Improving the Efficiency of the Later Stages of the Drug Development Process: Survey Results from the Industry, Academia, and the FDA

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SUBMITTED TO THE HARVARD-MIT DIVISION OF
HEALTH SCIENCES AND TECHNOLOGY
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE IN HEALTH SCIENCES AND TECHNOLOGY
AT THE
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

JUNE 2004

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Submitted to the Harvard-MIT Division of Health Sciences and Technology
on May 7, 2004 in Partial Fulfillment of the
Requirements for the Degree of Master of Science in Biomedical Enterprise

ABSTRACT

Drug development in the United States is a lengthy and expensive endeavor. It is estimated that average development times range from eleven to fifteen years and exceed costs of one billion dollars. The development pathway includes basic scientific discovery, pre-clinical testing in animals, clinical development in humans, and an application process. The Food and Drug Administration is responsible for the oversight and approval of drugs going through this process.

Numerous financial and economic studies have been conducted that show the benefits to accelerating the drug development process. In 1992, the United States Congress enacted the Prescription Drug User Fee Act I, which mandated faster response times from the FDA in return for user fee payments to the FDA by the drug developing companies. Data on approval times for new drugs indicate that this process was indeed shortened. In contrast, the average drug development process prior to the filing of an application has been increasing in cost and time.

The first purpose of this research is to quantify the benefits of accelerated new drug application review time under the Prescription Drug User Fee Acts I and II. The second purpose of the research is to investigate what industry and the FDA can do together to reduce the development process time between the IND and NDA without compromising patient safety and welfare, specifically the Phase II, Phase III, and NDA components.

The research indicates that PDUFA has improved approval times in a statistically significant way. Furthermore, the financial and social benefits as measured using net present value have far exceeded the PDUFA costs. Quantitative and qualitative surveys of fifty individuals in large pharmaceutical and biotech companies resulted in the identification of several significant opportunities and useful suggestions for reducing development times in Phase II, Phase III, and the NDA.

Specifically, company interviewees indicated that they were willing to pay additional monies for increased interaction and communication with the FDA from Phase II through the NDA in hopes of reducing information asymmetry and increasing information transparency. Other recommendations included a mandatory audit and review of a sample of NDAs post approval to identify best practices, implementation of metrics and performance tracking during clinical phases, and implementation of consistent project management and communication standards across therapeutic divisions.

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DEDICATION

To my parents, Frank and Karen:
For all the sacrifices you made that have afforded me these incredible opportunities.

To my brothers, Hilton and Michael:
For all the moral support and encouragement. I know I can always depend on you.

To Amy:
For all the love and support that has sustained us through my graduate studies.
I could not have done this without you.

ACKNOWLEDGEMENTS

The author wishes to thank the following individuals for research assistance, thoughtful discussion, and aid in completing this thesis project: Dr. Matthew Strobeck (HST/MIT), Professor Ernst Berndt (MIT Sloan), Roy Gross (MIT), Dr. Tomas Philipson, (FDA), Ed Hass (FDA), Dr. Joseph Bonventre (HST), Professor Fiona Murray (MIT Sloan), Marsha Warren (HST), Bernadette Fendrock (HST), Dr. Howard Golub (HST), and Dr. Lee Simon (Harvard Medical School).

Additionally, the author wishes to thank all the companies and their respective employees who agreed to be interviewed for the project or who helped organize the meetings. Their time and interest has made this project possible.

Funding for travel, meals, and accommodations related to this thesis research were provided by general funds from the Harvard-MIT Division of Health Sciences and Technology.

Ed Hass and Tomas Philipson provided the FDA NME data and significant research assistance. Without their aid, this project would not have been possible.

A significant portion of the research was performed in conjunction with Professor Ernst Berndt and Dr. Matthew Strobeck. The author extends a special thanks to both of them for all their assistance in completing the research and this thesis. In the text of the thesis, the pronoun “we” is used to refer to research performed in conjunction with Professor Berndt and Dr. Strobeck.

Any errors are the responsibility of the author alone.

BIOGRAPHICAL NOTE

The author is a graduate of Texas A&M University (B.S. Biochemistry – 1997) and of the MIT Sloan School of Management (M.B.A. – 2003). At the time of this writing, the author is a graduate student enrolled in the Harvard-MIT Division of Health Science and Technology (HST)- MIT Sloan Biomedical Enterprise Program, a graduate program designed to meld the business, science, and clinical aspects of the biomedical field. The author has over three years of work experience as a consultant for PricewaterhouseCoopers in the area of petroleum information technology. Most recently, the author worked as a consultant to Allergan's business development group and prior to that was an intern at Biogen Inc. in the business-planning group.

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Section 1.01 Motivation and Utility of Research

The process of drug development and drug approval in the United States has received an unprecedented level of attention during the end of 2003 and beginning of 2004. With public approval perceptions of drug companies at a low and the threat of drug importation from Canada and other countries, companies engaged in drug development, manufacturing, and marketing are scrambling to improve their reputation and justify the costs of their therapeutics. Finally, the skyrocketing costs of drug development and the decreasing output of new molecular entities (NMEs) are of great concern to private and public health officials in the United States.

In an attempt to address public health concerns in the early 1990's, the United States Congress enacted the Prescription Drug User Fee Act I (PDUFA I) with the goal of reducing the time needed to approve an NME. In several published studies, data indicate that new drug application (NDA) times[1], on average, decreased considerably in the mid and late 1990's during PDUFA. In contrast, great strides have not been made in reducing the clinical development time and cost for NMEs. The investigational new drug (IND) filing to NDA time period accounts for over 80% of the time and 90% of the cost of overall drug development. There are a myriad number of reasons for this, which include but are not limited to increasing safety requirements, difficulty of patient recruitment for clinical trials, incomplete understanding of novel drug mechanisms and targets, and inefficient use of information gathering technologies such as genomics. Given the burgeoning time and cost of the IND to NDA process, it is imperative that the Food and Drug Administration (FDA) and industry together address the issues of clinical development.

The motivation for this research stems from the apparent success that PDUFA has had on reducing new drug approval times. While several studies indicate that PDUFA has been successful in reducing NDA times, no studies of which I am aware have quantified the benefit. Assuming that PDUFA has conferred great benefits to industry and society, legislating better performance and accountability from the agency during clinical development might increase the efficiency of the clinical development process. Thus, the focus of this research is twofold. First, the research attempts to quantify the benefit of PDUFA I and PDUFA II to the industry and to the public. Second, the research attempts to identify some of the critical areas and opportunities for improvement within the IND to NDA process. This thesis will address specifically the benefits of PDUFA in the areas of cardiovascular and central nervous system (CNS) drugs. In regards to the IND to NDA process, this thesis will report the findings for parts of Phase II, Phase III, and the NDA periods.

This thesis is only one segment of the entire research project. It is my intent, in collaboration with Professor Ernst Berndt and Dr. Matthew Strobeck, to publish journal articles and a white paper that summarizes the collective research that was conducted on this project from August 2003 through May 2004.

[1] New Drug Applications (NDA) and Biological Licensing Applications (BLA) are interchangeable in the context of this thesis. Similarly the term "drug" can be interpreted broadly as new molecular entities.

At the time of the writing of this thesis, fifty industry individuals at seventeen companies (seven pharmaceutical, seven biotech, and three contract research organizations) have been interviewed using quantitative and qualitative surveys; however, formal interviews with FDA officials have not yet taken place. Interviews with several division directors and FDA staff have been scheduled and will be included in future articles. All interviewees were assured of confidentiality and anonymity as discussed in Chapter 3: Methods – Drug Development Surveys.

My aim is to provide a balanced and objective approach to this research. Thus, I advise the reader to review future publications related to this research by Berndt, Strobeck, and Gottschalk.

Section 1.02 Overview of Drug Development Time and Costs

The drug development process consists of the well-documented process of basic discovery through new drug approval. The process consists of pre-clinical and clinical development. This process is shown in Figure 1-1 and described below. The pre-clinical portion of development begins with basic discovery and research and extends through animal testing. Upon filing of an IND and subsequent approval, the drug is considered to have moved into the clinical development process.

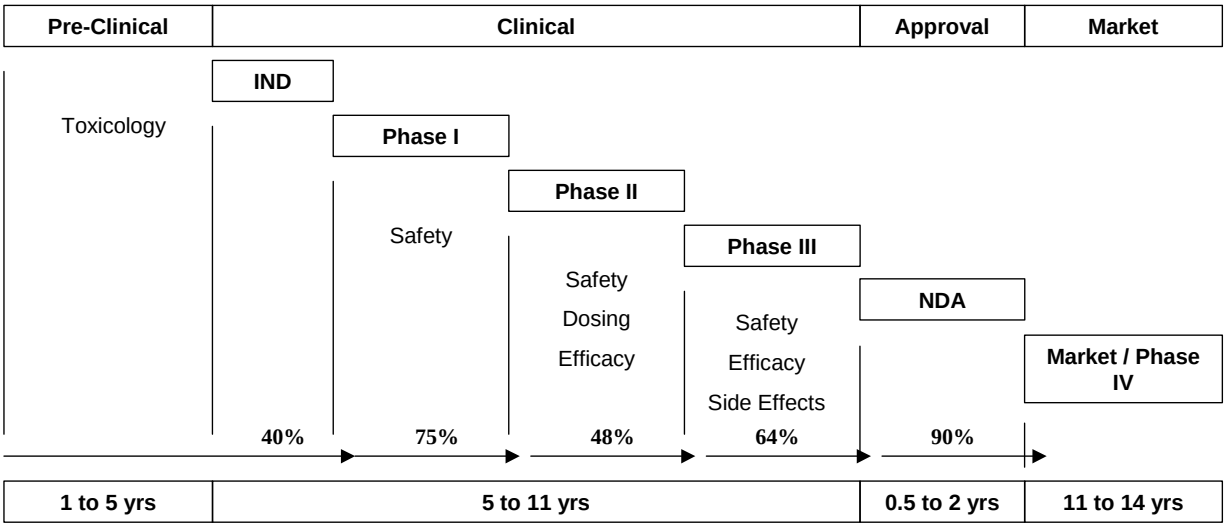
The early portions of pre-clinical development consist of scientific experiments and validation of principles within academic, government, or industry labs. These experiments are usually done in vitro. Upon identification of a lead compound or set of compounds, animal testing is conducted. Compounds and intellectual property developed outside of a company is in-licensed. Upon accumulation of adequate animal safety and efficacy data, the developing company, known as the sponsor, files an IND with the FDA to seek approval to move forward into experimentation in human subjects.

Upon approval of an IND application, a sponsor can initiate clinical development in humans, which consists of Phase I, Phase II, and Phase III clinical trials. Phase I clinical trials are designed mainly to test the preliminary safety of the drug in humans through the generation of pharmacokinetic data. Pharmacokinetic data consists of absorption, distribution, metabolism, and excretion of the drug. In general, this phase consists of a small group of healthy, paid volunteers ranging from twenty to one hundred patients. Phase I clinical trials last several months. Phase II clinical trials assess effectiveness and continue to monitor safety. The number of patients involved in this phase range from a few dozen to several hundred. Phase II trials can be several months to a few years long. Phase III clinical trials are also known as pivotal clinical trials. These trials are designed to assess efficacy in a statistically significant manner while continuing to monitor safety. Final formulations and doses of the drug are assessed as well. Phase III trials can range from a few hundred to several thousand participants depending on the therapeutic area.[2]

[2] US Food and Drug Administration. Testing Drugs in Humans. *US Food and Drug Administration* [online](cited 27 Apr 2004) < http://www.fda.gov/fdac/special/newdrug/testchrt.html > (2004).

There is an element of risk of NME failure associated with each phase of drug development. This probability of the NME moving forward from one phase of development to the next varies based on therapeutic area and several other drug and firm specific factors. The probabilities indicated in Figure 1-1 are used for illustrative purposes. When multiplied to achieve a cumulative probability, the chance of a drug making it from pre-clinical to approval is about 8% or for every thirteen drugs that is a serious candidate in pre-clinical, only one drug will make it to market. Upon reaching the market, a drug may have only a decade or so remaining before its patent expires, not to mention significant competition from other therapeutics.

Figure 1-1: Drug Development Timeline[3]



The drug development previously described tends to be lengthy and expensive. Studies by Dr. Joseph Dimasi and collaborators at the Tufts Center for the Study of Drug Development suggest that the cost of current drug development exceed $800 million and takes over ten years from basic discovery to market approval.[4] According to a manager at a biotech company in Cambridge, MA, this cost estimation is actually conservative; the estimates that his company spends in excess of one billion dollars to get a drug to market.[5] Additionally, a recent study by the consulting firm Bain & Company Inc. estimates that costs per successful drug launch may actually be closer to $1.7 billion.[6]

In a study focusing on improving the productivity of drug development, Dimasi shows empirically that increasing the probability of success (Phase I to Market) from 21.5% to 33%

[3] Mathieu, M.P., ed. "Development Pipeline Attrition." PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2003/2004, 2003, p. 184.
[4] Dimasi, Joseph A., Hansen, Ronald W., Grabowski, Henry G. "The Price of Innovation: New Estimates of Drug Development Costs." Journal of Health Economics, 2003;22:151-185.
[5] Lecture to Professor Fiona Murray's MIT Sloan Management class 15.968 Building a Biomedical Business by Bill Anderson, VP Business Planning, Biogen Idec, Inc., December 3, 2003.
[6] Gilbert, Jim, et al. "Rebuilding Big Pharma's Business Model." In Vivo, 2003;21(10).

could reduce capitalized cost per approved drug by $242 million. In comparison, a 50% reduction across all clinical phases lowers drug development costs per drug by $235 million.[7]

Of the drugs that make it to market, which is estimated to be only 22% of all drugs that enter clinical development, a limited number recoup their R&D costs.[8] In their analysis of returns on R&D for new drugs introduced into the market in the early 1990s, Grabowski, Vernon, and Dimasi find that the distribution of returns is very skewed. The top decile of new drugs accounts for over 50% of present value returns. The second and third deciles contribute an additional 30%. The research study indicates that roughly one-third of new drugs have a present value that exceeds the average R&D costs.[9]

The implication of the skewed returns and huge development costs is that companies continually seek to develop blockbusters, drugs with annual sales in excess of one billion dollars. This is not a sustainable model for drug development given the current development paradigm.

The trend over the last decade has been an increase in development costs with no significant reduction in time from IND filing to NDA. In contrast, the time for drug approval, NDA to FDA market approval, has decreased substantially in the 1990's.[10,11] The decrease has been attributed in part to the Prescription Drug User Fee Acts, which have legislated pre-defined response times from the FDA in exchange for user fees paid by the companies sponsoring an NDA.

While the industry and the public have appreciated the improvement in NDA approval times, the overall process of drug development remains lengthy and expensive, with estimates that the costs will continue to increase well above inflation rates. Indeed, significant research has been devoted to expounding on the costs of the FDA-imposed process and to describing the failures of drugs in the development process. The former FDA commissioner Dr. Mark McClellan, who recently left the FDA to head the Centers for Medicare and Medicaid services, has taken issue with the process. In an August 21, 2003 article in the Economist, Dr. McClellan "sees inefficiencies in the approval process that he wants to cure."[12]

In a study of the net benefits of the 1962 amendments to the Food, Drug, and Cosmetic Act, Sam Peltzman argued that the new efficacy and safety requirements quadrupled costs and doubled the time for innovative therapeutics to make it to market. Professor Peltzman essentially argues that there has been little benefit to consumers from the 1962 amendment and suggests that consumers

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[7] Dimasi, Joseph A. "The Value of Improving the Productivity of the Drug Development Process." Pharmacoeconomics. 2002;20(Suppl.3):1-10.
[8] Dimasi, Joseph A., Hansen, Ronald W., Grabowski, Henry G. "The Price of Innovation: New Estimates of Drug Development Costs." Journal of Health Economics, 2003;22:151-185.
[9] Grabowski, H Vernon, et al. "Returns on Research and Development for 1990s New Drug Introductions: The Cost and Value of New Medicines in an Era of Change". PharmacoEconomics, 2002;20(Suppl 3):11-29.
[10] Reichert, Janice M. "Trend in Development and Approval Times for New Therapeutics in the United States." Nature Reviews Drug Discovery. Sept. 2003;2.
[11] Kaitin, K., Cairns, C. "The New Drug Approvals of 1999, 2000, and 2001: Drug Development Trends a Decade after Passage of the Prescription User Fee Act of 1992." Drug Information Journal. 2003;7(1):357-371.
[12] "Food, Drugs, and Economics." Economist, Aug. 21, 2003.

might be better off without rigorous regulation. I cannot agree with Peltzman's suggestions due to evidence of corporate malfeasance and the high degree of information asymmetry between drug consumers, physicians, and the developing companies.[13]

In more recent publications, researchers suggest that the FDA "imposes more regulation of pharmaceuticals than is necessary and sufficient."[14] Comparisons are drawn between the FDA and the European Agency for the Evaluation of Medicinal Products (EMEA), which imply that the EMEA is more efficient in approving drugs on a lower budget. Suggestions to improve the efficiency of drug regulation include regulation via non-profit independent agencies or third party review by accredited groups[15]. While there may be some merit to some of these suggestions, the public and political hurdles are significant. As evidenced by recent legislation including September 11, 2001 related acts and the Sarbanes-Oxley regulations for accounting, the United States political body is very reactive rather than proactive.

