
S.E. of regression	0.015185	Sum squared resid	0.021674
F-statistic	2900.211	Durbin-Watson stat	1.998854
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	0.931962	Mean dependent var	0.114382
Adjusted R-squared	0.916762	S.D. dependent var	0.058339
S.E. of regression	0.016831	Sum squared resid	0.026630
Durbin-Watson stat	1.903626		

Regression Equation 5.7.1: Classic OLS for 28 Japanese Firms from 1994-1997

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1994 1997
Included observations: 4
Number of cross-sections used: 28
Total panel (unbalanced) observations: 86

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	0.011271	0.012268	0.918721	0.3609
CFM?	0.334797	0.056776	5.896814	0.0000
PCT?	0.049580	0.015614	3.175272	0.0021

R-squared	0.466307	Mean dependent var	0.100343
Adjusted R-squared	0.453447	S.D. dependent var	0.038544
S.E. of regression	0.028495	Sum squared resid	0.067394
F-statistic	36.26012	Durbin-Watson stat	1.712817
Prob(F-statistic)	0.000000		

Regression Equation 5.7.1a: Classic OLS Model for 28 Japanese Firms from 1994-1997 (with *PharMarg* employed as Profit Expectations Proxy)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1994 1997
Included observations: 4
Number of cross-sections used: 28
Total panel (unbalanced) observations: 86

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	0.045203	0.026324	1.717166	0.0897
CFM?	0.335808	0.056403	5.953747	0.0000
PCT?	0.049255	0.015512	3.175221	0.0021
PHARMARG?	-0.111250	0.076501	-1.454223	0.1497

R-squared	0.479725	Mean dependent var	0.100343
Adjusted R-squared	0.460691	S.D. dependent var	0.038544
S.E. of regression	0.028306	Sum squared resid	0.065699
F-statistic	25.20301	Durbin-Watson stat	1.547274
Prob(F-statistic)	0.000000		

Regression Equation 5.7.1b: Classic OLS Model for 28 Japanese Firms from 1994-1997 (with Year Dummy Variables to Control for Profit Expectations)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1994 1997
Included observations: 4
Number of cross-sections used: 28
Total panel (unbalanced) observations: 86

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	0.010792	0.013876	0.777806	0.4390
CFM?	0.338212	0.058257	5.805524	0.0000
PCT?	0.049006	0.015907	3.080698	0.0028
D94?	0.000704	0.009179	0.076714	0.9390
D95?	0.003082	0.008821	0.349368	0.7277
D96?	-0.002025	0.008758	-0.231263	0.8177

R-squared	0.468704	Mean dependent var	0.100343
Adjusted R-squared	0.435498	S.D. dependent var	0.038544
S.E. of regression	0.028959	Sum squared resid	0.067091
F-statistic	14.11504	Durbin-Watson stat	1.604265
Prob(F-statistic)	0.000000		

Regression Equation 5.7.1c: Classic OLS Model for 28 Japanese Firms from 1994-1997 (with Time Trend Variable to Control for Changing Profit Expectations)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1994 1997
Included observations: 4
Number of cross-sections used: 28
Total panel (unbalanced) observations: 86

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	1.570926	5.695349	0.275826	0.7834
CFM?	0.335907	0.057239	5.868533	0.0000
PCT?	0.049346	0.015725	3.137961	0.0024
YEAR?	-0.000782	0.002854	-0.273848	0.7849

R-squared	0.466795	Mean dependent var	0.100343
Adjusted R-squared	0.447288	S.D. dependent var	0.038544
S.E. of regression	0.028655	Sum squared resid	0.067332
F-statistic	23.92901	Durbin-Watson stat	1.613199
Prob(F-statistic)	0.000000		

Regression Equation 5.7.1d: Classic OLS Model for 28 Japanese Firms from 1994-1997 (with Time Trend Variable to Control for Changing Profit Expectations)

Dependent Variable: RDS?
Method: Pooled Least Squares

Sample: 1994 1997
Included observations: 4
Number of cross-sections used: 28
Total panel (unbalanced) observations: 86

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	0.791131	2.847771	0.277807	0.7819
CFM?	0.335908	0.057239	5.868530	0.0000
PCT?	0.049346	0.015725	3.137963	0.0024
YEAR?^2	-1.96E-07	7.15E-07	-0.273852	0.7849

R-squared	0.466795	Mean dependent var	0.100343
Adjusted R-squared	0.447288	S.D. dependent var	0.038544
S.E. of regression	0.028655	Sum squared resid	0.067332
F-statistic	23.92901	Durbin-Watson stat	1.699199
Prob(F-statistic)	0.000000		

Regression Equation 5.7.1e: Classic OLS Model for 28 Japanese Firms from 1994-1997 (with Time Trend Variable to Control for Changing Profit Expectations)

Dependent Variable: RDS?
Method: Pooled Least Squares
Date: 07/23/00 Time: 17:23
Sample: 1994 1997
Included observations: 4
Number of cross-sections used: 28
Total panel (unbalanced) observations: 86

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	3.130514	11.39052	0.274835	0.7841
CFM?	0.335907	0.057239	5.868534	0.0000
PCT?	0.049346	0.015725	3.137961	0.0024
YEAR?^.5	-0.069826	0.254982	-0.273846	0.7849

R-squared	0.466795	Mean dependent var	0.100343
Adjusted R-squared	0.447288	S.D. dependent var	0.038544
S.E. of regression	0.028655	Sum squared resid	0.067332
F-statistic	23.92901	Durbin-Watson stat	1.623199
Prob(F-statistic)	0.000000		

Regression Equation 5.7.2: FGLS Model (Common Intercept) for 28 Japanese Firms from 1994-1997

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1994 1997
Included observations: 4
Number of cross-sections used: 28
Total panel (unbalanced) observations: 86

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	0.008977	0.001818	4.937445	0.0000
CFM?	0.274116	0.036761	7.456794	0.0000
PCT?	0.062770	0.005733	10.94952	0.0000

Weighted Statistics			
R-squared	0.969461	Mean dependent var	0.179732
Adjusted R-squared	0.968725	S.D. dependent var	0.155828
S.E. of regression	0.027558	Sum squared resid	0.063033
F-statistic	1317.401	Durbin-Watson stat	1.790049
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	0.457439	Mean dependent var	0.100343
Adjusted R-squared	0.444365	S.D. dependent var	0.038544
S.E. of regression	0.028731	Sum squared resid	0.068514
Durbin-Watson stat	1.700837		

Regression Equation 5.7.2a: FGLS Model (Common Intercept) for 28 Japanese Firms from 1994-1997 (with *PharMarg* employed as Profit Expectations Proxy)

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)
Date: 07/23/00 Time: 17:35
Sample: 1994 1997
Included observations: 4
Number of cross-sections used: 28
Total panel (unbalanced) observations: 86

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	0.024778	0.013225	1.873559	0.0646
CFM?	0.279500	0.036917	7.571136	0.0000
PCT?	0.060676	0.005947	10.20272	0.0000
PHARMARG?	-0.050231	0.042619	-1.178600	0.2420

Weighted Statistics			
R-squared	0.937511	Mean dependent var	0.164303
Adjusted R-squared	0.935225	S.D. dependent var	0.107252
S.E. of regression	0.027297	Sum squared resid	0.061099
F-statistic	410.0784	Durbin-Watson stat	1.746670
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	0.468072	Mean dependent var	0.100343
Adjusted R-squared	0.448612	S.D. dependent var	0.038544
S.E. of regression	0.028621	Sum squared resid	0.067171
Durbin-Watson stat	1.600498		

Regression Equation 5.7.2b: FGLS Model (Common Intercept) for 28 Japanese Firms from 1994-1997 (with Year Dummy Variables to Control for Profit Expectations)

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1994 1997
Included observations: 4
Number of cross-sections used: 28
Total panel (unbalanced) observations: 86

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	0.008664	0.003008	2.880297	0.0051
CFM?	0.278554	0.039898	6.981628	0.0000
PCT?	0.061488	0.006334	9.708326	0.0000
D94?	-9.46E-05	0.003026	-0.031267	0.9751
D95?	0.001944	0.002842	0.683949	0.4960
D96?	0.001686	0.002813	0.599373	0.5506

Weighted Statistics			
R-squared	0.955290	Mean dependent var	0.170198
Adjusted R-squared	0.952496	S.D. dependent var	0.128128
S.E. of regression	0.027926	Sum squared resid	0.062390
F-statistic	341.8639	Durbin-Watson stat	1.838728
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	0.458357	Mean dependent var	0.100343
Adjusted R-squared	0.424504	S.D. dependent var	0.038544
S.E. of regression	0.029240	Sum squared resid	0.068398
Durbin-Watson stat	1.641315		

Regression Equation 5.7.2c: Classic OLS Model for 28 Japanese Firms from 1994-1997 (with Time Trend Variable to Control for Changing Profit Expectations)

Dependent Variable: RDS?
Method: GLS (Cross Section Weights)

Sample: 1994 1997
Included observations: 4
Number of cross-sections used: 28
Total panel (unbalanced) observations: 86

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	0.531222	1.597065	0.332624	0.7403
CFM?	0.280235	0.039197	7.149409	0.0000
PCT?	0.061818	0.006033	10.24658	0.0000
YEAR?	-0.000262	0.000800	-0.326977	0.7445

Weighted Statistics			
R-squared	0.959109	Mean dependent var	0.176278
Adjusted R-squared	0.957613	S.D. dependent var	0.134942
S.E. of regression	0.027782	Sum squared resid	0.063292
F-statistic	641.1063	Durbin-Watson stat	1.895476
Prob(F-statistic)	0.000000		

Unweighted Statistics			
R-squared	0.459197	Mean dependent var	0.100343
Adjusted R-squared	0.439412	S.D. dependent var	0.038544
S.E. of regression	0.028859	Sum squared resid	0.068292
Durbin-Watson stat	1.742399		

Regression 5.7.3: Random Effects Model with 28 Japanese Firms from 1994-1997

Dependent Variable: RDS?
Method: GLS (Variance Components)

Sample: 1994 1997
Included observations: 4
Number of cross-sections used: 28
Total panel (unbalanced) observations: 86

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	0.046477	0.022137	2.099579	0.0388
CFM?	0.168891	0.059679	2.829995	0.0058
PCT?	0.036122	0.024011	1.504401	0.1363
Random Effects				
_ASA--C	-0.013000			
_BAN--C	-0.022410			
_CHU--C	0.059071			
_DS--C	0.020145			
_DU--C	-0.006793			
_EIS--C	0.026814			
_FUJ--C	0.033439			
_FUS--C	-0.049966			
_GC--C	0.011060			
_HOK--C	0.084163			
_KAK--C	-0.001980			
_KYO--C	-0.023360			
_MS--C	-0.024910			
_MOC--C	0.035037			
_NIK--C	-0.039403			
_NIP--C	0.040336			
_ONO--C	-0.017906			
_SAN--C	-0.011428			
_SHI--C	-0.006462			
_SS--C	-0.036184			
_TAI--C	-0.032319			
_TAK--C	-0.012449			
_TS--C	-0.000532			
_TT--C	0.003388			
_TOR--C	-0.008672			
_TOY--C	0.030896			
_TSU--C	-0.010438			
_YAM--C	-0.017199			

GLS Transformed Regression			
R-squared	0.949403	Mean dependent var	0.100343
Adjusted R-squared	0.948184	S.D. dependent var	0.038544
S.E. of regression	0.008774	Sum squared resid	0.006389
Durbin-Watson stat	1.886964		

Unweighted Statistics including Random Effects			
R-squared	0.961336	Mean dependent var	0.100343
Adjusted R-squared	0.960404	S.D. dependent var	0.038544
S.E. of regression	0.007670	Sum squared resid	0.004882
Durbin-Watson stat	2.469354		

Diagnostic Test: Based Upon Residuals from Equation 5.4.2

Test for Equality of Variances Between Series

Sample: 1994 1997
Included observations: 4

Method	df	Value	Probability
Bartlett	27	42.54149	0.0291
Levene	(27, 58)	4.640829	0.0000
Brown-Forsythe	(27, 58)	2.875058	0.0004