Section 1.03 Brief Background and History of PDUFA

The concept of payment of "user fees" by individuals or firms "using" a government regulatory body's services is not entirely novel as evidenced by the precedent of the US Patent and Trademark office. The development of the Prescription Drug User Fee Act permitted the FDA to collect fees from sponsors submitting an NME for NDA or biologic licensing application (BLA) review. However, the passage of the Prescription Drug User Fee Act in 1992 was controversial given the large amount of money at stake on drug approvals. Since 1992 PDUFA has been renewed under the Food and Drug Modernization Act of 1997 (PDUFA II) and again under the Bioterrorism Preparedness and Response Act of 2002 (PDUFA III).[16]

In exchange for the collected user fees, the FDA is legally obligated to "review and act on" NDA/BLA submissions. According to the law:

> "'review and act on' is understood to mean the issuance of a complete action letter after the complete review of a filed complete application. The action letter, if it is not an approval, will set forth in detail the specific deficiencies and, where appropriate, the actions necessary to place the application in condition for approval."[17]

In essence, PDUFA mandates responses and action letters and not necessarily approvals. The major PDUFA goals are described in Figure 1-2 below. In the case of PDUFA I, II, and III, the FDA is obligated to deliver a complete review on 90% of priority applications within six months. For standard applications, the FDA was expected to review 90% of applications in twelve

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[13] Peltzman, Sam. Regulation of Pharmaceutical Innovation: The 1962 Amendments. Washington, D.C.: American Enterprise Institute for Public Policy Research, 1974.
[14] Miller, Henry I. "A Proposal for FDA Reform." Nature Reviews Drug Discovery. Aug. 2002;1:642-648.
[15] Ibid.
[16] US Food and Drug Administration. Prescription Drug User Fees – Overview. *US Food and Drug Administration*. [online] (cited 27 April 2004) <http://www.fda.gov/oc/pdufa/overview.html> (2004).
[17] US Food and Drug Administration. PDUFA Reauthorization Performance Goals and Procedures. *US Food and Drug Administration*. [online] (cited 27 April 2004) <http://www.fda.gov/oc/pdufa/PDUFAIIIGoals.html> (2004).

months under PDUFA I; currently, the FDA is expected to review 90% of standard applications in ten months. On the action date mandated by PDUFA, the FDA will issue one of three actions. The first action is a non-approvable letter indicating that the NDA/BLA has not satisfied the FDA's standards for safety and/or efficacy. The second type of letter is an "approvable" letter that indicates the NDA/BLA can be approved if certain deficiencies and questions are answered appropriately. The final action can be the much desired approval letter that gives the sponsor company the right to market the drug to the public.

According to Mary Olson, a researcher at Yale University, personnel at the FDA are greatly concerned with Type I errors. A Type I error is the mistake of approving a drug that is truly unsafe and ineffective. Type II errors which consist of not approving a safe and effective drug are not as important an issue to these individuals; however, the cost of delaying life saving drugs is equally as problematic as approving unsafe therapies. The individuals, both within the FDA and among detractors of the large pharmaceutical companies, discount the pain and suffering of patients awaiting new drugs by focusing more on Type I errors. The disproportionate focus on Type I errors is not surprising given the costs and punishment that can be meted out by Congress for these mistakes. Thus, it is not surprising that the FDA has tended to move very slowly when approving drugs. Due to the complexity of the drug laws, legislators have attempted to provide incentives for efficiency under the current process rather than attempting to amend the actual process. PDUFA is such an example.[18]

Figure 1-2: PDUFA Goals[19]

Goal	PDUFA I	PDUFA II	PDUFA III
Complete review of priority original new drug and biologic applications and efficacy supplements	90% in 6 months		
Complete review of standard original new drug and biologic applications and efficacy supplements	90% in 12 months	90% in 10 months	
Complete review of manufacturing supplements	90% in 6 months	90% in 4 months if prior approval needed, 6 months otherwise	
Complete review of resubmitted new drug and biologic applications	90% in 6 months	90% of class 1 in 2 months and 90% of class 2 in 6 months	
Complete review of resubmitted efficacy supplements	No Goal	90% in 6 months	90% of class 1 in 2 months and 90% of class 2 in 6 months *
Discipline review letters for pre-submitted "Reviewable Units" of new drug and biologic applications	No Goal		90% in 6 months *
Report of substantive deficiencies (or lack thereof)	No Goal		90% within 14 days of filing date *
Respond to industry requests for meetings	No Goal	90% within 14 days	
Meet with industry within set times	No Goal	90% within 30, 60, or 75 days, depending on type of meeting	
Provide industry with meeting minutes	No Goal	90% within 30 days	
Communicate results of review of complete industry responses to FDA clinical holds	No Goal	90% within 30 days	
Resolve major disputes appealed by industry	No Goal	90% within 30 days	
Complete review of special protocols	No Goal	90% within 45 days	
Electronic application receipt and review	No Goal	In place by the end of FY 2002	Enhanced by the end of FY 2007

[18] Olson, Mary K. "Pharmaceutical Regulation." *The New Palgrave Dictionary of Economics and the Law*. Ed. Peter Newman. New York: Stockton Press, 1998. 40-45.
[19] US Food and Drug Administration. PDUFA III Five-Year Plan. *US Food and Drug Administration*. [online] (cited 27 April 2004) <http://www.fda.gov/oc/pdufa3/2003plan/default.htm#update> (2004).

Section 1.04 Contract Research Organizations

Contract research organizations (CROs) play an instrumental role in the development of many drugs. CROs work with pharmaceutical and biotechnology companies of all sizes and across all phases of pre-clinical and clinical development. The CROs often provide specific therapeutic experience, which supplements lack of knowledge within a company. Very large CROs are often in a unique position, similar to the FDA in fact, in that they have experience across several drugs in a class and therapeutic area.[20] In many cases, CROs offer the potential to reduce risk and reduce development time for smaller companies with less experience in drug development.

Section 1.05 Hypotheses

Two hypotheses were assessed empirically during the research on PDUFA and the drug development process.

Hypothesis 1

Industry believes that communication with the FDA is inadequate during late stage clinical studies.

Hypothesis 2

Ceteris paribus, PDUFA I and PDUFA II reduced NDA/BLA approval times relative to pre-PDUFA time trends and had a net positive benefit to companies compared to PDUFA direct costs.

Section 1.06 Roadmap

The remainder of the thesis is divided into five additional chapters and an appendix. In Chapter 2: Methods – Drug Approval and PDUFA Analysis, the methods used to analyze NME data from 1979 to 2002 are discussed. I provide an explanation of the multivariate regression equation used to assess the significance of PDUFA and discusses how to calculate the net present value (benefit) of increased approval times. In Chapter 3: Methods – Drug Development Surveys, I review the methods that were used to survey and to collect data from the pharmaceutical, biotech, and contract research organization companies.

Chapter 4: Results – Drug Approval and PDUFA Analysis and Chapter 5: Results - Drug Development Surveys discuss the resulting analyses. The data indicate that PDUFA had a statistically significant effect on NDA times and show that aggregate incremental benefits of PDUFA exceed the incremental direct costs. Additionally, the data show that at the individual drug level, the net benefits will be highly skewed towards positive NPVs. Data from the quantitative and qualitative survey indicate that industry believes that additional quality communication and interaction between the FDA and industry in Phase II, Phase III, and during the NDA is likely to reduce drug development times and make it more efficient. Finally, in Chapter 6: Discussion and Conclusions, I attempt to bring all the information together and present several concrete suggestions for improving the efficiency of the drug development process.

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[20] Chapman, Ian. "Evolving with Contemporary Contract Research." Nature Reviews Drug Discovery. 2003: 2; 597.

Chapter 2: Methods – Drug Approval and PDUFA Analysis

Section 2.01 Drug Database Construction

The FDA provided a comprehensive list of NME's approved from 1965-2003 (designated as "NME Data 65-03 Original"). According to the provider of the data at the FDA, the list was error free and complete from the period of 1975 forward in regards to NDA approval length. The data fields provided by FDA are described in Figure A-1 in Appendix A: PDUFA Data and Information.

The FDA also provided an additional list that contained the NME name, NDA number, NDA sponsor, and a therapeutic class code. The FDA also provided a separate file that contained the therapeutic class code and respective code description. The therapeutic class code is a seven-digit code with the first three digits indicating a major class code. For example, major class code 304 was indicated as therapeutic class "Metabolic/Endocrine III" and detailed class code 3040300 indicated "Androgens/Anabolic Steroids."

In several instances, the major class code description between therapeutic classes was similar (i.e. "Metabolic/Endocrine I" vs. "Metabolic/Endocrine II"). We created a super major class code and developed a mapping table to cross reference the major class code to the aggregated super major class code. Finally, we added two therapeutic codes to account for biologics and pre-1979 data that did not contain a therapeutic class (B = BIOLOGIC; 0 = NO THERAPEUTIC AREA). The code tables and mappings are provided in Figure A-2, Figure A-3, and Figure A-4 in Appendix A: PDUFA Data and Information.

Using standard Microsoft Excel lookup functions, the "NME Data 65-03 Original" was enhanced to include the detailed seven-digit therapeutic class code and the corresponding major class code. Furthermore, the data fields were relabeled to adhere to a standard nomenclature (designated "NME MIT Data Reference").

For purposes of the PDUFA analysis, we were focused on NMEs submitted for approval from 1979 through 2002. The PDUFA I/II time period, as previously stated, extends from September 1, 1992 to September 30, 2002. In the case of one hundred and twenty-three NMEs during the 1979 to 2002 period, FDA did not supply the corresponding therapeutic class. For these drugs, a research assistant reviewed each drug in the 2003 Physician Desk Reference and entered a respective major class code. The detailed class code was left blank. Dr. Strobeck and I then reviewed the drug list and completed any further missing major therapeutic codes for this time period.

Using the standard sort and filter functions in Microsoft Excel, the data were initially filtered to ensure that only drugs submitted for NDA approval between October 1, 1979 and September 30, 2002 were included in the data set.[21] Per requirements of the analysis, the data were sorted further according to therapeutic class and NDA date of submission as needed. Great care was

[21] The government fiscal year is used. It extends from October 1st of a year to September 30th of the following year.

taken to ensure that sorted and filtered data sets were accurate in inclusion/exclusion of drugs based on the appropriate criteria. The sort/filter and analysis functions were repeated and checked by the research team. For purposes of conversion to months, days, or years, a month was defined as thirty days and a year was defined as 365.25 days in the calculations.

Section 2.02 Statistical and Regression Calculations

Basic statistics for desired date ranges and therapeutic classes were calculated using Microsoft Excel's Data Analysis function "Descriptive Statistics." The statistical calculations include mean, standard error, median, mode, standard deviation, sample variance, kurtosis, skewness, range, minimum, maximum, sum, and count. Appropriate graphs and tables were constructed in Microsoft Excel using the statistical data.

Multivariate linear regressions were performed using Microsoft Excel's Data Analysis function "Regression" on the set of NMEs submitted for NDA approval from 1979 to 2002 and on subsets of this data by date and therapeutic class. The dependent variable in the regression equation was the natural log of a drug's NDA approval time in months. The explanatory variables used in the regression are described in Figure 2-1 below.

Figure 2-1: Description of Variables Used in PDUFA Multivariate Regression

Variable Name	Description
LNAPPMONTHS	Natural log of NDA approval time in months - DEPENDENT VARIABLE
LNINDNDAMONTHS	Natural log of IND to NDA time in months
TIMETREND	A timetrend counter: 1 = 1979, 2 = 1980, …, 24 = 2002
PRIORITY	Binary variable with 0 = Standard and 1 = Priority
TREND_PDUFA1	TIMETREND variable multiplied by PDUFA1 variable
TREND_PDUFA2	TIMETREND variable multiplied by PDUFA2 variable
ORPHAN	Binary variable indicating orphan drug status: 0 = Non-orphan; 1 = Orphan Drug
NATION	Binary variable indicating foreign NDA sponsor: 0 = Foreign; 1 = USA
DRG_CARDIO	Dummy binary variable for cardiovascular class: 0 = Other Class; 1 = Cardio
DRG_ANTIINFECT	Dummy binary variable for anti-infective class: 0 = Other Class; 1= Anti-infect.
DRG_NEOPLASTIC	Dummy binary variable for neoplastic class: 0 = Other Class; 1 = Neoplastics
DRG_CNS	Dummy binary variable for CNS class: 0 = Other Class; 1 = CNS
DRG_BIO	Dummy binary variable for biologic class: 0 = Other Class; 1 = Biologic
DRG_AIDS	Dummy binary variable for AIDS drugs: 0 = Other Class; 1 = AIDS drug
DRG_OTHER	Dummy binary variable for all other drugs: 0 = ; 1 = All other classes
PDUFA1*	Binary variable for NDA submitted during PDUFA I: 0 = Non-PDUFA I; 1 = PDUFA I
PDUFA2*	Binary variable for NDA submitted during PDUFA II: 0 = Non-PDUFA II; 1 = PDUFA II

* Not used in regression equation directly

The regression equation was determined to be as follows:

Equation 2-1: PDUFA Approval Time Generic Regression Equation

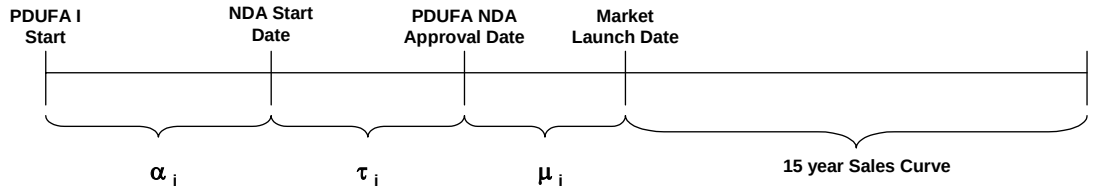
$$\ln(\text{approval time}) = \alpha + \beta_1 \cdot LNINDNDAMONTHS + \beta_2 \cdot TIMETREND + \beta_3 \cdot PRIORITY + \beta_4 \cdot TREND\_PDUFA1 + \beta_5 \cdot TREND\_PDUFA2 + \beta_6 \cdot ORPHAN + \beta_7 \cdot NATION + \beta_x \cdot DRG\_[\text{Therapeutic Area of Interest}] + \text{random disturbance term}$$

The dummy variable *DRG_*[Therapeutic Area of Interest] changes based on the therapeutic class of interest (it becomes 1) and other therapeutic terms drop out of the equation as their binary value is set to zero.

Section 2.03 Present Value Sales Calculations of PDUFA

In order to measure the net present value (NPV) benefit/cost of the PDUFA I and PDUFA II acts, we first calculated the present value (PV) of sales in two scenarios. The first case is the real world scenario using the actual FDA approval dates. The second case, denoted as the counterfactual, is the scenario where PDUFA does not exist and the approval date is predicted based on the regression described in Equation 2-1. The timeline for the approval process of a drug is represented in Figure 2-2 below.

Figure 2-2: Timeline for Drug Approval under PDUFA



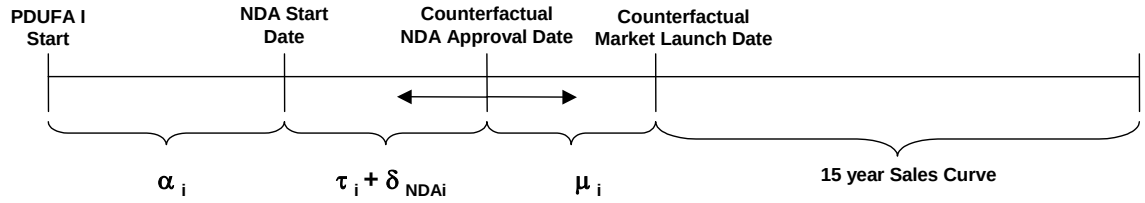
α_i denotes the time between the enactment of PDUFA I (September 1, 1992) and the NDA start date for a drug.

τ_i denotes the time between the NDA start date and the approval date for a drug.

μ_i denotes the time between approval date and market launch

In the counterfactual case, the NDA approval time τ_i is shifted by δ_{NDA}, the difference between the predicted NDA approval time under PDUFA and the predicted counterfactual NDA approval time, both of which are calculated using Equation 2-1. This difference is then added to the elapsed time between the NDA Start Date and the actual NDA Approval Date to determine the shift in time of approval in the counterfactual timeline as indicated by the bold arrows in Figure 2-3 below.

Figure 2-3: Timeline for Drug Approval under Counterfactual



The PV of the difference between the PDUFA NDA case and the counterfactual NDA case, denoted as *ΔBenefit*, is then the difference between Equation 2-2 and Equation 2-3.