Category Statistics

Variable	Count	Std. Dev.	Mean Abs. Mean Diff.	Mean Abs. Median Diff.
RESID_ASA	3	0.004547	0.003224	0.003008
RESID_BAN	1	NA	0.000000	0.000000
RESID_CHU	2	0.013532	0.009569	0.009569
RESID_DS	4	0.015480	0.012315	0.012315
RESID_DU	1	NA	0.000000	0.000000
RESID_EIS	4	0.008345	0.005593	0.005593
RESID_FUJ	4	0.008236	0.006271	0.006271
RESID_FUS	3	0.004006	0.003083	0.002349
RESID_GC	3	0.009623	0.007204	0.006151
RESID_HOK	2	0.018292	0.012935	0.012935
RESID_KAK	4	0.006599	0.004685	0.004685
RESID_KYO	3	0.006124	0.004600	0.003896
RESID_MS	4	0.001589	0.001181	0.001181
RESID_MOC	4	0.003001	0.002296	0.002296
RESID_NIK	2	0.001925	0.001361	0.001361
RESID_NIP	3	0.008745	0.006624	0.005489
RESID_ONO	1	NA	0.000000	0.000000
RESID_SAN	4	0.006488	0.004441	0.004147
RESID_SHI	4	0.025830	0.021310	0.021310
RESID_SS	3	0.003070	0.002298	0.001963
RESID_TAI	4	0.008500	0.007076	0.007076
RESID_TAK	4	0.003156	0.002543	0.002543
RESID_TS	3	0.004523	0.003195	0.002995
RESID_TT	1	NA	0.000000	0.000000
RESID_TOR	4	0.012225	0.008970	0.008970
RESID_TOY	3	0.013051	0.009856	0.008237
RESID_TSU	4	0.006873	0.005099	0.003865
RESID_YAM	4	0.004147	0.003035	0.003035
All	86	0.028158	0.005898	0.005618

Bartlett weighted standard deviation: 0.009932

Regression 6.1: OLS Regression of Pharmaceutical Profitability on % of Total Pharmaceutical Sales Accounted for by U.S. Pharmaceutical Sales (12 Firms 1996)[1]

Dependent Variable: MARG
Method: Least Squares

Sample: 1 12
Included observations: 12

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	0.116281	0.046998	2.474194	0.0329
US_TOT	0.351549	0.076361	4.603756	0.0010

R-squared	0.679431	Mean dependent var	0.323639
Adjusted R-squared	0.647374	S.D. dependent var	0.078283
S.E. of regression	0.046486	Akaike info criterion	-3.148304
Sum squared resid	0.021610	Schwarz criterion	-3.067486
Log likelihood	20.88983	F-statistic	21.19457
Durbin-Watson stat	1.424229	Prob(F-statistic)	0.000975

Regression 6.2: An OLS Model of the Determinants of Pharmaceutical R&D (Specification 1)

Dependent Variable: RDS
Method: Least Squares

Sample: 1 48
Included observations: 48

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	0.004789	0.012190	0.392899	0.6963
CFM	0.119770	0.046799	2.559266	0.0140
PCT	0.075855	0.022323	3.398023	0.0015
PMARG	0.102963	0.042730	2.409640	0.0202

R-squared	0.758082	Mean dependent var	0.115107
Adjusted R-squared	0.741588	S.D. dependent var	0.049739
S.E. of regression	0.025285	Akaike info criterion	-4.437592
Sum squared resid	0.028130	Schwarz criterion	-4.281658
Log likelihood	110.5022	F-statistic	45.95995
Durbin-Watson stat	0.642719	Prob(F-statistic)	0.000000

[1] It is important to note that the DW-statistic in this, and the following few models, cannot be interpreted in the usual way. This is because the data are pooled and the method of estimation used was OLS.

Regression 6.3: An OLS Model of the Determinants of Pharmaceutical R&D (Specification 2)

Dependent Variable: RDS
Method: Least Squares

Sample: 1 48
Included observations: 48

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.004086	0.013456	-0.303646	0.7629
CFM	0.119466	0.046190	2.586427	0.0132
PCT	0.075432	0.022034	3.423360	0.0014
PMARG	0.054006	0.053699	1.005708	0.3202
PCT_US	0.042046	0.028549	1.472768	0.1481

R-squared	0.769699	Mean dependent var	0.115107
Adjusted R-squared	0.748276	S.D. dependent var	0.049739
S.E. of regression	0.024955	Akaike info criterion	-4.445137
Sum squared resid	0.026779	Schwarz criterion	-4.250220
Log likelihood	111.6833	F-statistic	35.92807
Durbin-Watson stat	0.686372	Prob(F-statistic)	0.000000

Regression 6.4: An OLS Model of the Determinants of Pharmaceutical R&D (Specification 3)

Dependent Variable: RDS
Method: Least Squares
Date: 08/03/00 Time: 16:29
Sample: 1 48
Included observations: 48

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.001109	0.013128	-0.084481	0.9331
CFM	0.133384	0.044074	3.026389	0.0041
PCT	0.074951	0.022032	3.401901	0.0014
PCT_US	0.059820	0.022424	2.667655	0.0107

R-squared	0.764282	Mean dependent var	0.115107
Adjusted R-squared	0.748210	S.D. dependent var	0.049739
S.E. of regression	0.024958	Akaike info criterion	-4.463554
Sum squared resid	0.027409	Schwarz criterion	-4.307621
Log likelihood	111.1253	F-statistic	47.55457
Durbin-Watson stat	0.691635	Prob(F-statistic)	0.000000

Regression Model 6.5: A Model of the Determinants of Pharmaceutical R&D (Quadratic Profit Expectations)

Dependent Variable: RDS
Method: Least Squares

Sample: 1 48
Included observations: 48

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	0.019629	0.008232	2.384381	0.0215
CFM	0.092333	0.045044	2.049844	0.0464
PCT	0.083950	0.021056	3.987058	0.0002
(PMARG)^2	0.189834	0.053094	3.575442	0.0009

R-squared	0.787808	Mean dependent var	0.115107
Adjusted R-squared	0.773341	S.D. dependent var	0.049739
S.E. of regression	0.023680	Akaike info criterion	-4.568700
Sum squared resid	0.024673	Schwarz criterion	-4.412766
Log likelihood	113.6488	F-statistic	54.45319
Durbin-Watson stat	0.711232	Prob(F-statistic)	0.000000

Regression Model 6.6: A Model of the Determinants of Pharmaceutical R&D (Cubic Profit Expectations)

Dependent Variable: RDS
Method: Least Squares

Sample: 1 48
Included observations: 48

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	0.027558	0.007816	3.526120	0.0010
CFM	0.085783	0.043496	1.972207	0.0549
PCT	0.088827	0.020512	4.330524	0.0001
(PMARG)^3	0.288263	0.070649	4.080217	0.0002

R-squared	0.801329	Mean dependent var	0.115107
Adjusted R-squared	0.787783	S.D. dependent var	0.049739
S.E. of regression	0.022913	Akaike info criterion	-4.634538
Sum squared resid	0.023101	Schwarz criterion	-4.478605
Log likelihood	115.2289	F-statistic	59.15710
Durbin-Watson stat	0.744322	Prob(F-statistic)	0.000000

Regression Model 6.7: A Model of the Determinants of Pharmaceutical R&D (Interactive Variable Formulation)

Dependent Variable: RDS
Method: Least Squares

Sample: 1 48
Included observations: 48

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	0.013187	0.008357	1.577990	0.1217
CFM	0.091076	0.042863	2.124798	0.0393
PCT	0.082804	0.020291	4.080762	0.0002
(PMARG)*(PCT_US)	0.143363	0.034967	4.099935	0.0002

R-squared	0.801856	Mean dependent var	0.115107
Adjusted R-squared	0.788346	S.D. dependent var	0.049739
S.E. of regression	0.022883	Akaike info criterion	-4.637194
Sum squared resid	0.023040	Schwarz criterion	-4.481261
Log likelihood	115.2927	F-statistic	59.35344
Durbin-Watson stat	0.724653	Prob(F-statistic)	0.000000

Table 6.1: Regression Coefficient Summary Table

Estimated Models for the Determinants of R&D Intensity (International Data 1994-1997)

	Intercept	*CFM*	*PCT*	$E\pi$
Model 1 *(Linear Profit Expectations)*	**0.004789**	**0.11977**	**0.075855**	**0.10296**
Model 3 *(%US proxy for expected profits)*	**-0.0011**	**0.1334**	**0.07495**	**0.0598**
Quadratic Formulation *(Expected profits = Pmarg^2)*	**0.019629**	**0.092333**	**0.08395**	**0.189834**
Cubic Formulation *(Expected profits = Pmarg^3)*	**0.02755**	**0.08578**	**0.0888**	**0.28826**
Interactive Formulation *(Expected profits = (Pmarg)(%US)*	**0.013187**	**0.091076**	**0.0828**	**0.14336**

Table 6.2: Modeling the Impact of Pharmaceutical Price Controls in the U.S.

Estimating the Impact of a Pharmaceutical Price Control Policy in the U.S.

Model	*Pre-Price Control R&D Investment Intensity*	*Post-Price Control R&D Investment Intensity*	*Average Reduction in R&D Investment Intensity*	*Percentage Reduction*
Model 1 *(Linear Profit Expectations)*	**0.1151**	**0.0942**	**0.0209**	**18.12%**
Model 3 *(%US proxy for expected profits)*	**0.1151**	**0.0798**	**0.0353**	**30.64%**
Quadratic Formulation *(Expected profits = $Pmarg^2$)*	**0.1151**	**0.0964**	**0.0187**	**16.28%**
Cubic Formulation *(Expected profits = $Pmarg^3$)*	**0.1151**	**0.1030**	**0.0120**	**10.47%**
Interactive Formulation *(Expected profits = (Pmarg)(%US)*	**0.1151**	**0.0864**	**0.0287**	**24.98%**

Appendix 2

Examining the Issue of Causality: Industrial Research and Development and Firm Profit Margins in the Ethical Pharmaceutical Industry

Section A2.1: Introduction

The theoretical issue of causality between firm profitability and firm research and development spending has been addressed in virtually every major study of industrial research and development. Consequently, a possibility that was considered at the onset of this research was that of a simultaneous determination of R&D. Whilst the literature on *pharmaceutical* R&D has presumed a causal relationship whereby R&D is determined by lagged firm profits, it was deemed important to first consider the appropriateness of this specification. As will be shown in this appendix, the reduced form, one-way-causality specification employed by earlier researchers was found to have some econometric merit, however, the evidence was not overwhelming. In light of these findings, and because the research in this thesis builds considerably upon the earlier work in this field, the previously-established-non-simultaneous model was ultimately adopted.

It has been suggested that profits may drive future research and development for three primary reasons:

1) Increases in profits necessarily increase cash flows which, when capital market imperfections exist, are likely to increase the optimal level of R&D expenditures. This, in fact, was the primary hypothesis of this thesis. Thus, as profits rise, ceteris paribus, the increase in the cash flows of the firm will increase

expenditures on R&D. In short, higher profits increase cash flows, which, as developed fully in Chapter 3, are the cheapest source of R&D finance.

2) Secondly, as was originally posited by Schumpeter in 1950, monopoly power provides firms with above normal profits and greater security. This security, Schumpeter argued, provides firms with a greater opportunity and ability to undertake R&D--which is inherently risky relative to other forms of investment. Thus, firms in the pharmaceutical industry, which have been characterized as having substantial monopoly power, may respond to higher profit margins by increasing research and development intensity. While this is similar to the first reason, it is distinct in that it focuses on the relationship between profits and security for firms undertaking risky R&D, and not the cost of R&D finance.

3) Past or present profits may influence the expectations of returns from current R&D spending. Specifically, high firm profitability may elevate the expected returns on current R&D investments.

However, other possible relationships may exist. For example, research and development may influence future profitability. Alternatively, R&D and profits may be influenced simultaneously by a third factor, for example exogenous surges in demand. There has been empirical evidence to support both directions of causality as well as simultaneous causality (in the broader economic literature). The results found for the pharmaceutical industry during 1974-1994 time-period seem to suggest a simultaneous determination. However, there are strong theoretical, as well as empirical, reasons to support the position that causality may run primarily from profits to R&D. Consequently, the focus of this research has focused on the determinants of R&D intensity—with a focus on the marginal impact of cash flows on R&D intensity.

Section A2.2: The Data

To test the various model specifications, data were obtained on eleven major pharmaceutical firms over the period from1972 to1994.

Specifically, the firms included in this sample were:

1) Abbott Laboratories
2) American Home Products
3) Bristol Myers
4) Johnson & Johnson
5) Lilly
6) Merck
7) Pfizer
8) Schering Plough
9) Syntex
10) Upjohn
11) Warner Lambert

Section A2.3.1: The Models

To econometrically test for the direction of causality a model similar to Branch's (1974) was utilized. That is, distributed lag analyses were performed. This part of the analysis was not the focus of the dissertation, but it did provide a nice first step toward the development of the R&D intensity models that were ultimately developed and used to test the dissertation's primary hypothesis.