Equation 2-2: PV of Sales for PDUFA NDA

$$\sum_{i=1}^{n}\left[\left(\frac{1}{(1+r)^{(\alpha_i+\tau_i+\mu_i)}}\right)\left(\sum_{j=1}^{15}\frac{CF_j}{(1+r)^j}\right)\right]$$

Equation 2-3: PV of Sales for Counterfactual NDA

$$\sum_{i=1}^{n}\left[\left(\frac{1}{(1+r)^{(\alpha_i+\tau_i+\delta_{NDAi}+\mu_i)}}\right)\left(\sum_{j=1}^{15}\frac{CF_j}{(1+r)^j}\right)\right]$$

where:

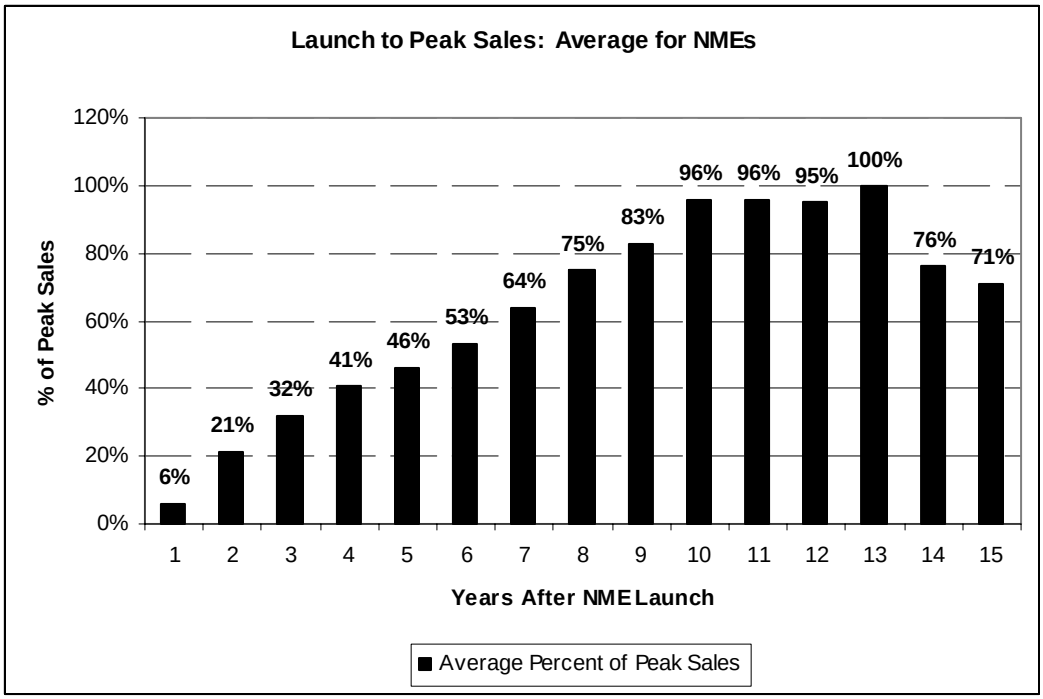
r = discount rate
CF = sales cash flow in a given year $\boldsymbol{j}$
α_i, τ_i, μ_i, are the time intervals as described in Figure 2-3
i = a drug in a given therapeutic class and ranges to the n^{th} drug in that class
δ_{NDA} = change in NDA approval time shift as predicted by regression equation

Section 2.04 Construction of NME Sales Curves

FDA, through a third party agreement with IMS Health Inc., provided comprehensive sales data for all drugs in the United States market from February 1998 to December of 2002. The sales data included the following channels according to the IMS information: independent pharmacies, chain pharmacies, mass merchandisers with and without pharmacies, mail order pharmacies, food stores with pharmacies, non-federal hospitals, federal facilities, clinics, long-term care facilities, home health care, HMOs, miscellaneous channels (starting in 1999; prisons, universities, other).[22]

Given that many drugs were approved prior to 1998 and given that future sales beyond 2002 were not available, complete fifteen-year sales curves were constructed using an average NME sales curve as shown in Figure 2-4 below.

Figure 2-4: Average NME Sales as Percentage of Peak Sales[23]



[22] The U.S. Food and Drug Administration provided IMS sales data via a signed contract with Professor Berndt at the MIT Sloan School of Management.
[23] Mathieu, M.P., ed. "An Analysis of Launch-to-Peak Sales for NCEs" PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2003/2004, 2003, p. 46.

For each NME, sales were annualized if the available sales data did not start in January of a given year. Next, the first annualized year of sales available from the IMS data was correlated with the year after launch and the respective percentage of peak sales. Dividing the annualized sales by the percentage of peak sales yielded the peak year sales.

The peak sales were then deflated to 1992 dollars using the appropriate GDP deflator corresponding to the first annualized year of sales. This was accomplished by first deflating or inflating sales as appropriate to 2000, the baseline year, and then deflating sales to 1992. The GDP deflator indices are shown Figure A-5: GDP Deflation Table in the appendix. The implication for deflation of sales to 1992 dollars means that the discount rates used for the time value of money calculations are all real discount rates.

The complete projected sales curve was then calculated by multiplying the percentage sales of peak for each year times the calculated peak sales. The complete sales curve was discounted as indicated in Equation 2-2 and Equation 2-3.

Section 2.05 Present Value Cost Calculations of PDUFA

The second component of the NPV calculation involved the calculation of costs of PDUFA over the lifetime of a NME. PDUFA fees consist of application fees, establishment fees, and product fees. FDA provided the PDUFA costs for these fees from 1993 to 2004 (See Figure A-6).[24] The current fees for 2004 are a $573,500 application with clinical data fee, a $286,750 fee for applications with no clinical data, a $286,750 fee for supplements with clinical data, a $226,800 establishment fee, and a $36,080 product fee. PDUFA fees for 2005 and forward were estimated based on the compound annual growth rates (CAGR) from 1993 to 2004. Given that the United States Congress has renewed PDUFA every five years (1998, 2003) and given that the renewal year has a dramatic percentage increase relative to adjustments made in follow on years, significant increases were forecasted for 2008 and 2013. The large percentage increases in reauthorization years and subsequent minor increases between reauthorization were structured to yield a CAGR of 15%. Similar to the sales curves, the actual PDUFA fees were deflated to 1992 dollars using the appropriate GDP deflator (See Figure A-7 in Appendix A: PDUFA Data and Information).

Novel NDA application fees were charged during the year of an NME's NDA application to FDA. Product fees and establishment fees were charged during each year of sales. One hundred percent of the establishment was allocated to each NME. The establishment fee covers the manufacturing location and can cover multiple drugs. On average, roughly three drugs are manufactured per location; thus, a 100% allocation will overestimate the PDUFA costs for each drug. This is therefore a conservative assumption.

In order to account for additional prescription label submissions per NME, we made a conservative assumption of two supplemental NDAs submitted in the second year post market

[24] Provided by Tomas Philipson, Ph.D., Senior Economic Advisor to the Commissioner, Office of Policy & Planning, Office of the Commissioner, Food and Drug Administration

launch. Supplemental NDAs do not increase the product fee or establishment fee already being paid by a company.

Section 2.06 PDUFA NPV Calculations and Analysis

The NPV for each PDUFA drug in a given therapeutic area of interest was calculated by subtracting the PDUFA fee costs from the *ΔBenefit*. The NPV for each drug was then summed across all PDUFA drugs in a therapeutic area and also computed for each individual NDA/BLA.

Section 2.07 FDA Commissioner Analysis

The effect of the presence or absence of a congressionally approved FDA commissioner on NDA approval times was assessed using multivariate regression analysis. First, for each NME, the overlap in time period of the vacancy of a commissioner was compared to the time period of the NDA. A software application was written in Visual Basic for Applications to iterate through the commissioner vacancies and calculate the total ratio of commissioner vacancy time to NDA time period. Given that an NDA could potentially span multiple vacancies, the software program accumulated the total number of days during the NDA on which there was no commissioner. A total of six vacancy periods occurred from June 30, 1979 to November 14, 2002 (See Figure 2-5 below).

Figure 2-5: FDA Commissioner List and Vacancies[25]

Commissioner	Start Term	End Term
Harvey W. Wiley, M.D.	1/1/1907	3/15/1912
Carl L. Alsberg, M.D.	12/16/1912	7/15/1921
Charles A. Browne	7/1/1924	6/30/1927
Walter G. Campbell	7/16/1921	6/30/1924
(two terms)	7/1/1927	4/30/1944
Paul B. Dunbar, Ph.D.	5/6/1944	5/31/1951
Charles W. Crawford	6/1/1951	7/31/1954
George P. Larrick	8/12/1954	12/27/1965
James L. Goddard, M.D.	1/17/1966	7/1/1968
Herbert L. Ley, Jr., M.D.	7/1/1968	12/12/1969
Charles C. Edwards, M.D.	12/13/1969	3/15/1973
Alexander M. Schmidt, M.D.	7/20/1973	11/30/1976
Donald Kennedy, Ph.D.	4/4/1977	6/30/1979
Vacancy	**6/30/1979**	**10/21/1979**
Jere E. Goyan, Ph.D.	10/21/1979	1/20/1981
Vacancy	**1/20/1981**	**4/13/1981**
Arthur Hull Hayes, M.D.	4/13/1981	9/11/1983
Vacancy	**9/11/1983**	**7/15/1984**
Frank E. Young, M.D., Ph.D.	7/15/1984	12/17/1989
Vacancy	**12/17/1989**	**11/7/1990**
David A. Kessler, M.D.	11/8/1990	2/28/1997
Vacancy	**2/28/1997**	**11/30/1998**
Jane E. Henney, M.D.	11/30/1998	1/19/2001
Vacancy	**1/19/2001**	**11/14/2002**
Mark B. McClellan, M.D., Ph.D.	11/14/2002	3/25/2004

[25] US Food and Drug Administration. FDA Commissioners and Their Predecessors. *US Food and Drug Administration* [online](cited 27 April 2004) <http://www.fda.gov/opacom/morechoices/comm1.html> (2004).

Multiple regressions, which include the variables listed in Figure 2-1, were run with the commissioner ratio variable. The ratio was manipulated or used as the basis for other variables as described in the four methods in Figure 2-6.

In the case of method 2, if the overlap ratio was equal to zero, it was not possible to take the natural log of the ratio. Thus, the value was set to 0.001 to indicate no overlap. An attempt to correct this manipulation was tried by using method three, which had the first variable, COMMISSX1 equal one when the ratio was zero. The second variable, COMMISSX2, took on a zero value if the ratio were zero; otherwise it was equal to the natural log of the ratio.

Figure 2-6: Commissioner Vacancy Ratio Regression Variable

Method	Variable(s)	Description
1	COMMISSIONER	Ratio of commissioner absent days
2	LNCOMMISS	Natural log of commissioner absent ratio
3	COMMISSX1	Binary variable indicating that if commissioner ratio is greater than zero then the value is zero, otherwise it is one.
	COMMISSX2	If the commissioner ratio is zero than the value is zero, otherwise take the natural log of the ratio.
4	COMMISS_VAC	Binary variable indicating a commissioner ratio greater than zero

Chapter 3: Methods – Drug Development Surveys

Section 3.01 Assessment of Drug Development Issues

To assess the issues associated with drug R&D and the FDA, I, in conjunction with a colleague and faculty member at the MIT Sloan School of Management, undertook a series of interviews with a total of seventeen industry companies that had locations in the United States. The interviews were conducted from January 8th, 2004 to April 23rd, 2004. In almost all cases, the companies had significant international offices. The study population consisted of seven medium to large biotech/biopharmaceutical firms, seven very large pharmaceutical companies, and three contract research organizations (CROs). All but one of the biotech/biopharmaceutical is a public company and has products on the market. Figure 3-1 shows the breakdown of companies, interviewees by function, and interviewees by firm type.

Figure 3-1: Number of Individuals Interviewed by Company Type

Company Type	Individuals
Biotech	1
Biotech	1
Biotech	2
Biotech	3
Biotech	3
Biotech	3
Biotech	9
Biotech SubTotal	**22**
CRO	1
CRO	2
CRO	3
CRO SubTotal	**6**
Pharmaceutical	1
Pharmaceutical	2
Pharmaceutical	2
Pharmaceutical	4
Pharmaceutical	4
Pharmaceutical	4
Pharmaceutical	5
Pharma SubTotal	**22**
GRAND TOTAL	**50**

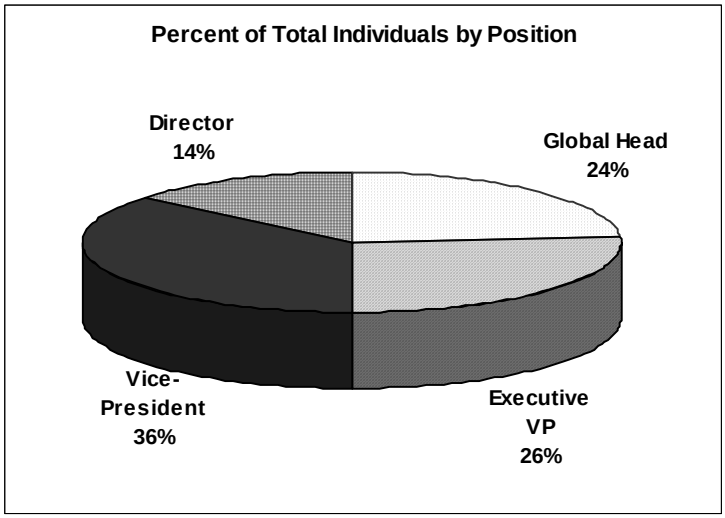
Position by Function	Individuals
R&D	
Global Head	9
Executive VP	11
Vice-President	13
Director	5
R&D Subtotal	***38***
Regulatory	
Global Head	3
Executive VP	2
Vice-President	5
Director	2
Reg Subtotal	***12***
Grand Total	***50***

Position by Firm Type	Individuals
Biotech	
Global Head	8
Executive VP	2
Vice-President	9
Director	3
Biotech Subtotal	***22***
Pharma	
Global Head	4
Executive VP	9
Vice-President	7
Director	2
Pharma Subtotal	***22***
CROs	
EVP	2
VP	2
Director	2
CRO Subtotal	***6***
Grand Total	***50***

We attempted to interview two or more individuals at each company. With the exception of four companies, this was accomplished. In most cases, we were able to interview one individual at a time. There was only one case where more than two individuals were interviewed at one time. The total number of individuals interviewed at biotech companies was equal to the total number of individuals interviewed at pharmaceutical companies. Six individuals at CROs were also interviewed. A total of fifty individuals in the industry were interviewed.

We attempted to interview individuals who were at very senior level positions within their company and who had significant responsibilities for pre-clinical development, clinical development, regulatory oversight, or combinations thereof. Of the fifty individuals interviewed, the vast majority of interviewees were at a Vice-President level in the company or higher. Figure 3-1 shows the breakdown of positions by function (R&D or regulatory) and by firm type (biotech-/pharmaceutical/CRO). The specific percentage breakdown by position is given in Figure 3-2.

Figure 3-2: Breakdown of Positions Interviewed at Biotechs, Pharmaceuticals, and CROs



We applied for and received approval from MIT's Committee on the Use of Humans as Experimental Subjects (COUHES) to perform an in person survey of individuals involved in the R&D and regulatory processes (See Figure B-1: Official COUHES Approval in the appendix). Interviewees were assured of confidentiality and anonymity to ensure candid responses. Written notes of interviews and information were stored in a locked file cabinet by the supervising professor at MIT.

Section 3.02 Questionnaire Development

We developed a qualitative and quantitative questionnaire based on advice from faculty at the MIT Sloan School of Management, Harvard Medical School, and selected chapters on survey research methods from textbooks by Singleton[26] and by Russell[27].

We first developed a pilot qualitative questionnaire with a very broad range of questions covering various topics from pre-clinical development through the value chain of drug development to Phase IV studies. The pilot questionnaire was tested with volunteers at a large biotech company and a large pharmaceutical company. The feedback from the interviewees coupled with the literature review and discussion with other academics helped us further refine the qualitative questionnaire and led to the development of the hypotheses.

[26] Singleton, Royce Jr., et al. *Approaches to Social Research*. New York, Oxford University Press, 1988.
[27] Bernard, H. Russell. *Social Research Methods: Qualitative and Quantitative Approaches.* 3rd ed. California: Sage Publications Inc., 2000.

In addition to the qualitative questionnaire, we developed a quantitative questionnaire based on the pilot interviews. The quantitative questionnaire required interviewees to rank the responses to various questions on a scale of one to five. The questions and the four different ranking scales are presented in the full quantitative questionnaire located in Appendix B: Interview Questionnaires.

Section 3.03 Interview Methodology

Forty-four interviews were conducted in person. Six interviews were conducted via teleconference or videoconference. In advance of all the interviews, we sent a brief background memo and a letter from the FDA endorsing the research and assuring confidentiality to the interviewees. Professor Berndt, Dr. Strobeck, or I led interviews as designated in a rotating schedule; all interviews were conducted consistently in the following format and order:

- The researchers introduced themselves to interviewees and exchanged business cards.
- The researchers provided a brief background on the project and on the interview format.
- The research leader of the interview reviewed the informed consent issues/rights and obtained verbal consent of the interviewee(s).
- The interviewee(s) was assured of confidentiality and anonymity to the extent that no company name, no individual name, and no drug name would be disclosed in any report.
- The interviewee(s) was then solicited for his/her educational and professional experience.
- The research leader of the interview administered the quantitative questionnaire verbally and explained any questions that the interviewee did not understand.
- Key issues and areas of interest were identified from the interviewee's response to the quantitative questionnaire, and provided the basis for some of the subsequent qualitative questions and discussion.
- The research team administered the qualitative questionnaire to the interviewee based on the individual's experience and responses to the quantitative questionnaire (i.e. an interview of an individual responsible for Phase II and Phase III clinical trials centered on these respective phases rather than on Phase I).
- The researchers wrapped-up the interview by expressing thanks and appreciation to interviewees and encouraged the subjects to contact the team with any questions or additional thoughts.

Upon conclusion of a company visit and interview session, we discussed major findings and ideas. The interview notes were typed up by one or more of us and reviewed for accuracy. The quantitative questionnaire responses were entered into a Microsoft Excel spreadsheet and analyzed using the Data Analysis function "Descriptive Statistics."

In all cases, Professor Berndt, Dr. Strobeck, and I signed thank you letters that were then mailed to the interviewees. In a few cases, interviewees followed up with us with additional information. Upon completion of the research, all interviewees will receive a copy of a white paper document edited by Professor Berndt, Dr. Strobeck, and me. The paper will include my and Dr. Strobeck's combined research theses, summarized and edited as appropriate, as well as information from interviews with FDA officials that will take place later in May, 2004.