Section A2.3.2: The Branch Model

Branch examined 7 industries using data from 1950 to 1965—the pharmaceutical industry was one of these industries. There are differences between the model Branch

used to explore the causality issue and the model outlined here; however, these differences were minor and were primarily the result of the data used to construct the model variables. Following Branch-type model specification and empirical findings, other models will be estimated and the results reported—specifically a series of Granger Causality model specifications will be tested to further examine the question of causality.

Section A2.3.3: *Hypothesis 1: R&D Leads to Firm Profitability*

There are several reasons why firms are likely to have differences in their rates of profitability. One of these reasons may be that firms have different levels of human and non-human resources. Another reason may be unexpected changes in demand for a firm's products. Furthermore, profits may be influenced over time by the business cycle, industry monopoly power, and past research and development. The aforementioned reasons suggest the following model:

$$r_{it} = \gamma_i F_i + \beta_0 H_t + \beta_1 I_t + \beta_2 \left[\varepsilon \frac{RD_{i\tau}}{S_{i\tau}} + \frac{RD_{i\tau-1}}{S_{i\tau-1}} + \lambda \frac{RD_{i\tau-2}}{S_{i\tau-2}} + \lambda^2 \frac{RD_{i\tau-3}}{S_{i\tau-3}} + \ldots + \lambda^{n-1} \frac{RD_{i\tau-n}}{S_{i\tau-n}} + \ldots \right] \quad (1)$$

Where the variables in (1) are defined as follows:

$r_{it} = \frac{profits}{sales}$ for firm i in year t;

$F_i = 1$ if Firm i, 0 if not firm i;

H_t = A measure of industry monopoly power obtained from U.S. census data for for the pharmaceutical industry. Note: this census data was collected at five year intervals. Consequently, linear interpolation was utilized to obtain

estimates for non-census years. Specifically, $H_t = \sum_i^n s_{it}^2$;

I_t = Percent deviation from the trend of the Federal Reserve Board's Production Index in year t. An exponential, constant percentage growth rate time trend model was estimated to generate the percentage deviation from the industry trend in year t. Data were obtained from the Federal Reserve Board's productivity index for the pharmaceutical industry;

$RD_{i\tau}$ = Research and development expenditures of firm i in year τ ,

(where τ = t- years before beginning of first lagged $\frac{RD_i}{S_i}$ variable);

$S_{i\tau}$ = Sales for firm i in year τ , where τ = t- years before beginning of the first lagged $\frac{RD_i}{S_i}$ variable.

Clearly, this specification assumes that current profits are, among other things, a function of a firm's geometrically lagged R&D intensity. To estimate this model a Koyck transformation was employed. Specifically, the equation was lagged one period and multiplied through by the weight parameter λ to obtain the following equation:

$$\lambda r_{it-1} = \lambda\gamma_i F_i + \lambda\beta_0 H_t + \lambda\beta_1 I_{t-1} + \lambda\beta_2 \left[\varepsilon \frac{RD_{i\tau-1}}{S_{i\tau-1}} + \frac{RD_{i\tau-2}}{S_{i\tau-2}} + \lambda \frac{RD_{i\tau-3}}{S_{i\tau-3}} + \lambda^2 \frac{RD_{i\tau-4}}{S_{i\tau-4}} + \ldots + \lambda^{n-1} \frac{RD_{i\tau-(n-1)}}{S_{i\tau-(n-1)}} + \ldots \right] \quad (2)$$

Equation (2) was then subtracted from equation (1) and the terms were collected. The resulting equation is the Koyck transformation and may be estimated statistically:

$$r_{it} = \gamma_t(1-\lambda)F_i + \beta_0(H_t - \lambda H_{t-1}) + \beta_1(I_t - \lambda I_{t-1}) + \beta_2(\varepsilon\frac{RD_{i\tau}}{S_{i\tau}} + (1-\varepsilon\lambda)\frac{RD_{i\tau-1}}{S_{i\tau-1}}) + \lambda r_{it-1} \quad (3)$$

In order to estimate this equation, a weight of ε was assigned to the first R&D intensity variable and an initial estimate of λ was selected to define the variables $I_t - \lambda I_{t-1}$ and $H_t - \lambda H_{t-1}$. This equation was then estimated and the coefficient on the lagged profit margin variable $\hat{\lambda}$ was substituted back into the original equation. The regression was then run again. This procedure was continued in an iterative fashion until the λ's were approximately equal. Various τs (beginning period of the lagged R&D) were tried and various ε s tried. The τ yielding the highest R^2 and the ε yielding the highest t-statistic for β_2 were selected. The Herfindahl proxy for monopoly power and market concentration was found insignificant in every variable and model specification tested. This affirmed earlier empirical findings for such variables (Grabowski 1967, Grabowski and Vernon 1978). This was not surprising due to the fact that there was little change in market concentration in the pharmaceutical industry over the study period (1974-1994). This is shown below in Table A.2.

Table A2.1

Pharmaceutical Industry Market Concentration Measures (1977-1992)

Year of Census	Herfindahl Index $H_t = \sum_i^n s_{it}^2$	Concentration Ratio (8 largest firms %)	Concentration Ratio (20 largest firms %)	Concentration Ratio (50 largest firms %)
1992	341	26	42	72
1987	273	22	36	65
1982	318	26	42	69
1977	NA	24	43	73

Source: U.S. Census Bureau--data for major industrial groups (major drugs), 1977, 1982, 1987, and 1992.

The regression results for this model are presented next. The first regression (A.2.1) is the model used to estimate the trend in the Federal Reserve Board's pharmaceutical industry productivity index from 1974 to 1994. An exponential, constant percentage growth rate specification was used (see Branch 1974). These results are presented below.

Regression A2.1: Estimating the Trend in Pharmaceutical Productivity

Dependent Variable: LN_Y
Method: Least Squares

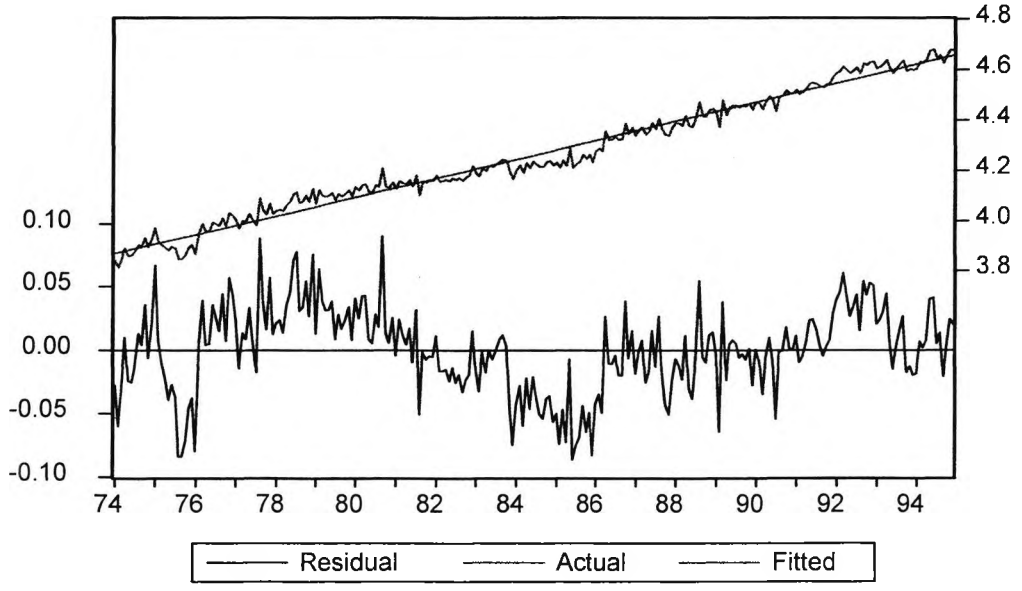
Sample: 1974:01 1994:12
Included observations: 252

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	3.864477	0.004308	897.0740	0.0000
TIME	0.003139	2.95E-05	106.3152	0.0000

R-squared	0.978360	Mean dependent var	4.261501
Adjusted R-squared	0.978274	S.D. dependent var	0.231285
S.E. of regression	0.034091	Akaike info criterion	-3.911666
Sum squared resid	0.290548	Schwarz criterion	-3.883655
Log likelihood	494.8699	F-statistic	11302.91
Durbin-Watson stat	0.742737	Prob(F-statistic)	0.000000

This estimated productivity trend is also depicted in Figure A.2.1

Figure A2.1: The Trend in Pharmaceutical Productivity (1974 to 1994)



The preceding results imply the following trend in pharmaceutical productivity.

$$\hat{Y}_t = \exp(c + 3.86time) \quad (4)$$

Therefore, the business cycle variable, which is defined as the percentage deviation from the industry trend, was calculated as follows:

$$\text{Business Cycle Variable} = \left[\frac{\hat{Y}_t}{Y_t} - 1\right] \times 100\% \quad (5)$$

This variable, whilst it performed better than the Herfindahl-type variable, was not found to be statistically significant. The regression results using the Koyck transformation, where profit margins were defined as the dependent variable, are reported next in A.2.2.

Equation A2.2: R&D Leads to Firm Profitability

Dependent Variable: PROFIT_MARG
Method: Least Squares

Sample: 4 21 25 42 46 63 67 84 88 105 109 126 130 147 151 168
172 188 192 209 213 230
Included observations: 197

Variable	Coefficient	Std. Error	t-Statistic	Prob.
.495*ABB	0.113725	0.023439	4.851865	0.0000
.495*AHP	0.142192	0.023859	5.959711	0.0000
495*BMS	0.000110	2.11E-05	5.207033	0.0000
.495*JNJ	0.078956	0.019337	4.083203	0.0001
.495*LIL	0.133290	0.026324	5.063448	0.0000
.495*MRK	0.159392	0.028160	5.660241	0.0000
.495*PFE	0.099165	0.020979	4.726892	0.0000
.495*SHP	0.119612	0.024075	4.968423	0.0000
.495*SYN	0.141825	0.029594	4.792284	0.0000
.495*UPJ	0.081569	0.023390	3.487299	0.0006
.495*WLA	0.048578	0.017052	2.848774	0.0049
BUS_CYC-.505*LAG1_BUS_CYC	0.001548	0.001105	1.401251	0.1628
.88*LAG2_RDS+.556*LAG3_RDS	0.099261	0.049126	2.020529	0.0448
LAG_PROFIT_MARG	0.504938	0.067209	7.512958	0.0000

R-squared	0.652717	Mean dependent var	0.131162
Adjusted R-squared	0.628046	S.D. dependent var	0.048614
S.E. of regression	0.029649	Akaike info criterion	-4.130387
Sum squared resid	0.160865	Schwarz criterion	-3.897063
Log likelihood	420.8431	F-statistic	26.45750
Durbin-Watson stat	2.068836	Prob(F-statistic)	0.000000

The results reported in A.2.2 are the results of the iterative search process described earlier. This process established the following parameter values for regression model A.2.2: $\lambda = 0.505$, $\varepsilon = 0.88$, and $\tau = 2$.

As may be seen above, the t-statistic on the geometrically lagged R&D variable is significant at the 5% level. This indicates that lagged R&D intensity does indeed exert a positive influence on firm profit margins. However, as will be seen shortly, the evidence is even more compelling for the argument that lagged firm profit margins positively affect R&D intensities. We will turn to this now.

Section A2.3.4: *Hypothesis 2: Firm Profitability Leads to R&D Investment*

For the model where R&D is a function of geometrically lagged profits, theory suggests the following model:

$$\frac{RD_{it}}{S_{it}} = \gamma_i F_i + \alpha_2(\varepsilon r_{i\tau} + r_{i\tau-1} + \lambda r_{i\tau-2} + \lambda^2 r_{i\tau-3} + \ldots + \lambda^{n-1} r_{i\tau-n} + \ldots) \qquad (6)$$

To estimate this equation, a Koyck transformation was performed to yield:

$$\frac{RD_{it}}{S_{it}} = \gamma_i(1-\lambda)F_i + \alpha_1(M_t - \lambda M_{t-1}) + \alpha_2(\varepsilon r_{i\tau} + (1-\varepsilon\lambda)r_{i\tau-1}) + \lambda\frac{RD_{it-1}}{S_{it-1}} \qquad (7)$$

The iterative process described in the last section, which was used to estimate equation (3), was also used to estimate equation (7). These regression results are presented below:

Equation A2.3: Firm Profitability Leads to R&D

Dependent Variable: RDS
Method: Least Squares

Sample: 2 21 23 42 44 63 65 84 86 105 107 126 128 147 149 168
170 188 190 209 211 230
Included observations: 219

Variable	Coefficient	Std. Error	t-Statistic	Prob.
.531*AB	0.013863	0.012684	1.093005	0.2757
.531*AH	-0.028464	0.013872	-2.051921	0.0414
.531*BM	0.004085	0.011944	0.342062	0.7327
.531*JJ	0.018422	0.010942	1.683519	0.0938
.531*LI	0.038612	0.015080	2.560480	0.0112
.531MK	0.012963	0.016162	0.802118	0.4234
.531*PZ	0.024653	0.011933	2.065898	0.0401
.531*SP	0.016814	0.014015	1.199685	0.2316
.531*SX	0.043506	0.017118	2.541468	0.0118
.531*UP	0.072373	0.013768	5.256618	0.0000
.531*WL	0.015933	0.010043	1.586460	0.1142
.42*LAG1_R+.803*LAG2_R	0.219636	0.039245	5.596591	0.0000
LG_RDS	0.469557	0.055227	8.502284	0.0000

R-squared	0.766783	Mean dependent var	0.084355
Adjusted R-squared	0.753198	S.D. dependent var	0.036983
S.E. of regression	0.018373	Akaike info criterion	-5.098356
Sum squared resid	0.069538	Schwarz criterion	-4.897179
Log likelihood	571.2700	F-statistic	56.44158
Durbin-Watson stat	1.465984	Prob(F-statistic)	0.000000

The results reported in A.2.3 are the results of the iterative search process described earlier. This process established the following parameter values for regression model A.2.3: $\lambda = 0.469$, $\varepsilon = 0.42$, and $\tau = 1$.

The regression results in A.2.3 show a very strong statistical association between lagged firm profit margin and R&D intensity. In fact, the t-statistic for this lagged profit margin variable was 5.60 (P<0.0001). This was much higher than the t-statistic of 2.02 for the lagged R&D variable in equation (3). Also, and of considerable interest, the coefficient for the lagged profit margin variable was more than twice that of the coefficient for the lagged R&D variable (0.220 versus 0.099, respectively).

The regression analyses indicate that the 'strongest' statistical relationship exists between R&D and lagged profits. However, because lagged R&D was also found to a marginally significant predictor of profits, there exists the possibility of dual causality, and hence a simultaneous determination of profits and R&D. This would imply that the two equations taken together constitute a dynamic system.

Indeed, if a dynamic system is the correct specification, it is important to consider the stability of such a system. To explore this we consider an initial change in $\frac{RD}{S}$, $\delta\frac{RD}{S}$. The initial effect is to change r by $\beta_2\delta\frac{RD}{S}$. However, this will then change $\frac{RD}{S}$ by $\alpha_2(\beta_2\delta\frac{RD}{S})$. Therefore, it is easy to see how this simultaneous interaction process continues until equilibrium is reached where an initial $\delta\frac{RD}{S}$ results in an ultimate change in $\frac{RD}{S}$, $\Delta\frac{RD}{S}$, equal to the sum of the following infinite series:

$$\Delta\frac{RD}{S}=\alpha_2\beta_2(\delta\frac{RD}{S})+\alpha^2\beta^2(\delta\frac{RD}{S})+\alpha^3\beta^3(\delta\frac{RD}{S})+\alpha^4\beta^4(\delta\frac{RD}{S})+...+\alpha^n\beta^n(\delta\frac{RD}{S})+..., \qquad (7)$$

Or, more succinctly:

$$\Delta\frac{RD}{S}=\sum_{i}^{\infty}(\alpha_2\beta_2)^i(\delta\frac{RD}{S}). \qquad (8)$$

This sum can then be shown to converge to $\frac{\delta\frac{RD}{S}}{(1-\alpha_2\beta_2)}$ when $\alpha_2\beta_2<1$.

Likewise, it can be shown that an initial change in r of δr results in an ultimate change in r of Δr.

Because the evidence obtained from these models are somewhat limited by the aforementioned Koyck and/or Branch assumptions, a more traditional causality analysis will also be undertaken. We will turn to this now.

Section A2.4.1: Granger Causality: Examining the Causal Relationship Between Firm Profits, Cash Flows, and R&D Investment

Another means by which the question of causality may be addressed is through the Granger Causality test. This test is theoretically grounded by the premise that the

future cannot cause the past or the present. Thus, if a particular event, say event x, occurs after event y, we know that event x cannot cause event y[1]. Therefore, Granger (1969) proposed estimating the following bivariate models:

$$y_t = \sum_{i=1}^{k} \alpha_i y_{t-i} + \sum_{i=1}^{k} \beta_i x_{t-i} + u_t \qquad (9)$$

$$x_t = \sum_{i=1}^{k} \alpha_i x_{t-i} + \sum_{i=1}^{k} \beta_i y_{t-i} + u_t \qquad (10)$$

In the above model, and specifically equation (9), if $\beta_i = 0 \ \ \forall i$ where $i \in (1...k)$, then x_t fails to Granger-cause y_t. Likewise, for equation (10), if $\beta_i = 0 \ \ \forall i$ where $i \in (1...k)$, then y_t is said to fail to Granger-cause x_t. Therefore, the test developed by Granger is one that tests the joint null hypothesis that $\beta_i = 0 \ \ \forall i$ where $i \in (1...k)$ for both equation (9) and (10). Whilst E-Views does not directly calculate the Granger-causality test for series in panel data sets, equations (9) and (10) may be directly estimated so that the aforementioned joint null hypothesis can be tested using Eviews Wald-coefficient test procedures. This was the approach undertaken in the forthcoming analyses. Before presenting the empirical results, it should be noted that the length of the lag k is, to some extent, arbitrary. However, the lag length should, if possible, correspond to reasonable beliefs about the longest time over which one of the variables may exert an effect on the other.

Using data on firm R&D intensity and firm profitability, equations (9) and (10) were estimated for lags ranging from 2 to 5 years. These bivariate regressions—and the Wald-coefficient tests for the previously discussed joint null hypotheses—are presented next.

***Section A2.4.2**: Empirical Results on the Direction of Causality: Profits and R&D*

[1] However, it is crucial to note that if event x does occur before event y, this does not necessarily imply that x 'causes' y. Hence, the Granger Causality test may be more accurately described as a test of precedence and not causality.

Granger Causality Test 1

***Null Hypothesis*:** Firm R&D investment intensity does not Granger-cause firm profitability.

***Lags employed*:** 5

Table A2.4: Bivariate Regression of Profitability on Lagged R&D Investment and Profitability

Dependent Variable: PROFIT?
Method: Pooled Least Squares

Sample(adjusted): 1974 1989
Included observations: 16 after adjusting endpoints
Number of cross-sections used: 10
Total panel (unbalanced) observations: 159

Variable	Coefficient	Std. Error	t-Statistic	Prob.
RD?(1)	0.041339	0.031529	1.311126	0.1920
RD?(2)	0.007953	0.031961	0.248824	0.8039
RD?(3)	0.011779	0.029075	0.405121	0.6860
RD?(4)	-0.010199	0.028359	-0.359638	0.7197
RD?(5)	0.016142	0.023683	0.681560	0.4967
PROFIT?(1)	1.105409	0.102108	10.82589	0.0000
PROFIT?(2)	-0.381266	0.131584	-2.897518	0.0044
PROFIT?(3)	-0.112806	0.129603	-0.870397	0.3856
PROFIT?(4)	0.296742	0.128052	2.317344	0.0219
PROFIT?(5)	-0.230398	0.095059	-2.423735	0.0166

R-squared	0.761147	Mean dependent var	0.256063
Adjusted R-squared	0.728499	S.D. dependent var	0.013319
S.E. of regression	0.006940	Sum squared resid	0.006695
Log likelihood	575.3763	F-statistic	49.21655
Durbin-Watson stat	1.910466	Prob(F-statistic)	0.000000

Wald-coefficient test results for the null hypothesis C(1)=C(2)=C(3)=C(4)=C(5)=0

(Note: C(i)= the i^{th} regression coefficient in the above table):

Wald Test:
Equation: FIRM

Null Hypothesis:	C(1)=0 C(2)=0 C(3)=0 C(4)=0 C(5)=0		
F-statistic	0.687773	Probability	0.633426
Chi-square	3.438863	Probability	0.632658

Granger Causality Test 2

***Null Hypothesis*:** Firm profitability does not Granger-cause firm R&D investment intensity.

***Lags employed*:** 5

Table A2.5: Bivariate Regression of R&D Investment Intensity on Lagged Profitability and R&D Investment

Dependent Variable: RD?
Method: Pooled Least Squares

Sample(adjusted): 1974 1989
Included observations: 16 after adjusting endpoints
Number of cross-sections used: 10
Total panel (unbalanced) observations: 159

Variable	Coefficient	Std. Error	t-Statistic	Prob.
RD?(1)	0.345200	0.072873	4.737030	0.0000
RD?(2)	0.171556	0.073871	2.322364	0.0217
RD?(3)	-0.069426	0.067200	-1.033118	0.3033
RD?(4)	-0.015746	0.065546	-0.240233	0.8105
RD?(5)	0.030937	0.054739	0.565174	0.5729
PROFIT?(1)	0.441346	0.235999	1.870116	0.0636
PROFIT?(2)	0.127519	0.304125	0.419296	0.6756
PROFIT?(3)	-0.105772	0.299547	-0.353106	0.7245
PROFIT?(4)	0.027658	0.295964	0.093451	0.9257
PROFIT?(5)	0.357997	0.219708	1.629426	0.1055

R-squared	0.831999	Mean dependent var	0.072241
Adjusted R-squared	0.809035	S.D. dependent var	0.036706
S.E. of regression	0.016040	Sum squared resid	0.035764
Log likelihood	442.1665	F-statistic	76.48641
Durbin-Watson stat	2.229170	Prob(F-statistic)	0.000000

Wald-coefficient test results for the null hypothesis C(6)=C(7)=C(8)=C(9)=C(10)=0

Wald Test:
Equation: FIRM

Null Hypothesis:	C(6)=0 C(7)=0 C(8)=0 C(9)=0 C(10)=0		
F-statistic	2.961262	Probability	0.014060
Chi-square	14.80631	Probability	0.011223

Granger Causality Test 3

***Null Hypothesis*:** Firm R&D investment intensity does not Granger-cause firm profitability.

***Lags employed*:** 4

Table A2.6: Bivariate Regression of Profitability on Lagged R&D Investment and Profitability

Dependent Variable: PROFIT?
Method: Pooled Least Squares

Sample(adjusted): 1974 1990
Included observations: 17 after adjusting endpoints
Number of cross-sections used: 10
Total panel (unbalanced) observations: 169

Variable	Coefficient	Std. Error	t-Statistic	Prob.
RD?(1)	0.028135	0.029316	0.959722	0.3387
RD?(2)	0.005493	0.028086	0.195566	0.8452
RD?(3)	0.005562	0.027649	0.201150	0.8409
RD?(4)	-0.016273	0.022784	-0.714236	0.4762
PROFIT?(1)	1.025372	0.092009	11.14423	0.0000
PROFIT?(2)	-0.303003	0.125749	-2.409585	0.0172
PROFIT?(3)	-0.065695	0.125769	-0.522343	0.6022
PROFIT?(4)	0.077461	0.092633	0.836218	0.4044

R-squared	0.788302	Mean dependent var	0.257509
Adjusted R-squared	0.764469	S.D. dependent var	0.014157
S.E. of regression	0.006871	Sum squared resid	0.007128
Log likelihood	611.4216	F-statistic	80.32590
Durbin-Watson stat	1.686941	Prob(F-statistic)	0.000000

Wald-coefficient test results for the null hypothesis C(1)=C(2)=C(3)=C(4)=0

Wald Test:
Equation: FIRM

Null Hypothesis:	C(1)=0 C(2)=0 C(3)=0 C(4)=0		
F-statistic	0.519757	Probability	0.721324
Chi-square	2.079028	Probability	0.721226

Granger Causality Test 4

***Null Hypothesis*:** Firm profitability does not Granger-cause firm R&D investment intensity.

***Lags employed*:** 4

Table A2.7: Bivariate Regression of R&D Investment Intensity on Lagged Profitability and R&D Investment