Chapter 4: Results – Drug Approval and PDUFA Analysis

Section 4.01 Drug Approval Trends

In order to evaluate the hypothesis that "ceteris paribus, PDUFA I and PDUFA II reduced NDA/BLA approval times relative to pre-PDUFA time trends and had a net positive benefit to companies compared to PDUFA direct costs," we analyzed average approval times from 1979 to 2002 and developed a multivariate regression equation to help evaluate the net benefits. Statistical analysis was performed on the NDA/BLA approval time for the following five distinct time periods: 1) 10/0/1979 to 09/30/2002 (n=649); 2) 10/01/1979 to 09/30/1986 (n=168);3) 10/01/1986 to 08/31/1992 (n=153); 4) 09/01/1992 to 09/30/1997 – PDUFA I (n=188); and 5) 10/01/1997 to 09/30/2002 – PDUFA II (n=140). As seen in Figure 4-1, the mean approval time decreased from 33.09 months during the 1979-1986 timeframe to 18.34 months during PDUFA I and 14.63 months during PDUFA II. Substantial decreases are also noted for the median. The complete descriptive statistics for these time periods can be found in Appendix C: PDUFA Analysis Additional Results.

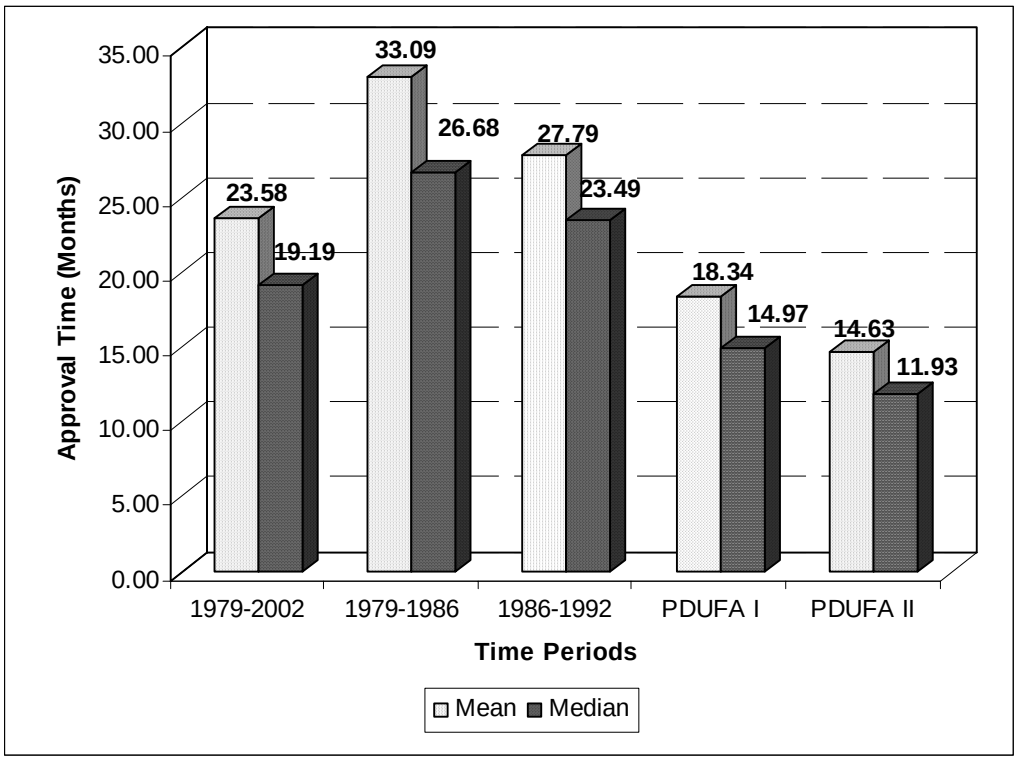
Therapeutic classes were investigated in a similar manner over these five time intervals. I was focused on CNS related drugs and cardiovascular related drugs. Additional information on anti-neoplastic and anti-infective drugs can be found in the thesis "The Drug Development Process: Evaluation of PDUFA I and II and an Investigation into Reducing Drug Development Times" by Dr. Matthew Strobeck.

By law, the FDA does not disclose what NMEs it is currently reviewing or which ones have failed. Thus, there is the issue of censoring of the data. It is entirely feasible that the FDA is currently reviewing NMEs that were submitted during the PDUFA II time period. The absence of these NMEs results in lower mean approval times and a lower sample size for PDUFA II. The last approved NDA/BLA in the data set during the PDUFA II time period was for the drug aprepitant (Emend™). The drug was submitted to the FDA for NDA review on 09/27/2002 and approved on 03/26/2003.

Similar trends as seen across all therapeutic areas were observed in the cardiovascular drugs as depicted in Figure 4-2. The same five time intervals as described for all therapeutics in Figure 4-1 were used. The sample size for all cardiovascular drugs from 1979 to 2002 was 113. The sample sizes for the time intervals 1979 to 1986, 1986 to 1992, PDUFA I, and PDUFA II were 37, 27, 32, and 17 respectively. The smaller sample size in the PDUFA II period may be indicative of right censoring of the data.

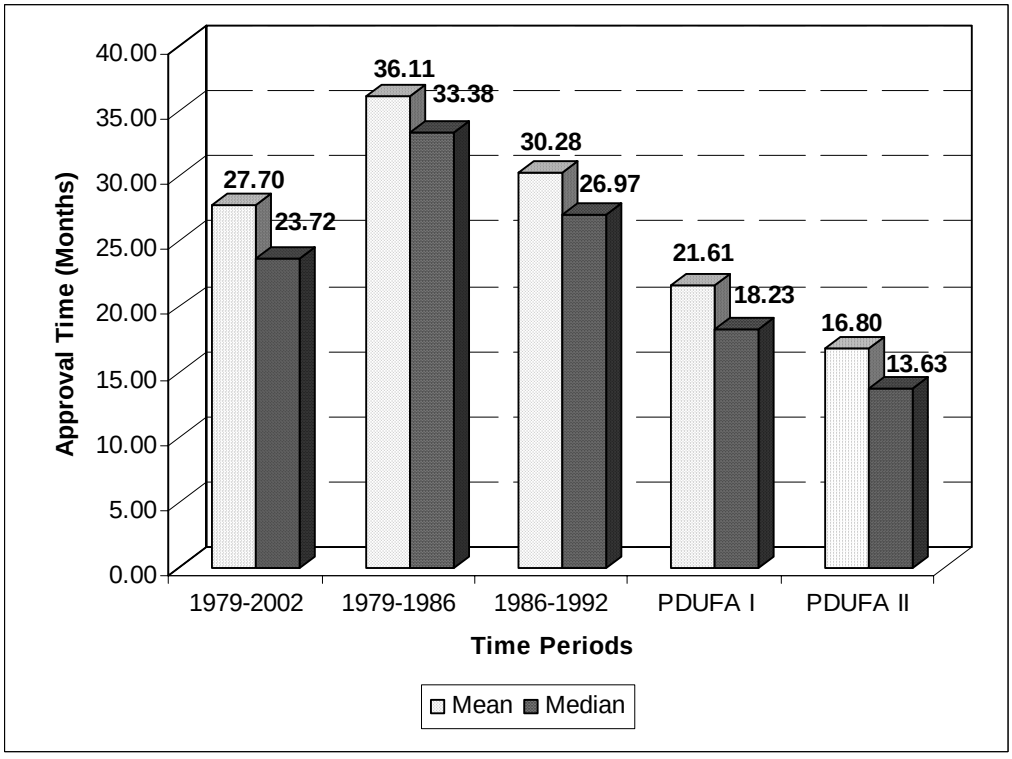
In contrast to the mean and median for all therapeutic areas and for cardiovascular drugs, the CNS drugs do not follow a decreasing trend. Figure 4-3 shows that approval times decrease steadily from the 1979-1986 period to PDUFA I; however, during PDUFA II, it appears that the mean and median time increased roughly 10% from PDUFA I. The sample size for all CNS drugs from 1979 to 2002 was 66. The sample sizes for the time intervals 1979 to 1986, 1986 to 1992, PDUFA I, and PDUFA II were 15, 13, 26, and 12 respectively. Similarly to the cardiovascular drugs, right censoring of data may be an issue for the CNS drugs.

Figure 4-1: Mean and Median Approval Times for All Drugs from 1979 to 2002



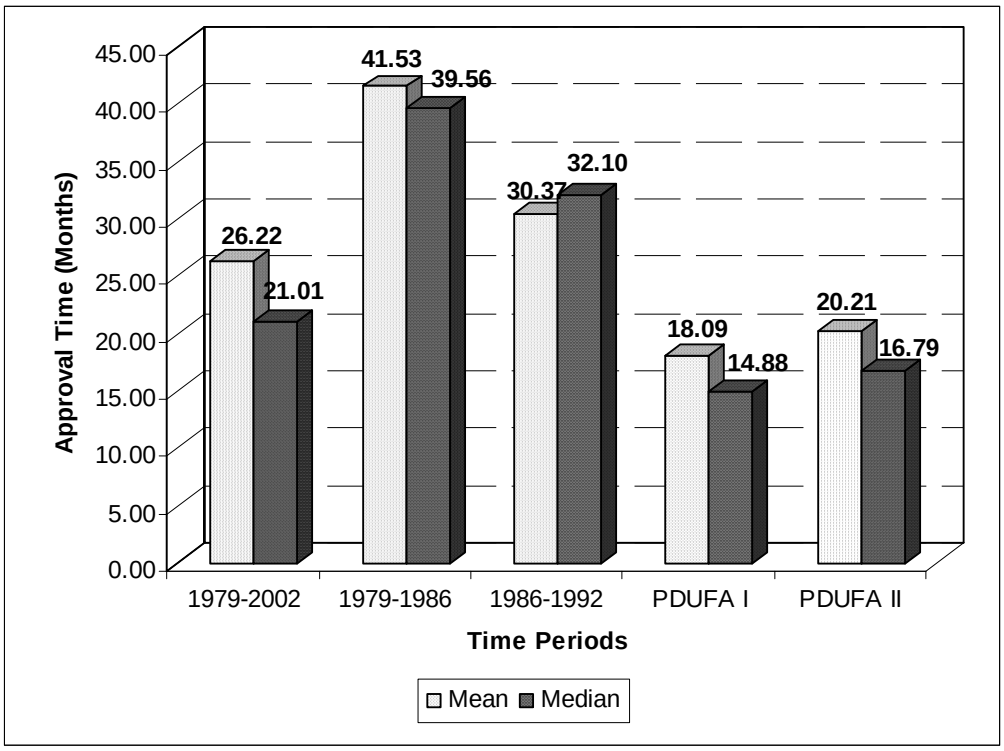
p-value < 0.00 by ANOVA indicating means are statistically different

Figure 4-2: Mean and Median Approval Times for Cardiovascular Drugs from 1979 to 2002



p-value < 0.00 by ANOVA indicating means are statistically different

Figure 4-3: Mean and Median Approval Times for CNS Drugs from 1979 to 2002



p-value < 0.00 by ANOVA indicating means are statistically different

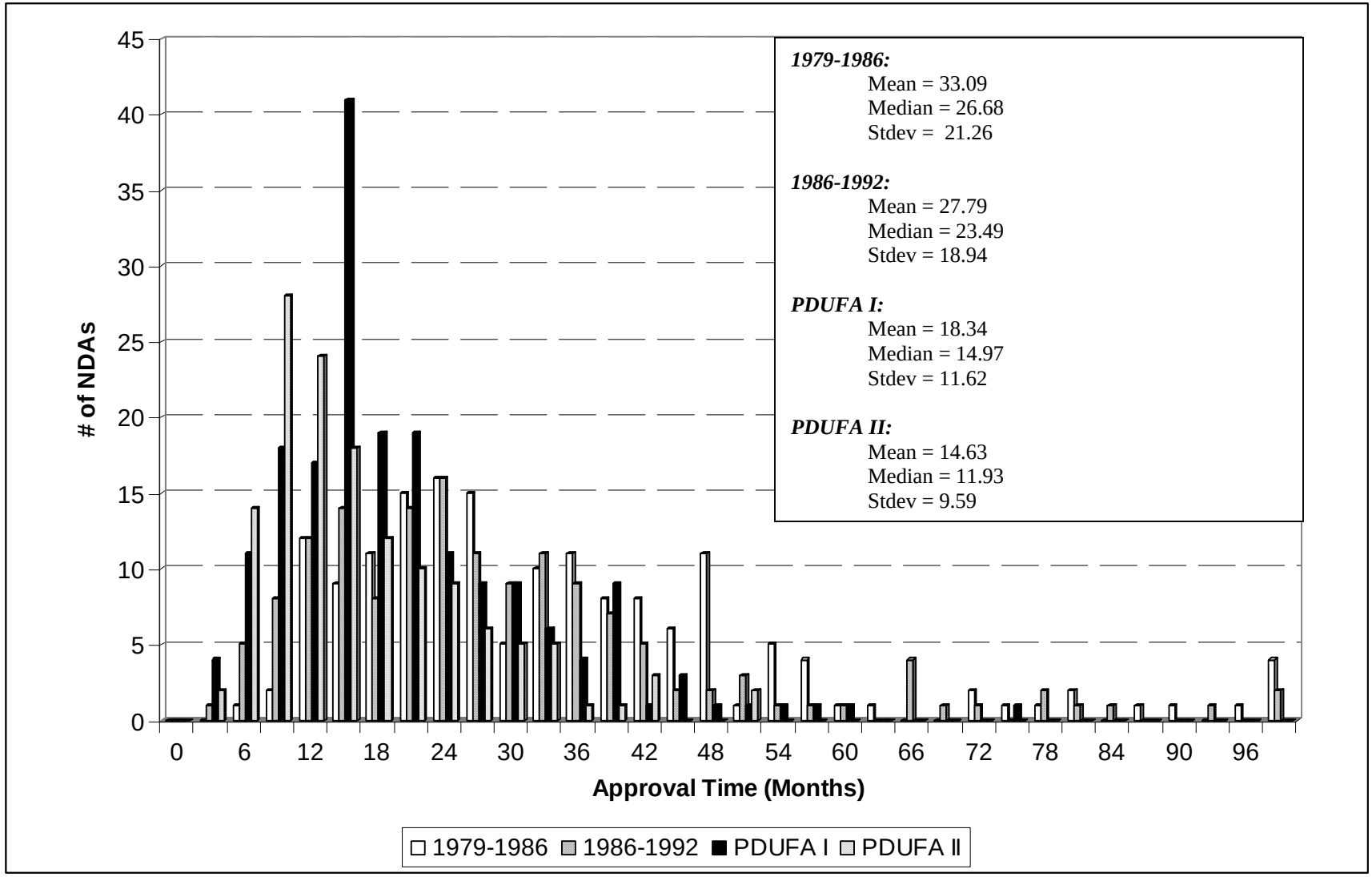
While the overall decreasing time trend in NDA approval times is not surprising and is supported by analysis by Reichert from Tufts[28], the potential increases in approval times in PDUFA II across certain therapeutic is concerning for the industry. Perceptions of PDUFA by the industry will be discussed in greater detail in Chapter 5: Results - Drug Development Surveys.

The impact of PDUFA can been seen in a histogram of the approval times per time period as shown in Figure 4-4. The four histograms show that approval time shifts substantially towards the left, a reduction in time. Additionally, moving from 1979 to PDUFA II, the variance (standard deviation) in approval times is compressed.

Survival curves for all NDA approvals, priority approvals, and standard approvals were constructed and are shown in Figure 4-5, Figure 4-6, and Figure 4-7 respectively. The use of the term "survival curves" is not completely accurate, as hazard models were not estimated; however, when looking at the proportion of approvals completed within a fixed time period, the graph is somewhat analogous to survival curves. The survival curves show the percentage of approvals remaining over time in months. As the time scale increases, more NDAs are approved for the time period grouping and thus the approval percentage declines.

[28] Reichert, Janice M. "Trend in Development and Approval Times for New Therapeutics in the United States." Nature Reviews Drug Discovery. Sept. 2003;2.

Figure 4-4: Histogram of Approval Times for '79-'86, '86-'92, PDUFA I, and PDUFA II



The faster decline in percentage approval remaining of the PDUFA I and II time periods relative to the pre-PDUFA time periods indicate faster approvals. The survival curves for all NDA approvals show clear separations between the PDUFA curves and the pre-PDUFA (1979-1986, 1986-1992) curves and indicate significant reductions in approval times. PDUFA II and PDUFA I had 50% of NDAs approved by twelve months and fifteen months, respectively, in contrast to twenty-seven and thirty months for 1979-1986 and 1986-1992 respectively.

The survival curves of priority approvals and standard approvals show similar separations among PDUFA and non-PDUFA curves. Contrasting the priority approvals with standard approvals reveals a dramatic reduction in 50% approval time – eight months for priority in PDUFA II compared to roughly seventeen months for standard in PDUFA II.

It is important to note that PDUFA I and II require actions within certain time frames as discussed in Chapter 1: Introduction and Background. These action dates should not be confused with approval dates. While FDA has met the PDUFA action dates, as they must by law, the approval times extend beyond the action dates. Based on the survival curves and histograms, it is feasible to argue that PDUFA, by mandating better response times via action dates, has lowered the NDA approval times substantially. This will be further demonstrated through the multivariate regression analysis.