Dependent Variable: RD?
Method: Pooled Least Squares

Sample(adjusted): 1974 1990
Included observations: 17 after adjusting endpoints
Number of cross-sections used: 10
Total panel (unbalanced) observations: 169

Variable	Coefficient	Std. Error	t-Statistic	Prob.
RD?(1)	0.336055	0.077234	4.351138	0.0000
RD?(2)	0.143131	0.073992	1.934419	0.0549
RD?(3)	-0.047146	0.072841	-0.647237	0.5185
RD?(4)	0.115168	0.060024	1.918677	0.0569
PROFIT?(1)	0.632893	0.242400	2.610944	0.0099
PROFIT?(2)	-0.041916	0.331289	-0.126525	0.8995
PROFIT?(3)	-0.131170	0.331341	-0.395878	0.6928
PROFIT?(4)	0.328574	0.244044	1.346374	0.1802

R-squared	0.822438	Mean dependent var	0.076021
Adjusted R-squared	0.802448	S.D. dependent var	0.040724
S.E. of regression	0.018101	Sum squared resid	0.049473
Log likelihood	447.7112	F-statistic	99.91540
Durbin-Watson stat	1.835668	Prob(F-statistic)	0.000000

Wald-coefficient test results for the null hypothesis C(5)=C(6)=C(7)=C(8)=0

Wald Test:
Equation: FIRM

Null Hypothesis:	C(5)=0 C(6)=0 C(7)=0 C(8)=0		
F-statistic	3.919942	Probability	0.004590
Chi-square	15.67977	Probability	0.003480

Granger Causality Test 5

***Null Hypothesis*:** Firm R&D investment intensity does not Granger-cause firm profitability.

***Lags employed*:** 3

Table A2.8: Bivariate Regression of Profitability on Lagged R&D Investment and Profitability

Dependent Variable: PROFIT?
Method: Pooled Least Squares

Sample(adjusted): 1974 1991
Included observations: 18 after adjusting endpoints
Number of cross-sections used: 10
Total panel (unbalanced) observations: 179

Variable	Coefficient	Std. Error	t-Statistic	Prob.
RD?(1)	0.008853	0.026150	0.338546	0.7354
RD?(2)	0.030434	0.027759	1.096387	0.2745
RD?(3)	0.011099	0.022825	0.486254	0.6274
PROFIT?(1)	1.055221	0.091953	11.47567	0.0000
PROFIT?(2)	-0.347361	0.126374	-2.748672	0.0067
PROFIT?(3)	0.023763	0.094070	0.252612	0.8009

R-squared	0.813288	Mean dependent var	0.259324
Adjusted R-squared	0.796105	S.D. dependent var	0.015673
S.E. of regression	0.007077	Sum squared resid	0.008164
Log likelihood	640.5944	F-statistic	142.0001
Durbin-Watson stat	1.820099	Prob(F-statistic)	0.000000

Wald-coefficient test results for the null hypothesis C(1)=C(2)=C(3)=0

Wald Test:
Equation: FIRM

Null Hypothesis:	C(1)=0 C(2)=0 C(3)=0		
F-statistic	0.916433	Probability	0.434222
Chi-square	2.749298	Probability	0.431915

Granger Causality Test 6

***Null Hypothesis*:** Firm profitability does not Granger-cause firm R&D investment intensity.

***Lags employed*:** 3

Table A2.9: Bivariate Regression of R&D Investment Intensity on Lagged Profitability and R&D Investment

Dependent Variable: RD?
Method: Pooled Least Squares

Sample(adjusted): 1974 1991
Included observations: 18 after adjusting endpoints
Number of cross-sections used: 10
Total panel (unbalanced) observations: 179

Variable	Coefficient	Std. Error	t-Statistic	Prob.
RD?(1)	0.392617	0.068700	5.714911	0.0000
RD?(2)	0.124162	0.072926	1.702568	0.0906
RD?(3)	-0.020839	0.059965	-0.347523	0.7286
PROFIT?(1)	0.778133	0.241575	3.221084	0.0015
PROFIT?(2)	-0.151697	0.332005	-0.456912	0.6483
PROFIT?(3)	0.294864	0.247137	1.193118	0.2346

R-squared	0.822830	Mean dependent var	0.079037
Adjusted R-squared	0.806526	S.D. dependent var	0.042271
S.E. of regression	0.018593	Sum squared resid	0.056350
Log likelihood	467.6978	F-statistic	151.4044
Durbin-Watson stat	2.134538	Prob(F-statistic)	0.000000

Wald-coefficient test results for the null hypothesis C(4)=C(5)=C(6)=0

Wald Test:
Equation: FIRM

Null Hypothesis:	C(4)=0 C(5)=0 C(6)=0		
F-statistic	9.539651	Probability	0.000007
Chi-square	28.61895	Probability	0.000003

Granger Causality Test 7

***Null Hypothesis*:** Firm R&D investment intensity does not Granger-cause firm profitability.

***Lags employed*:** 2

Table A2.10: Bivariate Regression of Profitability on Lagged R&D Investment and Profitability

Dependent Variable: PROFIT?
Method: Pooled Least Squares

Sample(adjusted): 1974 1992
Included observations: 19 after adjusting endpoints
Number of cross-sections used: 10
Total panel (unbalanced) observations: 189

Variable	Coefficient	Std. Error	t-Statistic	Prob.
RD?(1)	0.011677	0.025145	0.464389	0.6429
RD?(2)	0.034110	0.021687	1.572853	0.1176
PROFIT?(1)	1.068721	0.086679	12.32965	0.0000
PROFIT?(2)	-0.305943	0.088776	-3.446228	0.0007

R-squared	0.835244	Mean dependent var	0.260810
Adjusted R-squared	0.823005	S.D. dependent var	0.016504
S.E. of regression	0.006943	Sum squared resid	0.008437
Log likelihood	678.4188	F-statistic	295.7252
Durbin-Watson stat	1.826146	Prob(F-statistic)	0.000000

Wald-coefficient test results for the null hypothesis C(1)=C(2)=0

Wald Test:
Equation: FIRM

Null Hypothesis:	C(1)=0 C(2)=0		
F-statistic	1.979238	Probability	0.141090
Chi-square	3.958476	Probability	0.138174

Granger Causality Test 8

***Null Hypothesis*:** Firm profitability does not Granger-cause firm R&D investment intensity.

***Lags employed*:** 2

Table A2.11: Bivariate Regression of R&D Investment Intensity on Lagged Profitability and R&D Investment

Dependent Variable: RD?
Method: Pooled Least Squares

Sample(adjusted): 1974 1992
Included observations: 19 after adjusting endpoints
Number of cross-sections used: 10
Total panel (unbalanced) observations: 189

Variable	Coefficient	Std. Error	t-Statistic	Prob.
RD?(1)	0.395942	0.075358	5.254169	0.0000
RD?(2)	-0.023742	0.064994	-0.365297	0.7153
PROFIT?(1)	0.806644	0.259769	3.105232	0.0022
PROFIT?(2)	0.276381	0.266054	1.038814	0.3003

R-squared	0.787591	Mean dependent var	0.081487
Adjusted R-squared	0.771812	S.D. dependent var	0.043561
S.E. of regression	0.020809	Sum squared resid	0.075774
Log likelihood	470.9757	F-statistic	216.2935
Durbin-Watson stat	1.891452	Prob(F-statistic)	0.000000

Wald-coefficient test results for the null hypothesis C(3)=C(4)=0

Wald Test:
Equation: FIRM

Null Hypothesis:	C(3)=0 C(4)=0		
F-statistic	22.57556	Probability	0.000000
Chi-square	45.15111	Probability	0.000000

The results reported in Tables A.2.4 through A.2.11 provide strong evidence to suggest that causality, in the U.S. pharmaceutical industry, runs primarily from profitability to R&D investment. Using lags from 2-to-5 years in length, the null hypothesis of "profitability does not Granger-cause R&D intensity" was easily rejected in

every model specified. To the contrary, however, the null hypothesis "R&D does not Granger-cause profitability" could not be rejected in any of the models. These results are summarized below in Table A.2.12.

Table A2.12: Summary of Granger-causality Tests for R&D and Profitability

	Null Hypothesis: Profitability Does Not Granger-cause R&D Intensity		Null Hypothesis: R&D Intensity Does Not Granger-cause Profitability	
Lags included in regression model	F	χ^2	F	χ^2
2	22.58^^	45.15^^	1.98	3.96
3	9.54^	28.61^	0.92	2.75
4	3.92**	15.68**	0.51	2.08
5	2.96*	14.80*	0.69	3.44

* Significant at the 0.05 level
** Significant at the 0.01 level
^ Significant at the 0.00001 level
^^ Significant at the 0.000001 level

Whilst the results reported in A.2.12 appear to establish empirically a clear direction of causality, this finding should be tempered with the fact the investment in pharmaceutical R&D, more so than in any other industry, typically takes a very long time to generate returns—possibly 10 years or more (refer to Chapter 2 and the average development times for new drugs). Therefore, the results in Table A.2.12 make a great deal of sense. When lags of longer lengths were examined the results were essentially unchanged. Because the lags employed in the formulation of the key variables in this thesis were all less than 5 years, the focus of this appendix has been on lags of similar lengths.

***Section A2.4.3**: Empirical Results on the Direction of Causality: Cash Flows and R&D*

Another related, yet sufficiently distinct, relationship that was also examined for directional causality was the relationship between firm cash flow margins and firm R&D

intensity. Using the same econometric procedures already outlined, Granger-causality tests were preformed[2]. These results are presented next.

Granger Causality Test 9

***Null Hypothesis*:** Firm R&D intensity does not Granger-cause firm cash flows.

***Lags employed*:** 4

Table A2.13: Bivariate Regression of Firm Cash Flow Margins on Lagged R&D Investment Intensities and Cash Flow Margins

Dependent Variable: CFM?
Method: Pooled Least Squares

Sample(adjusted): 1974 1990
Included observations: 17 after adjusting endpoints
Number of cross-sections used: 10
Total panel (unbalanced) observations: 169

Variable	Coefficient	Std. Error	t-Statistic	Prob.
RD?(1)	-0.015607	0.398383	-0.039176	0.9688
RD?(2)	-0.080507	0.544576	-0.147833	0.8827
RD?(3)	0.182487	0.373662	0.488376	0.6260
RD?(4)	0.075828	0.074051	1.023998	0.3075
CFM?(1)	0.452240	0.074977	6.031698	0.0000
CFM?(2)	0.254210	0.302984	0.839022	0.4028
CFM?(3)	0.036240	0.415667	0.087186	0.9306
CFM?(4)	-0.084968	0.285728	-0.297372	0.7666

R-squared	0.852281	Mean dependent var	0.192982
Adjusted R-squared	0.835651	S.D. dependent var	0.058472
S.E. of regression	0.023705	Sum squared resid	0.084848
Log likelihood	402.1280	F-statistic	124.4589
Durbin-Watson stat	2.174015	Prob(F-statistic)	0.000000

Wald-coefficient test results for the null hypothesis C(1)=C(2)=C(3)=C(4)=0

Wald Test:
Equation: FIRM

Null Hypothesis:	C(1)=0 C(2)=0 C(3)=0 C(4)=0		
F-statistic	0.452546	Probability	0.770429
Chi-square	1.810183	Probability	0.770619

[2] The maximum lagged cash flow margin employed by the models in this thesis was, for theoretical reasons, two years. However, to be conservative while testing for causality, lags of up to four years were considered.

Granger Causality Test 10

***Null Hypothesis*:** Firm cash flows do not Granger-cause firm R&D intensity.

***Lags employed*:** 4

Table A2.14: Bivariate Regression of Firm R&D Investment Intensity on Lagged Cash Flow Margins and R&D Investment Intensities

Dependent Variable: RD?
Method: Pooled Least Squares

Sample(adjusted): 1974 1990
Included observations: 17 after adjusting endpoints
Number of cross-sections used: 10
Total panel (unbalanced) observations: 169

Variable	Coefficient	Std. Error	t-Statistic	Prob.
RD?(1)	0.975130	0.076952	12.67198	0.0000
RD?(2)	-0.007085	0.105190	-0.067349	0.9464
RD?(3)	-0.126251	0.072177	-1.749194	0.0823
RD?(4)	0.035862	0.014304	2.507206	0.0132
CFM?(1)	0.707109	0.014483	48.82469	0.0000
CFM?(2)	-0.728432	0.058524	-12.44664	0.0000
CFM?(3)	0.001987	0.080290	0.024750	0.9803
CFM?(4)	0.120610	0.055191	2.185303	0.0304

R-squared	0.988638	Mean dependent var	0.076021
Adjusted R-squared	0.987359	S.D. dependent var	0.040724
S.E. of regression	0.004579	Sum squared resid	0.003166
Log likelihood	680.0038	F-statistic	1876.948
Durbin-Watson stat	1.862599	Prob(F-statistic)	0.000000

Wald-coefficient test results for the null hypothesis C(5)=C(6)=C(7)=C(8)=0

Wald Test:
Equation: FIRM

Null Hypothesis:	C(5)=0 C(6)=0 C(7)=0 C(8)=0		
F-statistic	613.4415	Probability	0.000000
Chi-square	2453.766	Probability	0.000000

Granger Causality Test 11

***Null Hypothesis*:** Firm R&D intensity does not Granger-cause firm cash flows.

Lags employed*: *3

Table A2.15: Bivariate Regression of Firm Cash Flow Margins on Lagged R&D Investment Intensities and Cash Flow Margins

Dependent Variable: CFM?
Method: Pooled Least Squares

Sample(adjusted): 1974 1991
Included observations: 18 after adjusting endpoints
Number of cross-sections used: 10
Total panel (unbalanced) observations: 179

Variable	Coefficient	Std. Error	t-Statistic	Prob.
RD?(1)	0.111876	0.367818	0.304161	0.7614
RD?(2)	-0.095426	0.378425	-0.252167	0.8012
RD?(3)	0.226018	0.073112	3.091404	0.0023
CFM?(1)	0.439430	0.073491	5.979336	0.0000
CFM?(2)	0.116439	0.289227	0.402587	0.6878
CFM?(3)	0.079332	0.289070	0.274439	0.7841

R-squared	0.848757	Mean dependent var	0.196898
Adjusted R-squared	0.834839	S.D. dependent var	0.061444
S.E. of regression	0.024971	Sum squared resid	0.101638
Log likelihood	414.9080	F-statistic	182.9474
Durbin-Watson stat	1.929332	Prob(F-statistic)	0.000000

Wald-coefficient test results for the null hypothesis C(1)=C(2)=C(3)=0

Wald Test:
Equation: FIRM

Null Hypothesis:	C(1)=0 C(2)=0 C(3)=0		
F-statistic	3.557664	Probability	0.015552
Chi-square	10.67299	Probability	0.013632

Granger Causality Test 12

***Null Hypothesis*:** Firm cash flows do not Granger-cause firm R&D intensity.

***Lags employed*:** 3

Table A2.16: Bivariate Regression of Firm R&D Investment Intensity on Lagged Cash Flow Margins and R&D Investment Intensities

Dependent Variable: RD?
Method: Pooled Least Squares

Sample(adjusted): 1974 1991
Included observations: 18 after adjusting endpoints
Number of cross-sections used: 10
Total panel (unbalanced) observations: 179

Variable	Coefficient	Std. Error	t-Statistic	Prob.
RD?(1)	1.038629	0.069624	14.91763	0.0000
RD?(2)	-0.174693	0.071632	-2.438759	0.0158
RD?(3)	0.043271	0.013839	3.126689	0.0021
CFM?(1)	0.727452	0.013911	52.29263	0.0000
CFM?(2)	-0.777653	0.054748	-14.20427	0.0000
CFM?(3)	0.131431	0.054718	2.401965	0.0174

R-squared	0.988550	Mean dependent var	0.079037
Adjusted R-squared	0.987496	S.D. dependent var	0.042271
S.E. of regression	0.004727	Sum squared resid	0.003642
Log likelihood	712.8490	F-statistic	2814.567
Durbin-Watson stat	2.130126	Prob(F-statistic)	0.000000

Wald-coefficient test results for the null hypothesis C(4)=C(5)=C(6)=0

Wald Test:
Equation: FIRM

Null Hypothesis:	C(4)=0 C(5)=0 C(6)=0		
F-statistic	933.9966	Probability	0.000000
Chi-square	2801.990	Probability	0.000000

Granger Causality Test 13

***Null Hypothesis*:** Firm R&D intensity does not Granger-cause firm cash flows.

Lags employed*: *2

Table A2.17: Bivariate Regression of Firm Cash Flow Margins on Lagged R&D Investment Intensities and Cash Flow Margins

Dependent Variable: CFM?
Method: Pooled Least Squares

Sample(adjusted): 1974 1992
Included observations: 19 after adjusting endpoints
Number of cross-sections used: 10
Total panel (unbalanced) observations: 189

Variable	Coefficient	Std. Error	t-Statistic	Prob.
RD?(1)	0.120981	0.186930	0.647201	0.5184
RD?(2)	0.100300	0.074800	1.340903	0.1817
CFM?(1)	0.517886	0.065857	7.863773	0.0000
CFM?(2)	0.132425	0.150487	0.879980	0.3801

R-squared	0.839600	Mean dependent var	0.200055
Adjusted R-squared	0.827684	S.D. dependent var	0.062092
S.E. of regression	0.025775	Sum squared resid	0.116262
Log likelihood	430.5215	F-statistic	305.3403
Durbin-Watson stat	2.186738	Prob(F-statistic)	0.000000

Wald-coefficient test results for the null hypothesis C(1)=C(2)=0

Wald Test:
Equation: FIRM

Null Hypothesis:	C(1)=0 C(2)=0		
F-statistic	1.632032	Probability	0.198334
Chi-square	3.264064	Probability	0.195532

Granger Causality Test 14

***Null Hypothesis*:** Firm cash flows do not Granger-cause firm R&D intensity.

***Lags employed*:** 2

Table A2.18: Bivariate Regression of Firm R&D Investment Intensity on Lagged Cash Flow Margins and R&D Investment Intensities

Dependent Variable: RD?
Method: Pooled Least Squares

Sample(adjusted): 1974 1992
Included observations: 19 after adjusting endpoints
Number of cross-sections used: 10
Total panel (unbalanced) observations: 189

Variable	Coefficient	Std. Error	t-Statistic	Prob.
RD?(1)	0.900257	0.037563	23.96627	0.0000
RD?(2)	-0.001355	0.015031	-0.090178	0.9282
CFM?(1)	0.756791	0.013234	57.18560	0.0000
CFM?(2)	-0.676164	0.030240	-22.35980	0.0000

R-squared	0.986840	Mean dependent var	0.081487
Adjusted R-squared	0.985862	S.D. dependent var	0.043561
S.E. of regression	0.005179	Sum squared resid	0.004695
Log likelihood	733.8104	F-statistic	4374.225
Durbin-Watson stat	1.661280	Prob(F-statistic)	0.000000

Wald-coefficient test results for the null hypothesis C(3)=C(4)=0

Wald Test:
Equation: FIRM

Null Hypothesis:	C(3)=0 C(4)=0		
F-statistic	1689.152	Probability	0.000000
Chi-square	3378.304	Probability	0.000000

The results shown in Tables A.2.13 through A.2.18 provide compelling evidence for the hypothesis that Granger-causality runs one-way: from cash flows to R&D intensity. Indeed, the F-statistics and Chi-squared statistics were extremely large for the null hypothesis that firm cash flows *do not* Granger-cause firm R&D intensity. This null

hypothesis was rejected in every model at the 0.000001 level. A summary of these findings is presented below in Table A.2.19.

Table A2.19: Summary of the Granger-causality Tests for R&D Investment Intensity and Cash Flows

	Null Hypothesis: Cash Flows Do Not Granger-cause R&D Intensity		Null Hypothesis: R&D Intensity Does Not Granger-cause Cash Flows	
Lags included in regression model	F	χ^2	F	χ^2
2	1689.15^^	3378.30^^	1.63	3.26
3	934.00^^	2802.00^^	3.56*	10.67*
4	613.44^^	2453.77^^	0.45	1.81

* Significant at the 0.05 level
** Significant at the 0.01 level
^ Significant at the 0.00001 level
^^ Significant at the 0.000001 level

Section A2.5: Conclusions on Causality

The evidence uncovered in this appendix overwhelming support the model specification used throughout the thesis—namely the specification that cash flows determine R&D investment intensity. This finding is also consistent with the model specifications employed in earlier research by other authors. Theoretically, these empirical results make a great deal of sense for two principle reasons. Firstly, as chapter 3 illustrated, there are a number of reasons to expect cash flows (and/or profits) to be influential in firm R&D investment behavior because of capital market imperfections for external finance. Secondly, the pharmaceutical industry, more so than any other industry, is characterized by extremely long research and development times for new products. Consequently, relatively short lags of R&D are not to be expected to exert a significant influence on firm profitability or cash flows (which are largely determined by firm profitability). Therefore, from a theoretical standpoint, econometric models that presume

this one-way causality are the appropriate models for examining pharmaceutical R&D investment behavior.

Section A2.6: Graphs of Lagged Cash Flows and R&D-to-Sales for 11 Leading U.S. Firms

The lagged firm cash flows and R&D-to-sales ratios for the major U.S. drug firms are depicted graphically in the following figures.