Figure 4-5: Survival Curves for All NDA Types

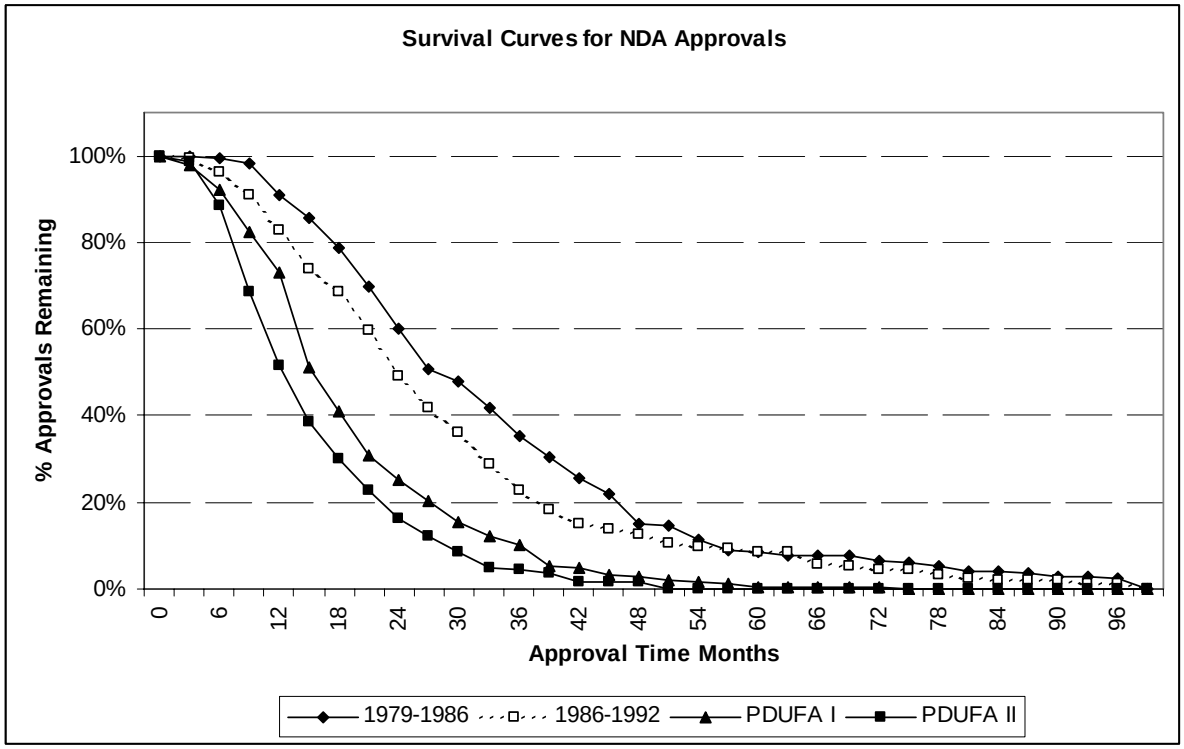


Figure 4-6: Survival Curves for Priority Approvals

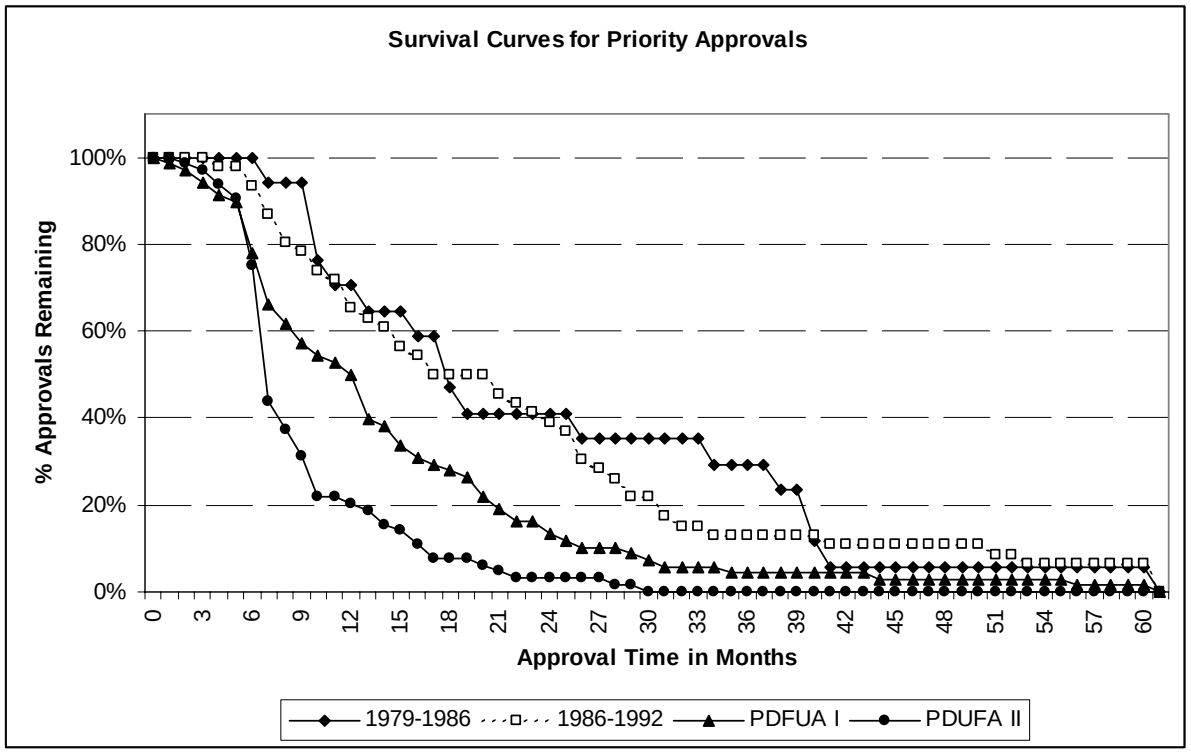
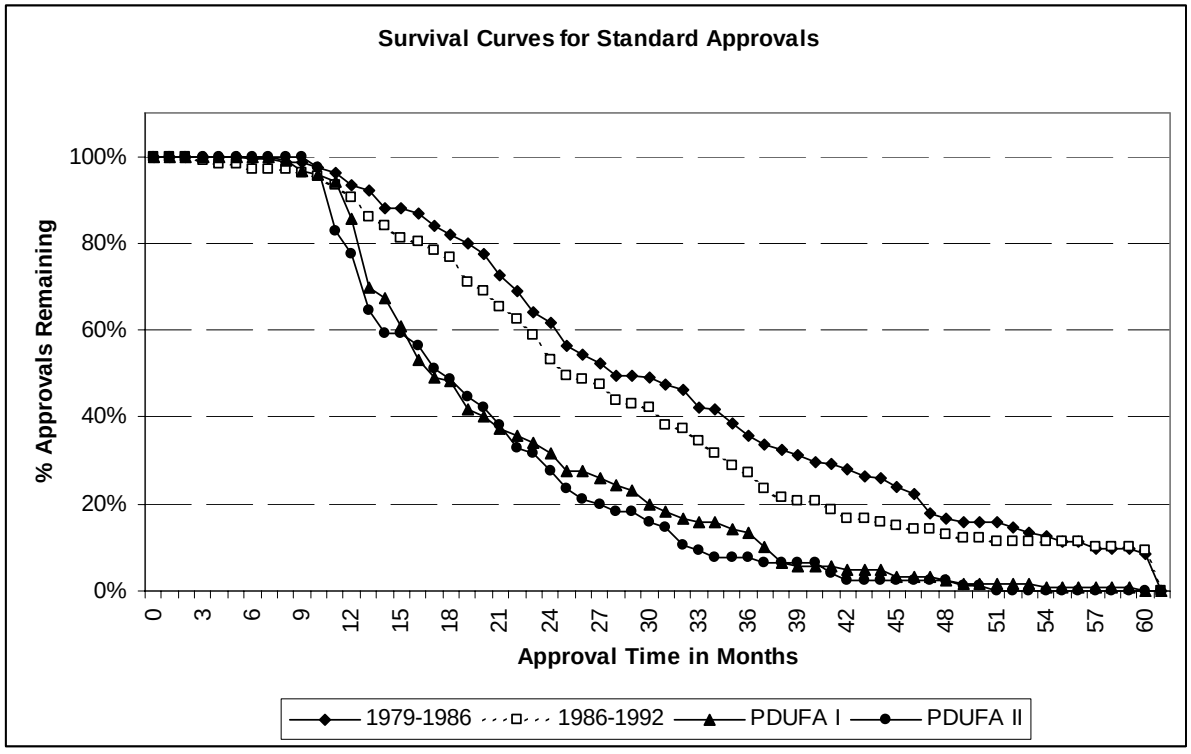


Figure 4-7: Survival Curves for Standard Approvals



Section 4.02 Multivariate Linear Regression Results

Multivariate linear regression was used to estimate the coefficients for the regression variables as described in Figure 2-1. The regression coefficients are displayed in the table in Figure 4-8 along with their respective p-values. The variables (coefficient, p-value) that are statistically significant include PRIORITY (-0.495, >0.000), TREND_PDUFA1 (-0.018, 0.002), TREND_PDUFA2 (-0.020, 0.001), DRG_ANTIINFECT (-0.283, >0.000), DRG_NEOPLASTIC (-0.261, 0.009), and DRG_AIDS (-0.857, >0.000).

Figure 4-8: Regression Coefficients and P-Values

	Coefficients	P-value
INTERCEPT	3.405	< 0.001
LNINDNDAMONTHS	0.025	0.302
TIMETREND	-0.015	0.079
PRIORITY	**-0.495**	**< 0.001**
TREND_PDUFA1	**-0.018**	**0.002**
TREND_PDUFA2	**-0.020**	**0.001**
ORPHAN	0.095	0.145
NATION	-0.049	0.274
DRG_CARDIO	0.113	0.090
DRG_ANTIINFECT	**-0.283**	**< 0.001**
DRG_NEOPLASTIC	**-0.261**	**0.009**
DRG_CNS	0.066	0.418
DRG_BIO	0.034	0.660
DRG_AIDS	**-0.857**	**< 0.001**

Regressions were run which excluded all therapeutic areas or included one therapeutic area at a time. These regressions indicated that the coefficients for the variables LNDINDNDAMONTHS, TIMETREND, PRIORITY, TREND_PDUFA1, TREND_PDUFA2, ORPHAN, and NATION were stable across therapeutic areas. Regressions were performed that indicated that the coefficients were temporally stable as well.

The TREND_PDUFA1 and TREND_PDUFA2 variables have a negative coefficient, indicating a reductive effect of about 2% annually on NDA approval times relative to pre-PDUFA years. Additional variables (coefficient, p-value, 95% confidence interval) that appear to be trending toward significance include DRG_CARDIO (0.113, 0.090, [-0.0175, 0.2437]) and TIMETREND (-0.015, 0.079, [-0.0325 0.0018]). The therapeutic category DRG_ANTIINFECT did not include any of the drugs included in the DRG_AIDS category.

Drugs that received a priority designation by the FDA were approved considerably faster than standard approvals. This was visible as well in the survival curve graphs across all time segments from 1979 to 2002. As stated in Chapter 1: Introduction and Background, PDUFA set short action dates of six months for priority-designated drugs. It is reassuring to see that this action date did indeed result in faster approvals on average for priority therapeutics.

The signs of the coefficients for all the variables, with the exception of the DRG_CNS and DRG_CARDIO variables, were expected to be less than zero assuming that the variables reduced approval times. The LNDINDNDAMONTHS and ORPHAN variables were greater than zero, indicating that approval times were higher for drugs with longer IND to NDA times and for orphan designated drugs. I assumed that orphan drugs, due to their novelty and benefit in areas of high unmet medical need, would be approved faster relative to other NDAs. In fact, 60% of drugs designated as orphan drugs during 1979 to 2002 received priority approval. The effect of priority designation is likely to be more important for review than the designation of orphan drug. The ORPHAN variable had a positive coefficient indicating a longer approval time. A possible explanation, as stated during interviews with industry interviewees experienced with

orphan drugs, was that the novel nature of the orphan therapeutic often complicates and extends the review process.

Contrary to my expectations, the variable that measures the time spent in development was not statistically significant in decreasing the NDA approval time (p-value = 0.302). The sign of the coefficient was positive; however, arguments supporting a coefficient of either sign could be made. For example, one could argue that longer IND-NDA development times reflect more complicated drugs and thus NDA approval times would be longer. Conversely, once could argue that the FDA has more experience and knowledge with the drug and NDA approval times would be accelerated. The more detailed testing of either of these assumptions is beyond the scope of this research.

The omitted category in the regression was the DRG_OTHER class that accounted for all other therapeutics. The coefficients for the therapeutic dummy variables were an indication in increase or reduction in approval time relative to this omitted class.

Applying the generated regression coefficients to the generic regression in Equation 2-1, the definitive regression equation below is derived.

Equation 4-1: PDUFA Approval Time Definitive Regression Equation

$$\ln(\text{approval time}) = 3.405 + 0.025 \cdot LNINDNDAMONTHS - 0.015 \cdot TIMETREND - 0.495 \cdot PRIORITY - 0.018 \cdot TREND\_PDUFA1 - 0.020 \cdot TREND\_PDUFA2 + 0.095 \cdot ORPHAN - 0.049 \cdot NATION + 0.113 \cdot DRG\_CARDIO - 0.283 \cdot DRG\_ANTIINFECT - 0.261 \cdot DRG\_NEOPLASTIC + 0.066 \cdot DRG\_CNS + 0.034 \cdot DRG\_BIO - 0.857 \cdot DRG\_AIDS$$

In order to better visualize the effects of PDUFA, the regression equation variables were evaluated and the graph in Figure 4-10 was constructed evaluating the variables as described in the following paragraphs.

For the binary dummy variables for the therapeutic areas (*DRG*_[Therapeutic Area]), the variables were evaluated at their sample means, which is their respective proportion of the sample of drugs. This percent of the total drugs is shown in Figure 4-9. Similarly, the variables PRIORITY, ORPHAN, and NATION were evaluated at their sample means with values of 0.300, 0.179, and 0.435 respectively.

The sample mean for LNDINDNDAMONTHS equaled 4.265. This average included four zero values for drugs that were missing IND to NDA data. Excluding the zero values did not have a significant effect on the sample mean or the graphed outcome so the values were included for completeness.

The TIMETREND variable was incremented from one to twenty-four with one corresponding to the government fiscal year starting on 10/01/1979 and ending on 09/30/1980. TREND_PDUFA1 and TREND_PDUFA2 were the product of the TIMETREND variables at a given year multiplied respectively by the PDUFA1 or PDUFA2 binary that was either zero or one for the timeframe. For example in the 1993 government fiscal year, PDUFA1 equaled one

and TIMETREND equaled fifteen so TREND_PDUFA1 equals fifteen. The resulting natural log of approval months for each year was converted to NDA time in months via Equation 4-2. The standard error of regression, used as a correction factor, was 0.575.

Figure 4-9: NME Therapeutic Area Composition

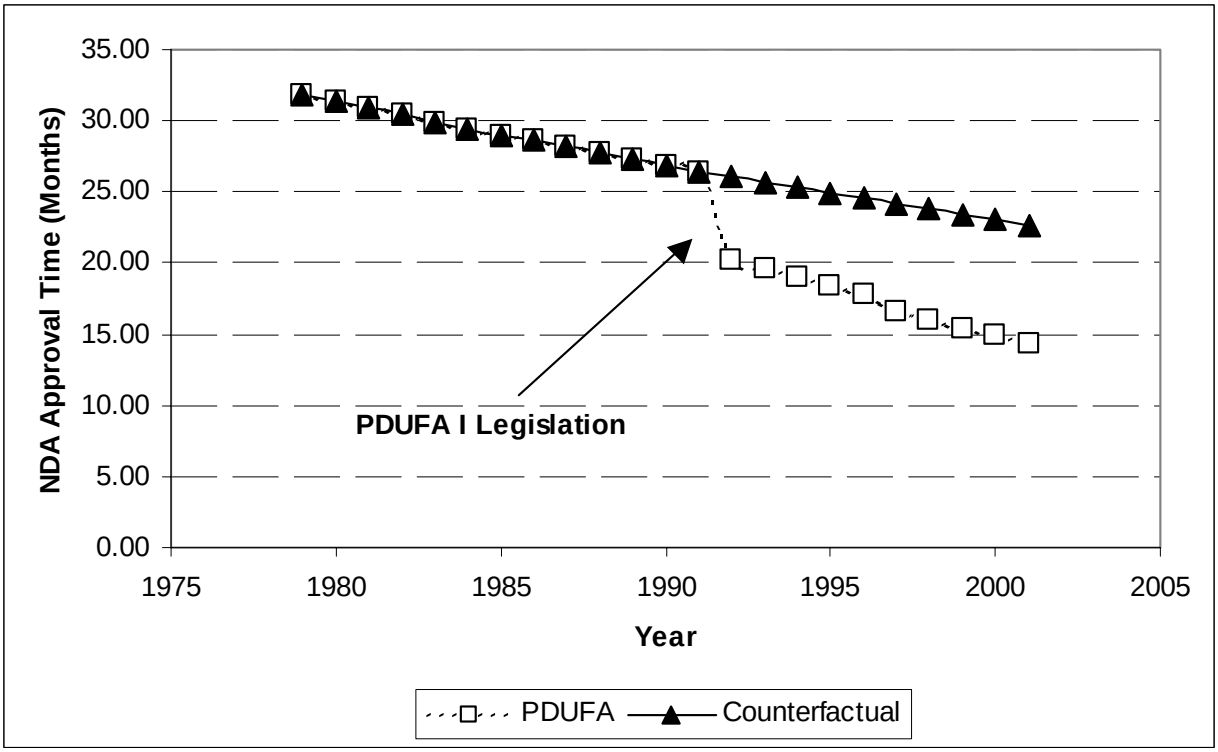
Therapeutic Area	Number of NMEs	% of Total
Cardiovascular	113	17.4%
Anti-infectives	96	14.8%
Anti-neoplastic	44	6.8%
CNS	66	10.2%
Biologics	86	13.3%
AIDS	13	2.0%
All other areas	231	35.6%
TOTAL	**649**	

Equation 4-2: Predicted NDA Time

$$\text{Predicted Approval NDA Time} = e^{(LNAppMonths + 0.5 \bullet (StndErr\ of\ Rgrsn)^2)}$$

As shown in Figure 4-10 below, evaluation of the regression equation with the PDUFA binary variables turned on (PDUFA) and with the PDUFA variables turned off (counterfactual) show a significant divergence of the lines upon enactment of the PDUFA I legislation.