R&D-to-Sales and Lagged Cash Flow Margins for the Leading U.S. Firms

Figure A2.1: Abbott Laboratories

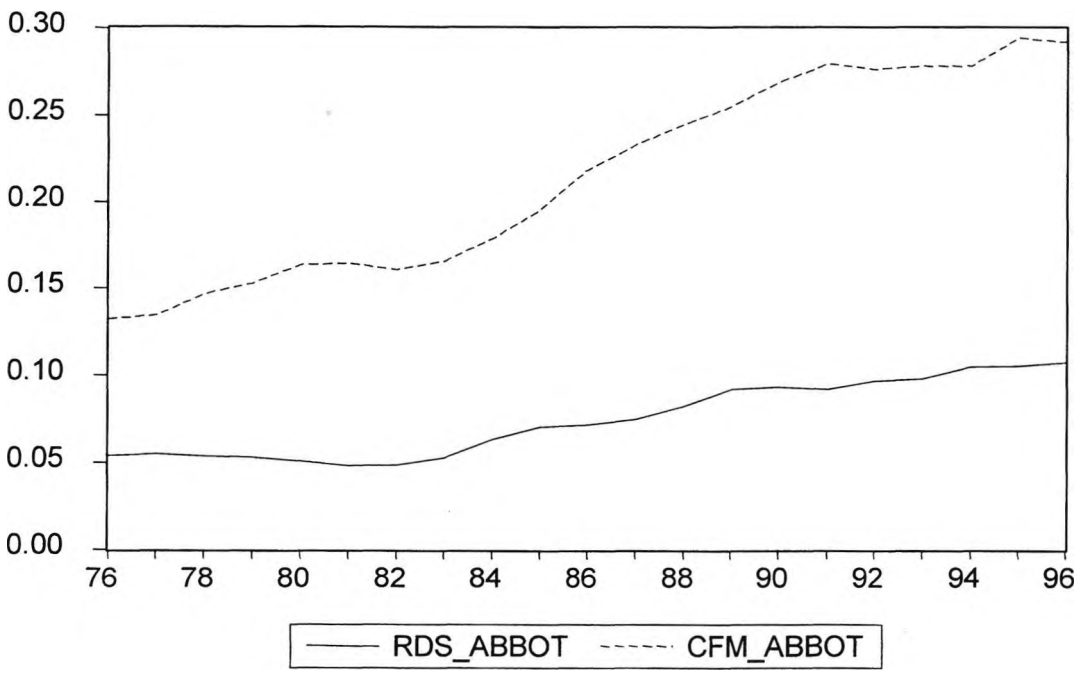


Figure A2.2: American Home Products

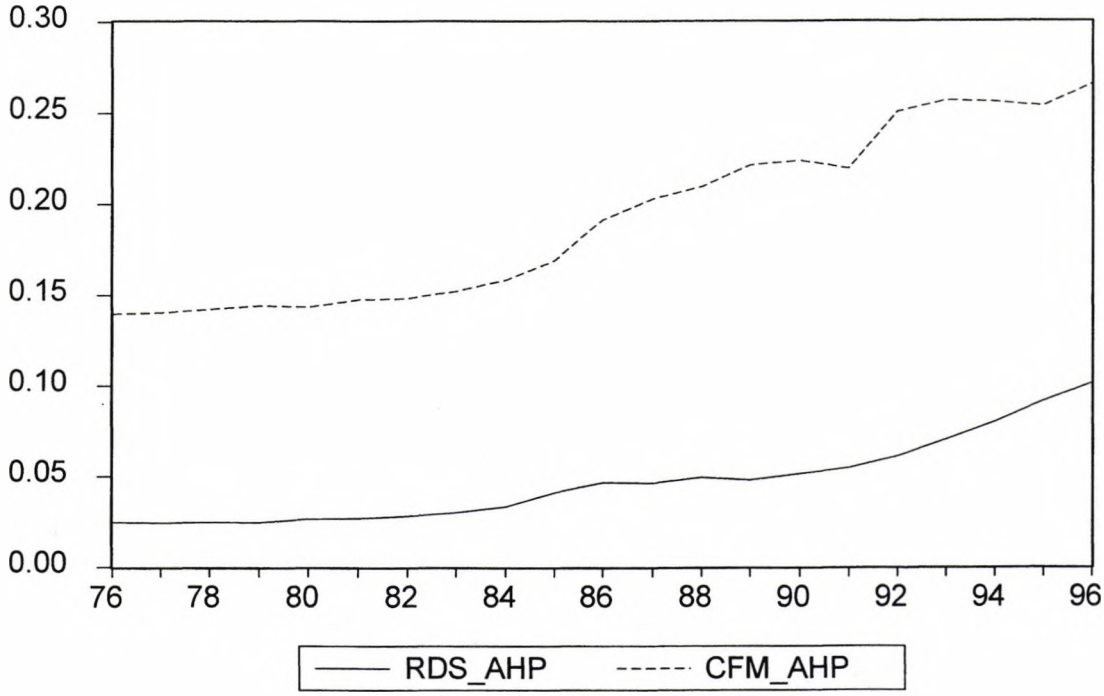


Figure A2.3: Bristol-Myers Squibb

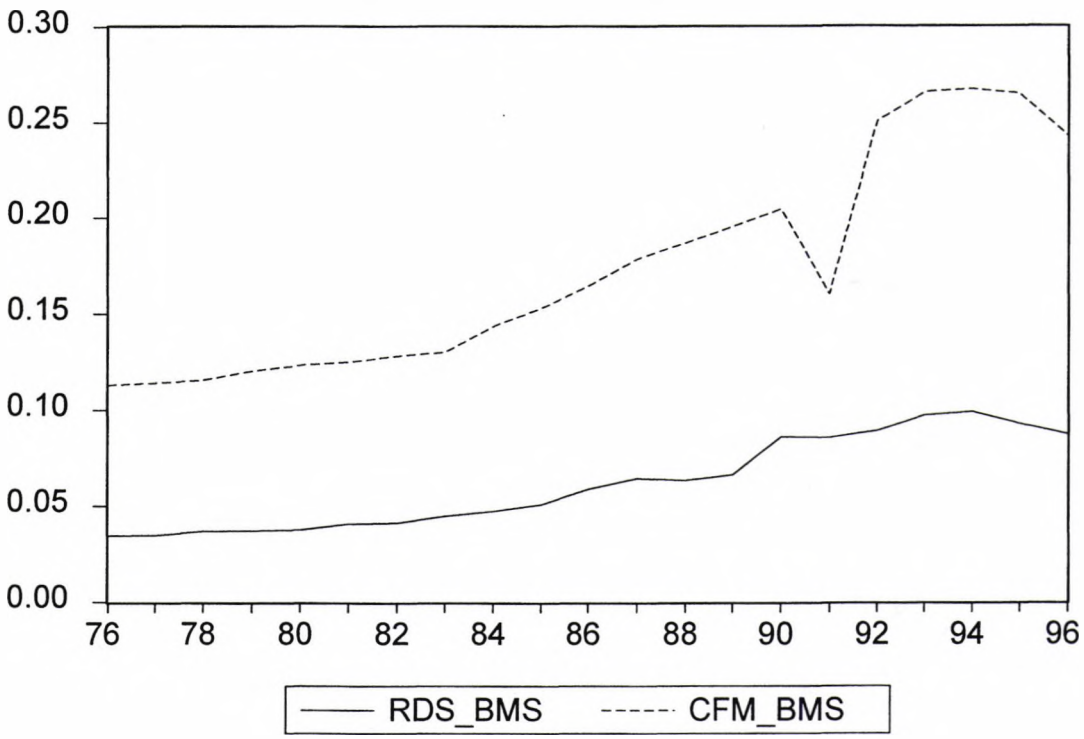


Figure A2.4: Johnson & Johnson

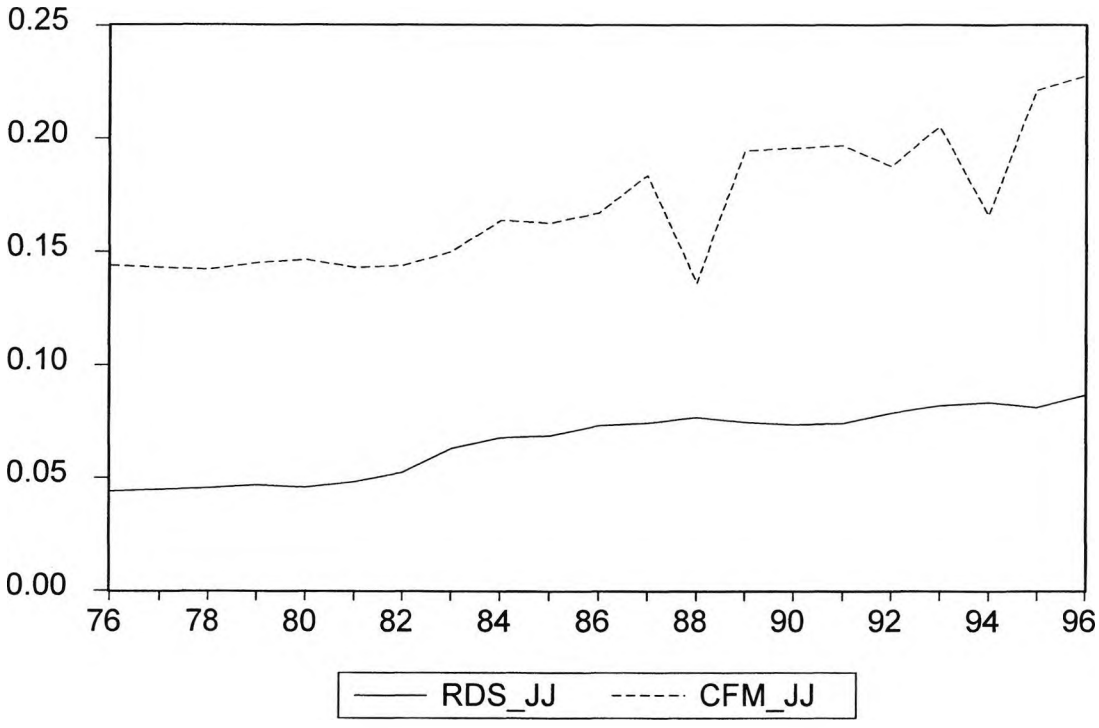


Figure A2.5: Eli Lilly & Company

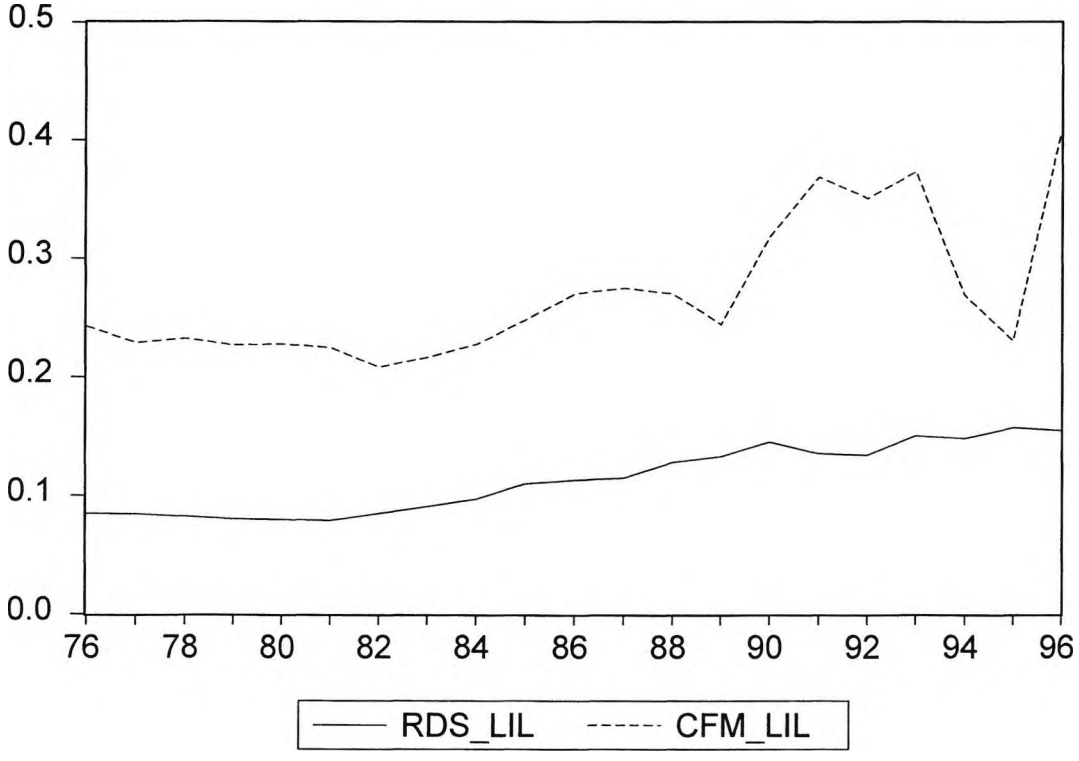


Figure A.2.6: Merck & Company

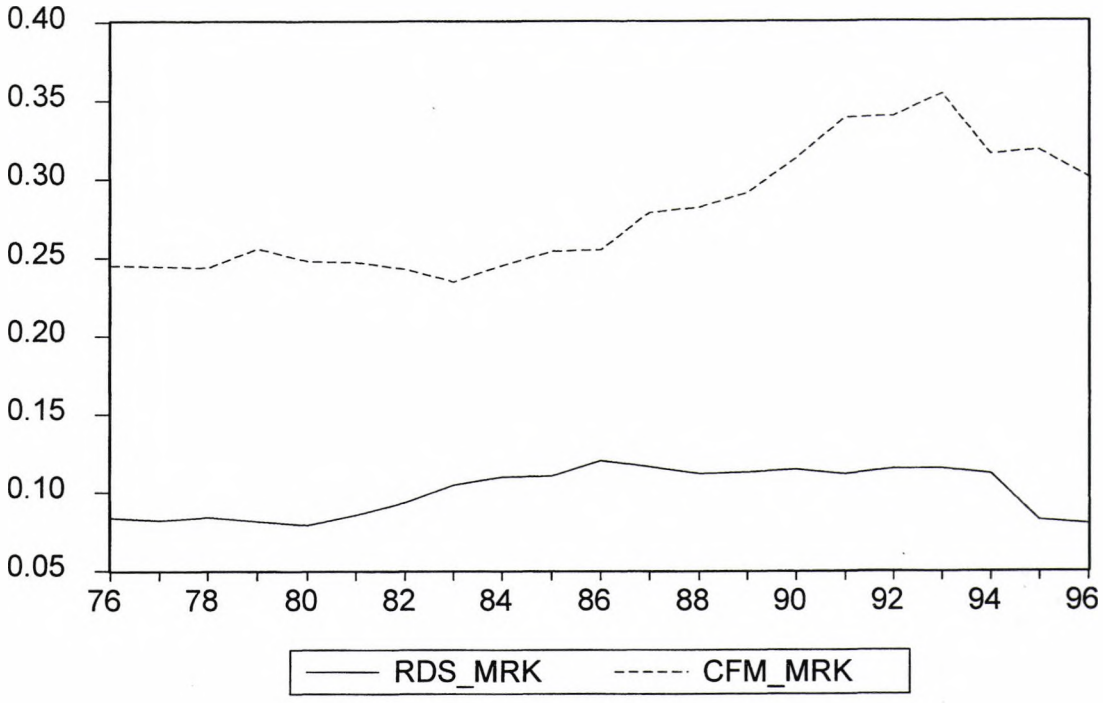


Figure A2.7: Pfizer Inc.

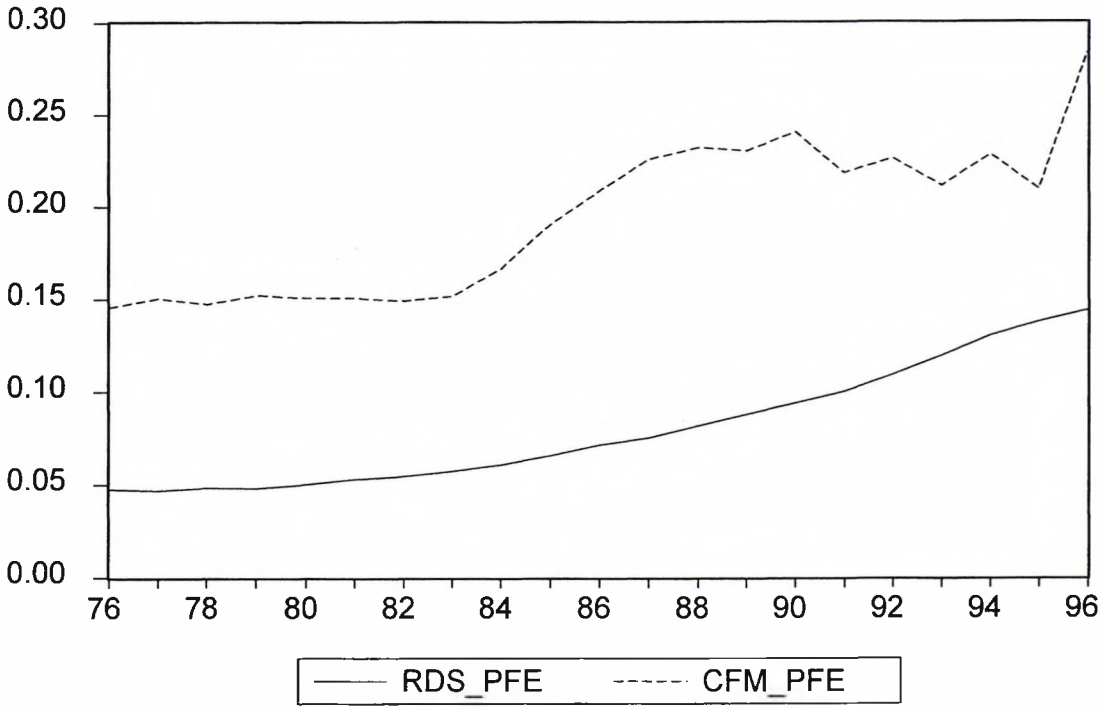


Figure A2.8: Schering-Plough

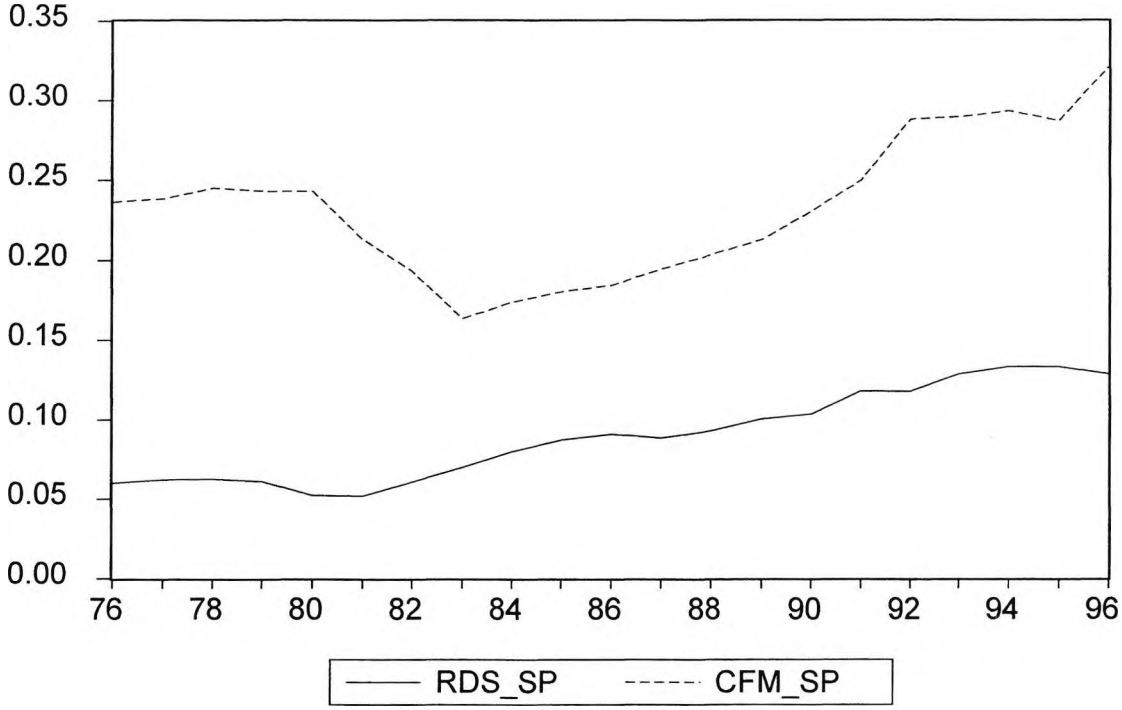


Figure A2.9: Syntex Corporation

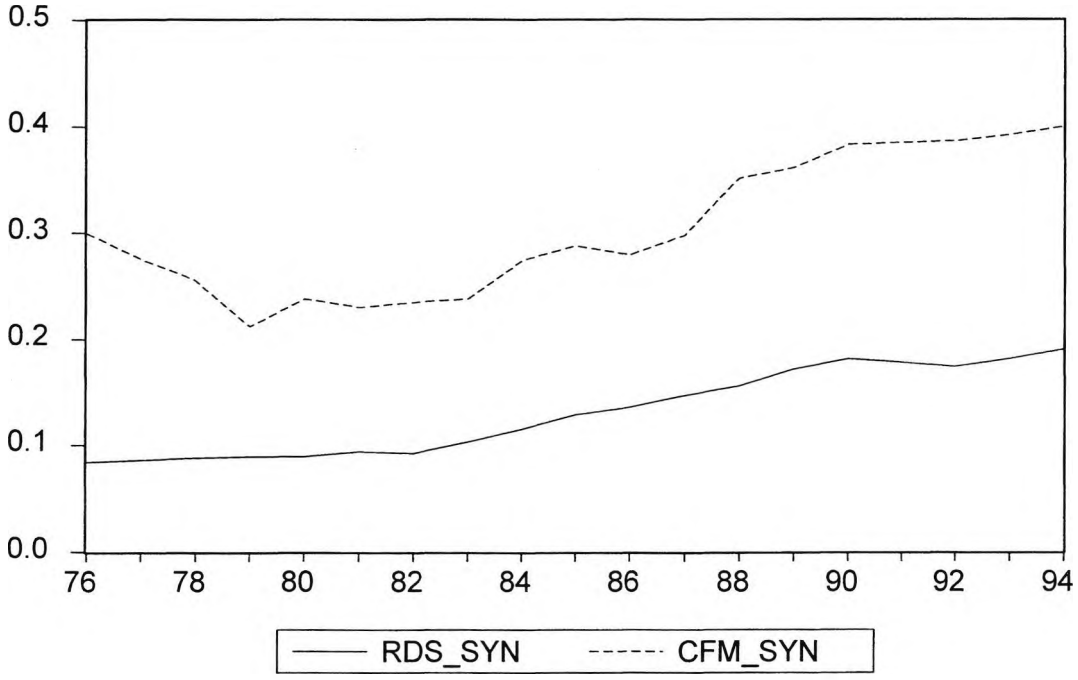


Figure A2.10: Upjohn & Company

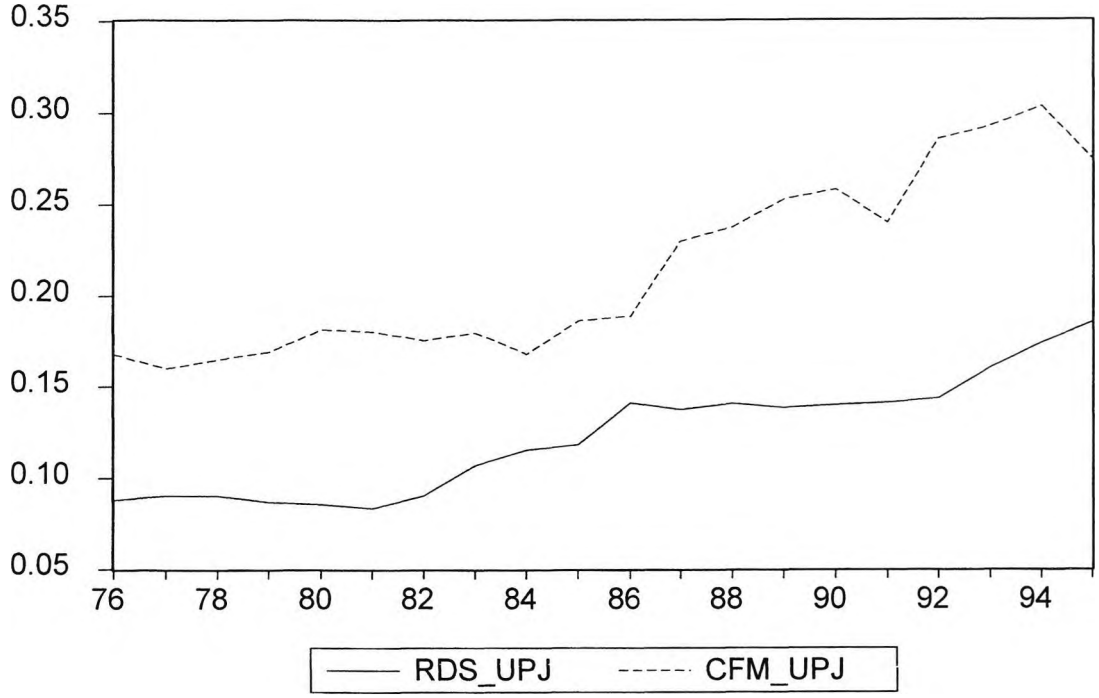
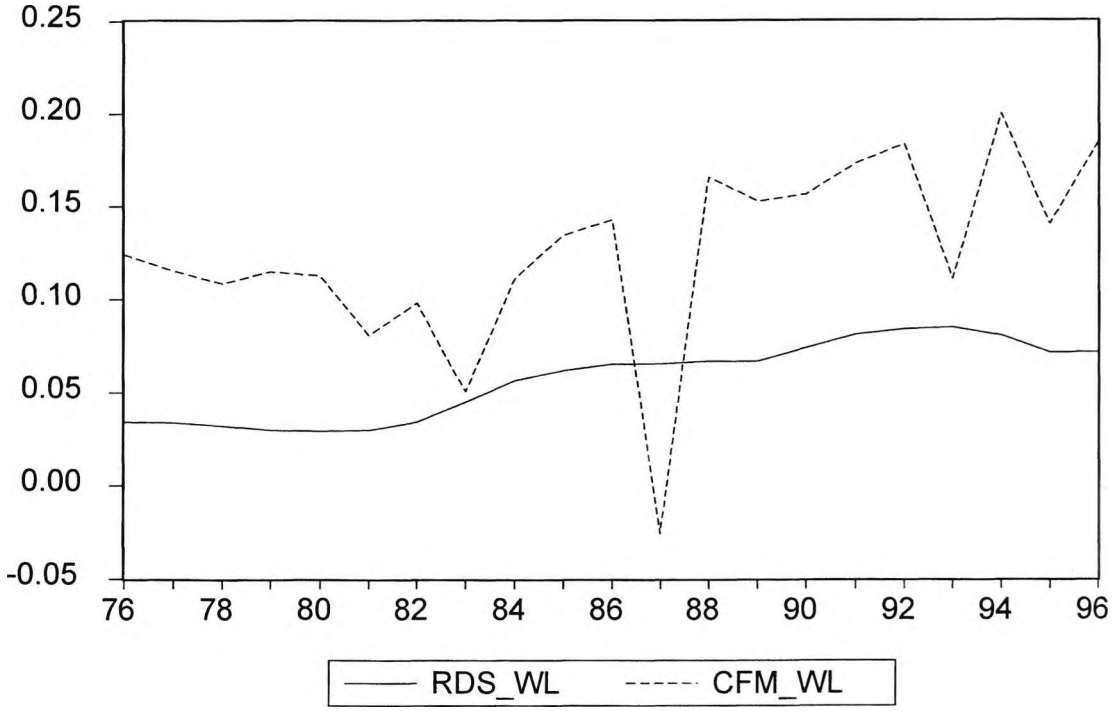


Figure A2.11: Warner-Lambert



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