Figure 4-10: Regression Predicted NDA Approval Time in PDUFA and Counterfactual



The approval times are predicted for an NDA submitted in the given year. According to the regression coefficients and p-values, NDAs in the cardiovascular or CNS therapeutic fields

would have longer approval relative to the "other" class of drugs; however, these coefficients were not statistically significant whereas the coefficients for anti-infectives and anti-neoplastics were significant, as was that for AIDS.

Section 4.03 FDA Commissioner Vacancy Analysis

As discussed in Chapter 2: Methods – Drug Approval and PDUFA Analysis, four different methods were used in regression analysis with the commissioner vacancy ratio. As shown in Figure 4-3, the coefficients are positive in methods two and four but negative in methods one and three. Additionally, the p-values are all significant with the exception of method one.

In method three, given that COMMISSX1 is one when the ratio is zero and given that COMMISSX2 is the natural log of the ratio when the ratio is greater than zero, the expectation is that the signs on the coefficients would be opposite (COMMISSX1 negative, COMMISSX2 positive). However, while the sign is negative for COMMISSX2, it is positive for LNCOMMISS and COMMIS_VAC, which is inconsistent.

Equation 4-3: Commissioner Vacancy Regression Coefficients

Method	Variable(s)	Coefficients	P-value
1	COMMISSIONER	-0.038	0.635
2	LNCOMMISS	0.051	0.017
3	COMMISSX1 COMMISSX2	-0.138 -0.155	0.023 < 0.001
4	COMMISS_VAC	0.322	< 0.001

A potential explanation for the contradictory coefficients lies in the distribution of the vacancy ratios. From Figure 4-11, it is observed that 61% of the total vacancy days lie in the PDUFA timeframe. Given the shortened NDA approval times as shown by the histograms, survival curves, and regression, it is not surprising that a greater number of NDAs will have some vacancy ratio greater than zero during the PDUFA periods. In point of fact, of the 321 NDAs approved pre-PDUFA, only 6% had a ratio >= 0.5 as compared to 33% of NDAs approved during PDUFA.

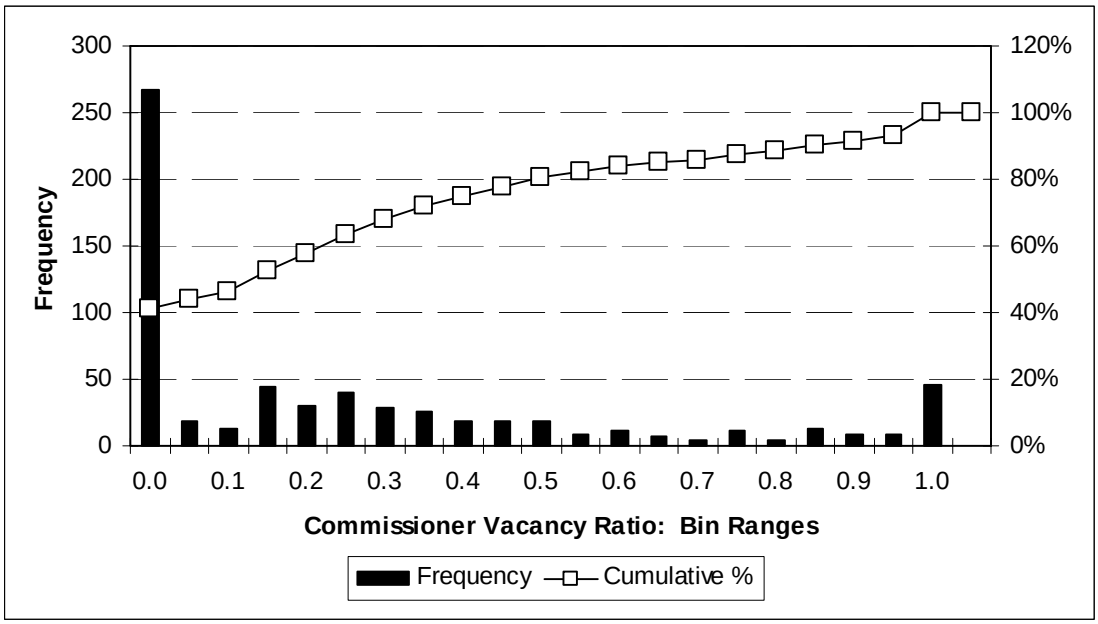
Figure 4-11: Commissioner Vacancy – Distribution of Days

Vacancy Start	Vacancy End	Elapsed Days	% of Total Days
6/30/1979	10/21/1979	113	5%
1/20/1981	4/13/1981	83	4%
9/11/1983	7/15/1984	308	14%
12/17/1989	11/7/1990	325	15%
2/28/1997	11/30/1998	640	30%
1/19/2001	11/14/2002	664	31%
TOTAL		**2,133**	100%

Figure 4-12: Commissioner Vacancy PDUFA Distribution

	Non-PDUFA NDAs (n = 321)	PDUFA NDAs (n = 328)
Ratio = 0	41%	41%
Ratio >= 0.5	6%	33%
Ratio < 0.5 and > 0	54%	26%

Figure 4-13: Distribution of Commissioner Vacancy Ratio



The distortion of ratios greater than 0.5 falling under PDUFA and the ratios less than 0.5 falling under pre-PDUFA time periods is potentially responsible for the conflicting regression information. Manipulations of this ratio yield various results indicating a lack of robustness in the analysis. This suggests that there are other confounding issues at hand. According to a source at FDA, other factors such as incidence of safety withdrawals, reviewing division turnover, medical reviewer turnover, and new data submissions for the NDA would need to be taken into account.

Section 4.04 PDUFA NPV Analysis

The NPV in 1992 dollars of PDUFA, PV of PDUFA *ΔBenefit* minus the PV of PDUFA fees, across four therapeutic areas was calculated using real discount rates from 0.5% to 10% as shown in Figure 4-14. The therapeutic classes included in the calculation are cardiovascular (n = 41), CNS (n = 36), anti-infectives (n = 37), and anti-neoplastics (n = 22). Unfortunately, sales data was not readily available for some of the drugs in the therapeutic class and thus the sample sizes indicated were lower than the total drugs in the therapeutic class. The total number of PDUFA drugs in each therapeutic class is as follows: cardiovascular (n = 49), CNS (n = 38), anti-infective (n = 40), and anti-neoplastics (n = 26). The number of drugs evaluated for these classes totaled 136 of the 150 possible or approximately 90%.

The NME data provided by FDA had a total of 328 NDAs approved during PDUFA I and II. The NDAs with available sales data from the four therapeutic classes total 136 and represent 42% of all the NDAs approved during PDUFA I and II. Significant therapeutic areas such as gastrointestinal and metabolic/endocrine, which represent at least 15% of worldwide drug sales[29], were not evaluated but would add significantly to the overall NPV.

[29] Mathieu, M.P., ed. "Therapeutic Categories: Drug Sales as a Percentage of Worldwide Market, 2002 vs. 2006" PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2003/2004, 2003, p. 17.

The total PV benefit of sales, indicated in solid black in Figure 4-14, ranges from 1.64 billion dollars to just over eight billion dollars. The solid white bars indicate the NPV after the PDUFA fees are subtracted. Relative to the PV benefit, the total PDUFA fees are very small (See Figure 4-15). At a real discount rate of 5%, the PDUFA fees are only 3.9% of the *ΔBenefit*.

Figure 4-14: PV of Sales and NPV of PDUFA

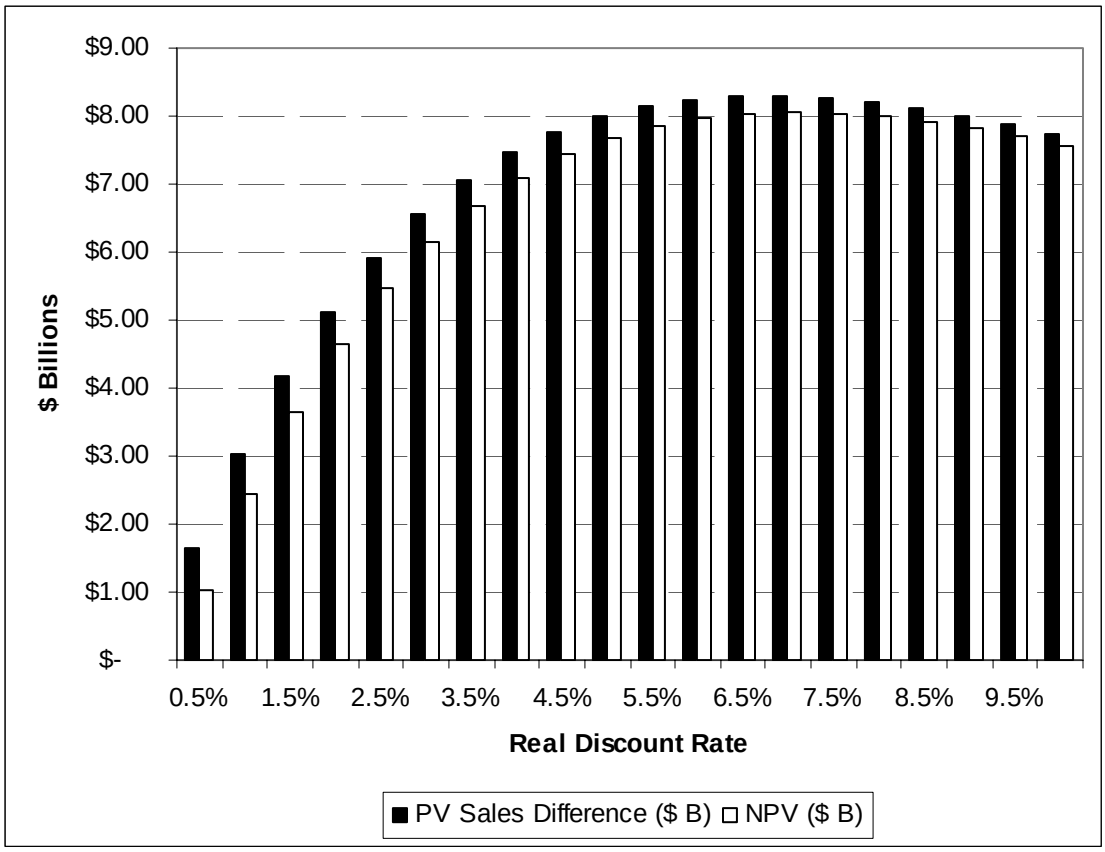
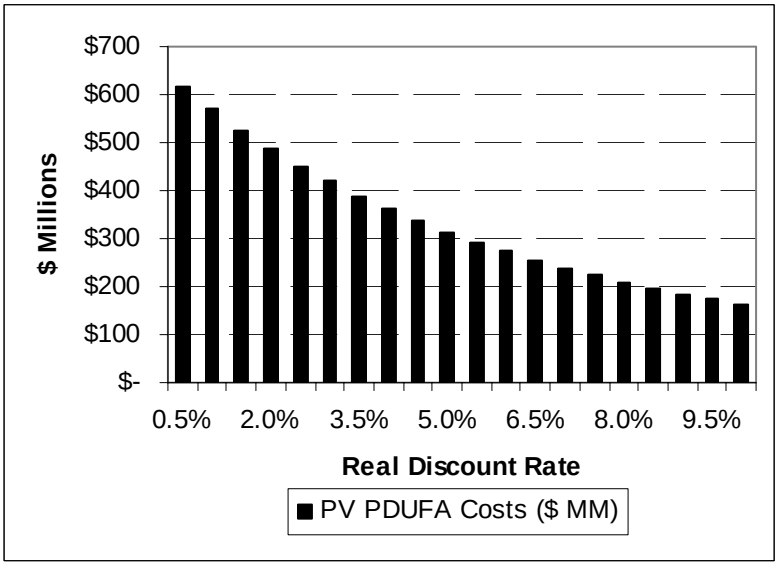


Figure 4-15: PV of Total PDUFA Fees

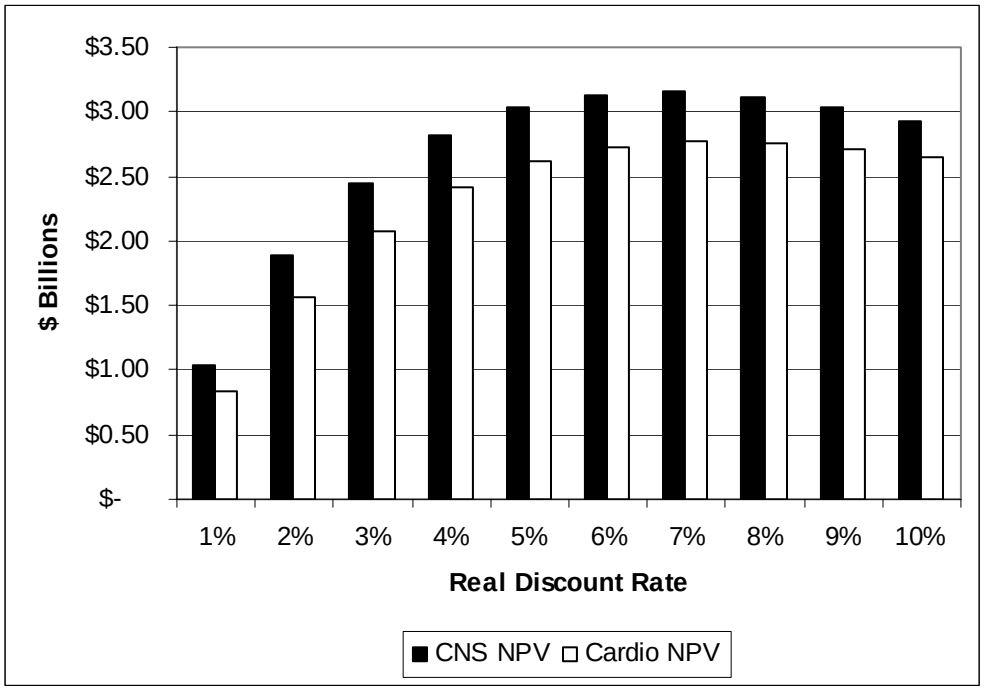


A subset of the NPVs for the cardiovascular and CNS therapeutic areas is reported in Figure 4-16. The NPVs for the cardiovascular and CNS class were analyzed using a real discount rates from 0.5% to 10%. The complete information is reported in Figure C-5 in Appendix C: PDUFA Analysis Additional Results.

For the NPVs of the anti-neoplastics and anti-infectives,

please refer to the thesis "The Drug Development Process: Evaluation of PDUFA I and II and an Investigation into Reducing Drug Development Times" by Dr. Matthew Strobeck.

Figure 4-16: NPVs for Cardiovascular and CNS Therapeutic Areas



Investigation of the distribution of NPVs on an NME by NME basis shows that several NMEs in each therapeutic class do not have a positive NPV. Simply stated, the sales did not offset the costs of PDUFA. It is likely that these drugs did not recoup their development costs either given the low cost of PDUFA fees relative to overall research and development fees. Note that in calculating the NPVs of the NDAs, relatively conservative assumptions were made and the benefits of PDUFA were still overwhelmingly positive at an aggregate level.

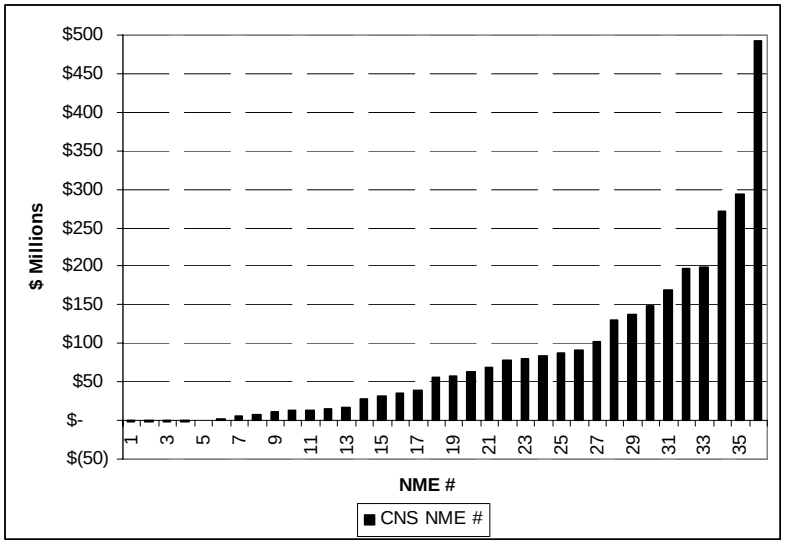
At a disaggregated level, the distribution of NPVs for CNS and cardiovascular drugs was skewed in the positive direction as shown for both therapeutic areas in Figure 4-17and Figure 4-18. The negative NPVs as a percentage of the sample were 11% and 12% for CNS and cardiovascular respectively at a real discount rate of 5%.

From an economic perspective, the NPV of PDUFA can be viewed as innovative returns, returns that can be plowed back into the company to generate growth. At the real discount rate of 5%, there is roughly $7.68 billion of innovative returns. If one accepts the premise that PDUFA was in a large part responsible for speeding up NDA approvals, the $7.68 billion represents a significant benefit accrued to industry. Additionally, the NPV of PDUFA can be viewed as a proxy for the social benefit enjoyed by healthcare consumers and society. However, it is difficult to evaluate the consumers' surplus due to the moral hazard associated with health insurance.[30] In this sense, there is excess consumption of healthcare by individuals because they

[30] Moral hazard is the propensity of individuals or groups to take on riskier or hazardous behavior because of guarantees or provisions in a contract.

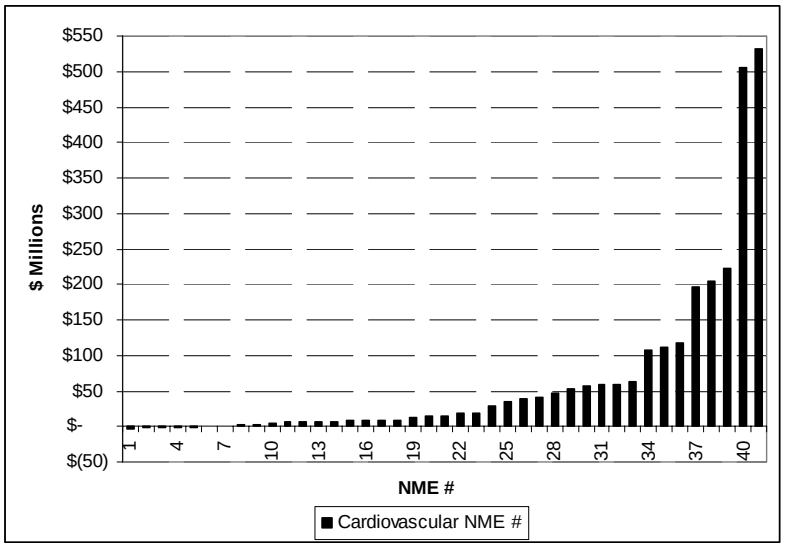
are not paying at their marginal cost of care, which in many cases exceeds the cost of their insurance. It is difficult to estimate what consumers would be willing to pay for the drug in the absence of insurance and even more challenging to separate out the individuals who are not necessarily benefiting from the drug. Ideally, measurement of the social benefit would include a measurement of change in quality of life, change in workplace productivity as a result of fewer days missed due to illness, change in healthcare management practices around the therapeutic area, cost of treatment of any related side effects and toxicities, and cost of withdrawal in the case where the therapeutic is deemed unsafe.

Figure 4-17: Distribution of NPVs for CNS Drugs at Real Discount Rate of 5%



n = 36
negative values = 4
% of total = 11%

Figure 4-18: Distribution of NPVs for Cardiovascular Drugs at Real Discount Rate of 5%



n = 41
negative values = 5
% of total = 12%

An often-stated concern of accelerated approval is that unsafe or ineffective drugs will reach the market and then be withdrawn. The cost in terms of mortality and morbidity of patients who

were treated with the drug can be significant. A study by the General Accounting Office[31] (GAO) found that from 1985 to 1992, pre-PDUFA, the percentage of drugs withdrawn was 3.10% versus 3.47% for the period of 1993 to 2000 (PDUFA). In absolute numbers, 193 NMEs were approved pre-PDUFA and six were withdrawn. During this 1993 to 2000 period, FDA approved 259 NMEs and nine were withdrawn.

The FDA disagreed with the GAO findings and had the following criticisms: 1) the GAO excluded biologics from the withdrawal analyses; 2) fourteen drugs were listed as being withdrawn but not all were included in the analyses; 3) the timeframes analyzed by the GAO do not match the pre-PDUFA/post-PDUFA time periods; 4) statistical significance and data censoring is not addressed. According to FDA analysis, the withdrawal percentage from 1979 to1992 was close to 2.5%. For NDAs approved during PDUFA I until 1999, the withdrawal rate has been 2.6%.[32]

Section 4.05 Profitability Calculations

An additional calculation of interest is the percentage increase in PV of profitability. Assuming that Selling, General &Administrative (SG&A), Cost of Goods Sold (COGS), and other standard costs remained relatively constant in the actual or counterfactual PDUFA scenarios, the % increase in PV profitability can be measured as indicated below in Equation 4-4 since this common cost terms fall out of the equation.

Equation 4-4: PDUFA Profitability Percentage Increase

$$\%\ increase\ in\ PV\ \ profitability = \frac{\Delta NPV\ \ Sales}{NPV_{Counterfactual}}$$

Figure 4-19: PDUFA Related Percentage Increase in Profitability

Real Discount Rate	Aggregate	CNS	Cardio	Anti-Inf.	Anti-Neo.
1%	0.46%	0.61%	0.56%	0.27%	0.26%
2%	1.01%	1.31%	1.23%	0.63%	0.64%
3%	1.56%	2.01%	1.90%	0.98%	1.02%
4%	2.11%	2.70%	2.56%	1.33%	1.39%
5%	2.65%	3.38%	3.22%	1.68%	1.76%
6%	3.18%	4.07%	3.87%	2.02%	2.12%
7%	3.71%	4.74%	4.52%	2.36%	2.47%
8%	4.24%	5.41%	5.17%	2.69%	2.82%
9%	4.76%	6.08%	5.81%	3.02%	3.16%
10%	5.28%	6.74%	6.45%	3.35%	3.49%

As indicated in Figure 4-19, the aggregate percentage increase in profitability at a real discount rate is 2.65%. Sensitivity analysis by varying the discount rate indicates substantial increases in

[31] Mathieu, M.P., ed. "A GAO Study on Drug Withdrawal Rates and PDUFA." PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2003/2004, 2003, p. 250.
[32] FDA internal analysis and presentation provided by Ed Hass.

profitability. In a sense, this can be interpreted as the return to profitability that companies get for "investing" in the FDA via PDUFA fees.

Given the substantial number of blockbuster products in the CNS and cardiovascular therapeutic classes, it is not surprising to see larger percentage increases in profitability due to accelerated time to market. A more robust analysis of profitability conferred by PDUFA would include average free cash flows from therapeutics. It is my intention to conduct this analysis in future studies.

Section 4.06 PDUFA Study Limitations

As previously stated, the sales data used in the calculations represents United States sales only. The extent to which accelerated approval in the United States affects international approvals was not investigated or accounted for in this research study. If earlier United States approval encourages earlier approval in foreign countries, then the NPV benefit will be even greater.

Patent protection expiration issues and the reduction of effective patent life due to increased approval time length in the counterfactual analysis was not accounted for in this model. The analysis here is likely understating the net benefits of PDUFA for if anything, reducing patent life would decrease the sales in the counterfactual and increase the NPV benefit.

Of significant concern regarding the validity of this analysis is the lack of data on NDAs that were not approved or withdrawn from review. Due to confidentiality obligations to sponsor companies, the FDA was unable to provide detailed or aggregate information on NDAs that were rejected or withdrawn. In order to fully account for the costs and benefits of PDUFA, we would want to consider the costs associated with failed or withdrawn NDAs. It is possible that failure rates of NDAs did not change from the pre-PDUFA time period to the PDUFA time period; however, if failure rates increased during PDUFA, this added cost is unaccounted for in the current analysis. This could have a significant negative impact on the overall benefit of the findings that are reported herein. Likewise, a reduction in failure or withdrawal rates would increase the benefits delivered by PDUFA. A more robust analysis would have performed a sensitivity analysis regarding percentage failures with associated costs. However, this issue does not negate the benefit of faster approval to sponsors that receive approval.

Chapter 5: Results - Drug Development Surveys

Section 5.01 Variability – A Constant Theme

A consistent theme throughout the interviews conducted during this research was the high degree of variability in almost all facets of interaction, communication, and organization between industry and the FDA. From an industry perspective, drug development consists of reducing uncertainty and variability through planned clinical trials. Increased volatility and consequently reduced predictability of interactions with a regulatory agency make a difficult and expensive process even more cumbersome and fraught with risk. As mentioned in the study by Dimasi in Chapter 1: Introduction and Background, increasing the probability of success of a drug across phases of development can have a substantial impact on reducing costs of development. Reducing the variability of the interactions with the FDA may aid in reducing this risk according to industry interviewees.

The hypothesis "industry believes that communication with the FDA is inadequate during late stage clinical studies" was evaluated mainly by quantitative questions regarding communication; however, the sections discussed in this chapter all have the consistent theme that additional communication and interaction could help resolve the ambiguity and information asymmetry between the FDA and industry.

Section 5.02 Quantitative Survey Analysis – General Points

The quantitative survey was administered to a total of thirty-six people. Seven additional questions were added to the survey after nine individuals had been interviewed. It was not possible to obtain their responses to those questions post interview. In these cases, the question response is designated as Not Administered (NA). A value of No Response (NR) is indicated when the interviewee did not have knowledge regarding the question or declined to respond to the question. The sample size (n) for each question is determined by subtracting the no responses and not administered from the thirty-six respondents. The descriptive statistics (mean, median, etc.) for each question are based on the sample size (n) and exclude the NR and NA responses.

As shown in Figure B-2 in Appendix B: Interview Questionnaires, the quantitative questionnaire had four different sections, each employing a scale from one to five with different rankings associated with the numbers. In many cases, interviewees responded with a value between the integer rankings (denoted as a dashed line between the stated values in the graphs). These responses were deemed to be acceptable and are included in the analysis. Descriptive statistics for all the quantitative questions are provided in the appendix Figure D-1. A subset of the quantitative questions are addressed in this thesis; the remainder are addressed by Dr. Matthew Strobeck or in future publications.

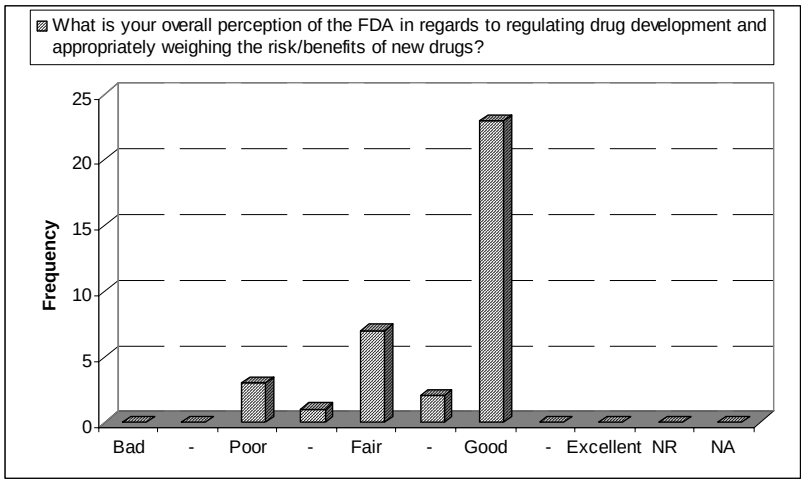
The quantitative responses were analyzed in three major ways: 1) in aggregate; 2) separated according to company type – biotech versus pharmaceutical; and 3) according to interviewee position - executive vice president and higher compared to vice president and lower. Students t-test was used to compare results in methods two and three within a question; only a small

number of results were found to be statistically significant in the comparisons. These results are reported where appropriate. This absence is not surprising given a maximum sample size of thirty-six. The p-values for all the t-test comparisons are reported in the appendix in Figure D-1.

Section 5.03 Industry's Perception of the FDA

To evaluate the commonly held perception that industry has a negative opinion of the FDA, we asked interviewees to rate the agency's ability to regulate drug development and appropriately weigh risk/benefits of new drugs. Sixty-four percent of respondents, as seen in Figure 5-1, rated the agency's competency in these areas as "Good." Qualitative comments from interviewees indicated a great respect for the FDA as a whole and the challenging role that the agency plays in evaluating drugs.

Figure 5-1: Rating - Overall Perception of FDA

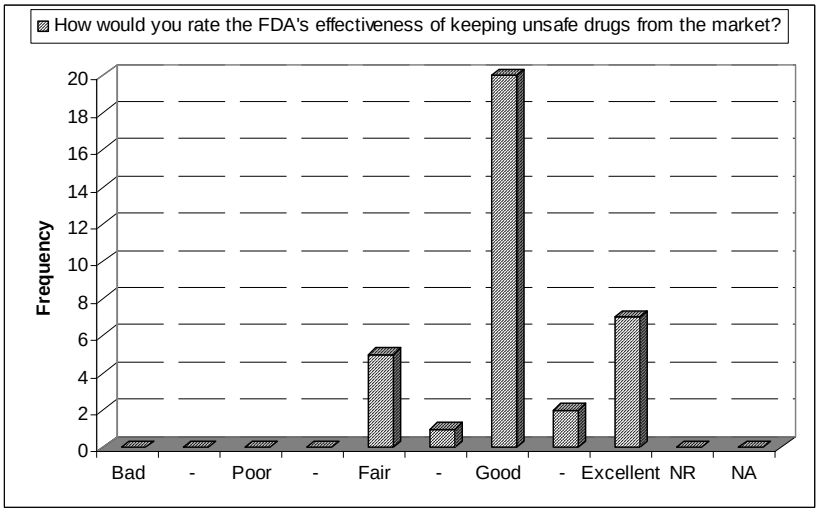


n = 36
mean = 3.57
median = 4
mode = 4
stdev = 0.66

1 = Bad
2 = Poor
3 = Fair
4 = Good
5 = Excellent

Interviewees were asked to rate the FDA's effectiveness of keeping unsafe drugs from the market. Again, the vast majority of responses were positive, with 83% of respondents indicating the agency did a "Good" to "Excellent" job (See Figure 5-2).

Figure 5-2: Rating - Keeping Unsafe Drugs from Market

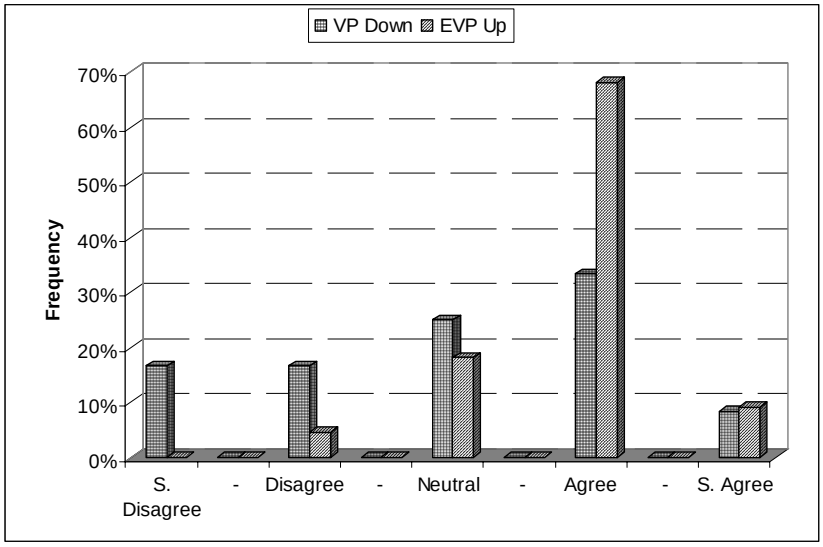


n = 36
mean = 4.07
median = 4
mode = 4
stdev = 0.60

1 = Bad
2 = Poor
3 = Fair
4 = Good
5 = Excellent

The overall positive ratings for both these questions were relatively surprising to me given the vitriol that is often apparent in the press. However, many respondents qualified their answers to the question regarding unsafe drugs with the comment that the agency was partly responsible for delaying the progress of some very good drugs to market and in some cases being overly vigilant. A global head of research and development stated that the agency weighed drug development as a risk-benefit analysis. The individual suggested that a risk-risk analysis might instead be more appropriate where the trade off between the risks of approving a drug with certain safety issues is weighed against the risks that patients face without the therapeutic available as a treatment option. This particular interviewee stated that often it is the risk of the drug being used in inappropriate populations or combinations that causes safety concerns.

Figure 5-3: Comparison by Position of Response to "Efforts to Reduce Approval Times" Question



1 = Strongly Disagree
2 = Disagree
3 = Neutral
4 = Agree
5 = Strongly Agree

Interviewees were asked to indicate how much progress the FDA had made in reducing approval and development times. Sixty-five percent of the interviewees (n=34, mean = 3.53, median = 4, mode = 4, stdev = 0.99) indicated that at a minimum they "Agree" that the FDA has made significant efforts to reduce approval times. Additionally, 65% of the interviewees (n=34, mean = 2.15, median = 2, mode = 1, stdev = 1.10) did not think that the EMEA was more efficient at approving drugs than the FDA. However, 71% of interviewees (n=34, mean = 2.12, median = 2, mode = 2, stdev = 0.91) indicated that at a minimum they "Disagree" that the FDA has made significant efforts to reduce drug development times.

None of the t-test comparisons of the questions above for company type and level was statistically significant. However, the t-test comparison by position within the company for the question of whether the interviewee believed the FDA had made significant efforts to reduce approval times was trending towards significance (p-value = 0.057). The responses were normalized as percentages of the sample size and are compared in Figure 5-3 above.

Section 5.04 Organization and Structure at the FDA

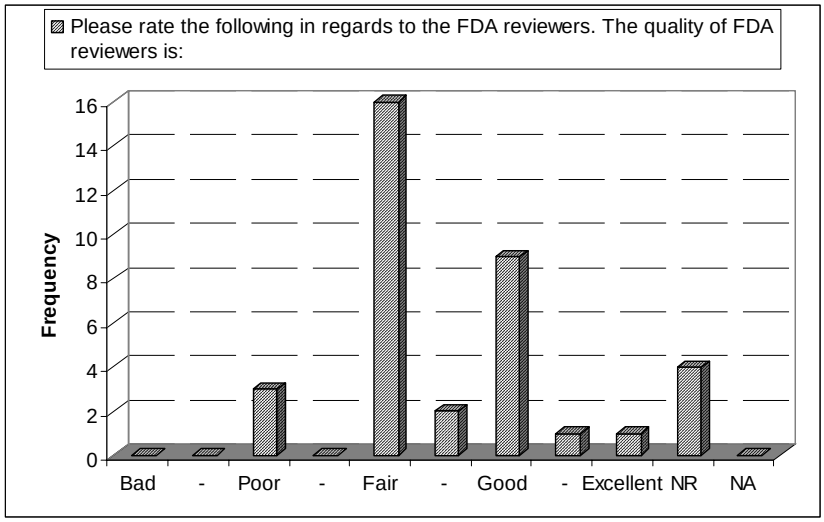
A recurrent theme in the qualitative survey of industry was the perception that the FDA is organized like a "cottage" industry. In other words, the divisions are relatively independent and

do not function in a similar manner when interacting with the drug sponsor. It is not debatable that the FDA divisions under the Center for Drug Evaluation and Research (CDER) are engaged in different therapeutic areas and will thus have different requirements for safety and efficacy. However, the way in which the divisions interact and respond to sponsors is highly variable in regards to simple things such as returning phone calls to more complex issues such as feedback on clinical protocols and NDAs.

Many of the interviewees acknowledged that the FDA medical reviewers have a very difficult job to do and believe that the reviewers are overworked and underpaid for their efforts. Again the consistent theme in regards to the reviewers was the high degree of variability in training, accountability, and quality. As seen in Figure 5-4, interviewees most often ranked medical reviewer quality as "Fair."

Similarly, the respondents indicated that the accountability, defined as responsiveness and commitment to agreed upon protocols, of medical reviewers to the sponsor company was most often "Fair" (n = 33, mean = 3.06, median = 3, mode = 3, stdev = 0.76). Interviewees indicated that they believed the training of medical reviewers upon joining the agency, not previous education and experience, was generally "Fair" to "Poor" (n=22, mean = 2.86, median = 3, mode = 3, stdev = 0.82).

Figure 5-4: Rating - Quality of FDA Reviewers



n = 32
mean = 3.33
median = 3
mode = 3
stdev = 0.70

1 = Bad
2 = Poor
3 = Fair
4 = Good
5 = Excellent

In contrast, when asked to evaluate the direct leadership (team lead, deputy division director, division director) of medical reviewers, respondents ranked the leadership higher than the reviewers (See Figure 5-5). Qualitatively, interviewees indicated that interactions with leadership one or more levels above the medical reviewer were generally very positive.

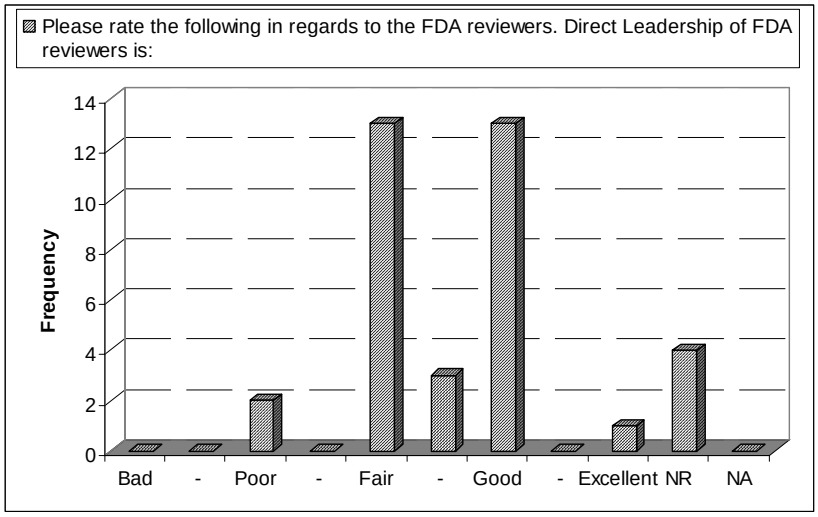
During the qualitative survey, respondents often stated that excellent medical reviewers would become team leads and move up through the hierarchy at the agency. This might help explain the higher ratings for the direct leadership. Quantitative responses regarding the medical reviewers were not statistically different by company type or by interviewee position according to t-test comparisons.

Interviewees expressed significant concern over the turnover rate of medical reviewers at the agency. While most companies acknowledged that turnover was inevitable during the long drug development process, their perception was that turnover rates were too high. More importantly, upon turnover of a medical reviewer, companies were often required to revisit many previous decisions that had been agreed upon with the agency. Respondents indicated that they believe this caused unnecessary delays. For example, interviewees from one company indicated that they experienced six months of back and forth communications to re-justify previous decisions and agreements made with the previous medical reviewer that had retired from the agency. Several respondents suggested that a formal handoff procedure and reorientation process would be appropriate in which major issues are resolved in a more expeditious manner. Companies acknowledged that turnover within their company also delayed drug development in some cases.

Unfortunately, no quantitative questions were asked directly on the consistency of the various therapeutic divisions within the FDA; however, in almost every interview, respondents indicated that there was a high degree of variability in competency, communication, and implementation of rules and regulations across divisions.

Several divisions were described to have "best" practices that accelerated drug development. These practices included the following: 1) rapid turnaround of agreement on meeting minutes (in some cases before the end of the meeting); 2) invitation to the sponsor to give a half day presentation to the therapeutic division on a novel drug and the science; 3) open communication policy and twenty-four hour acknowledgement of phone call.

Figure 5-5: Rating - Direct Leadership of Medical Reviewers



n = 32
mean = 3.45
median = 3.5
mode = 4
stdev = 0.65

1 = Bad
2 = Poor
3 = Fair
4 = Good
5 = Excellent

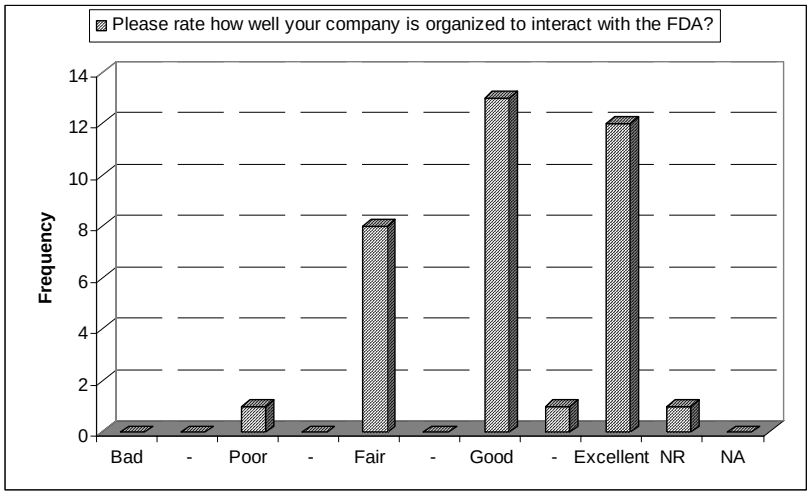
Unfortunately, several divisions were accused of having "worst" practices which included very poor communication (only willing to discuss issues via letters and not the phone), extended time delay in resolving issues relative to FDA commitments, ambiguous advice and unwillingness to commit to protocols, obsession with minor statistical issues that are not therapeutic related (e.g. a patient's bowel surgery while on an anti-depressant), and poor project management that resulted in multiple changes in agreed upon decisions between the sponsor and the FDA.

In many cases, the biotech companies in particular expressed concern over the merger of CBER and CDER. Interviewees indicated that they believed CBER had many best practices (quick response to sponsor inquiries, accessibility of reviewers and leadership, proactive interest in science), which they fear might not continue under the auspices of CDER.

Section 5.05 Measures of Industry's Interactions with the FDA

The pharmaceutical and biotech companies engaged in drug development report that they believe they are generally well organized to interact with the FDA (See Figure 5-6). An elaborate regulatory group is setup within a company and it acts as the link between the rest of the company and the FDA. This structure usually works very well according to the majority of interviewees. However, several interviewees indicated that pressures from general management and marketing often forced the regulatory group into confrontational situations with the FDA.

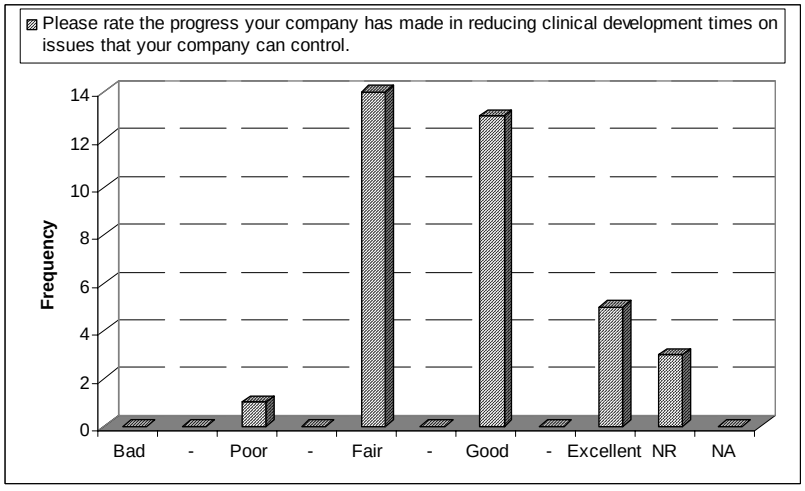
Figure 5-6: Rating – Company Organized to Interact with FDA



n = 35
mean = 4.07
median = 4
mode = 4
stdev = 0.84

1 = Bad
2 = Poor
3 = Fair
4 = Good
5 = Excellent

Figure 5-7: Rating - Company Progress in Reducing Dev. Times



n = 33
mean = 3.67
median = 4
mode = 3
stdev = 0.78

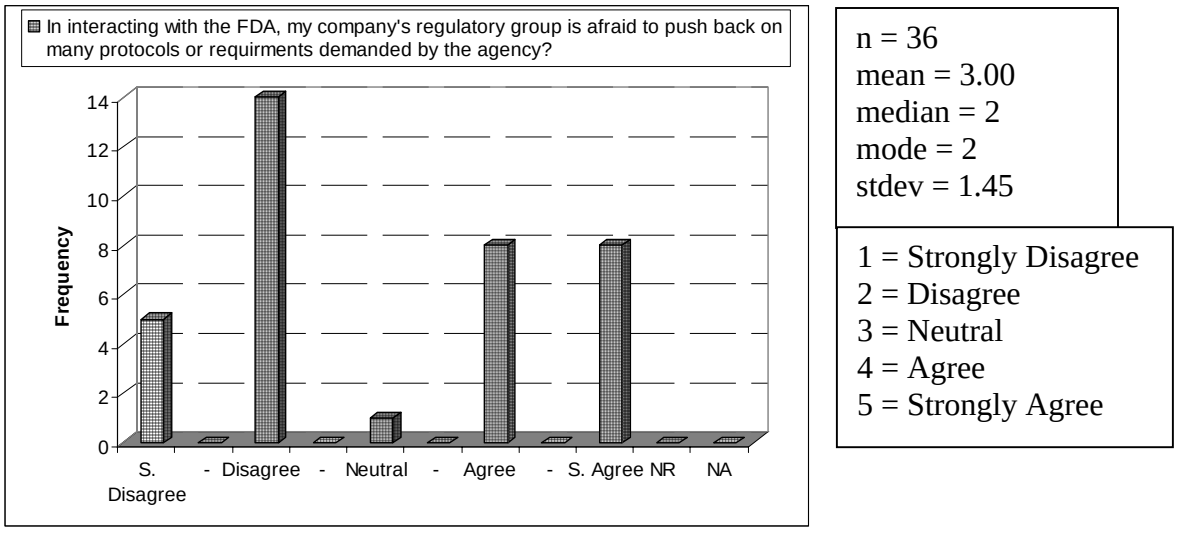
1 = Bad
2 = Poor
3 = Fair
4 = Good
5 = Excellent

When asked how much progress their company had made in reducing drug development times on issues that their company could control, interviewees indicated their company had done a

"Fair" to "Average" job (See Figure 5-7). Many individuals acknowledged that mergers or acquisitions had made reducing development times more difficult, in part because of inconsistent regulatory practices among the new partners.

Interviewees were asked a series of questions regarding their company's interaction with the FDA. The questions probed whether the company was afraid to disagree with the agency on protocols and whether the company would run additional trials that were not required by the agency. Interestingly, the responses from interviewees in regards to the regulatory group being afraid to pushback were distributed in a bimodal fashion (See Figure 5-8). Sixteen individuals at a minimum "Agreed" that their company was afraid to pushback and sixteen at a minimum "Disagreed." According to the t-test comparison by company type, the biotechs and pharmaceutical company responses were trending towards being significantly different (p-value = 0.095). Pharmaceutical company interviewees were more likely to agree that their regulatory groups were hesitant to confront the agency whereas biotech companies indicated they were more willing to confront the agency regarding clinical protocol requirements.

Figure 5-8: Rating- Regulatory Group Afraid to Pushback

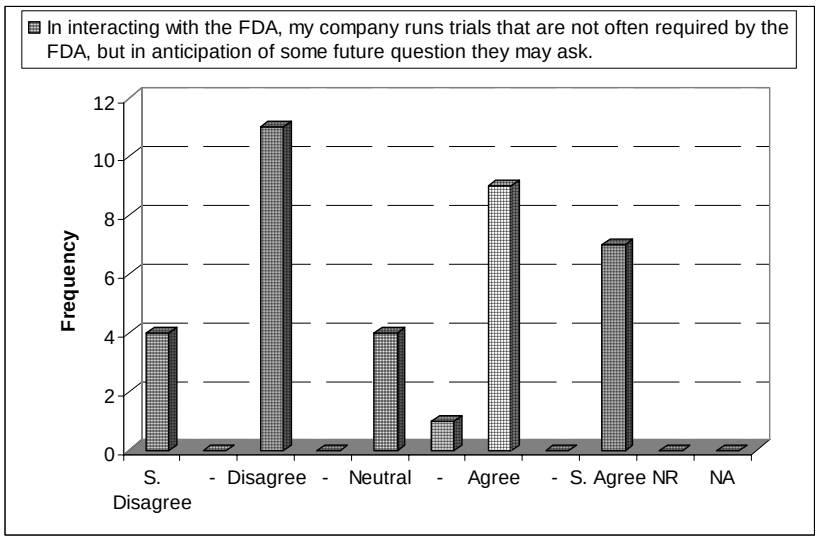


A similar bimodal distribution existed in regards to the company running additional clinical trials that were not required but in anticipation of questions the FDA might ask (See Figure 5-9). T-test comparison according to company type indicated statistical significance (p-value = 0.006) See Figure 5-10. Biotech companies often responded that they did not run additional trials whereas the pharmaceutical companies indicated that they did. Qualitative responses indicated that this might be dependent on the division with which the sponsor was interacting. Respondents who indicated that their company ran additional trials indicated that the high level of ambiguity or lack of understanding between their company and the FDA was one potential cause.

Furthermore, interviewees indicated that their companies did run additional trials in many cases for marketing and labeling purposes, but that these trials were almost always discussed with the FDA. In a strict sense, a few interviewees agreed that these trials were not necessary for the approval of the drug based on what the FDA required. However, some companies indicated that

they would run additional Phase II trials to ensure that they had identified the proper dose effective range in an effort to reduce the risk associated with Phase III trials.

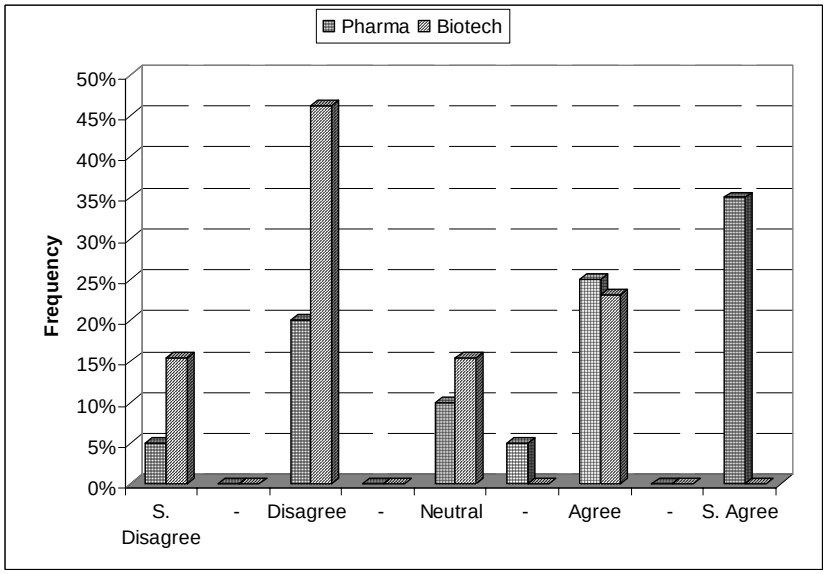
Figure 5-9: Rating – Company Runs Additional Trials in Anticipation of Questions



n = 36
mean = 3.13
median = 3
mode = 2
stdev = 1.35

1 = Strongly Disagree
2 = Disagree
3 = Neutral
4 = Agree
5 = Strongly Agree

Figure 5-10: Comparison by Company Type of Response to "Additional Clinical Trials" Question



1 = Strongly Disagree
2 = Disagree
3 = Neutral
4 = Agree
5 = Strongly Agree

Many executives stated that failure to run appropriate Phase II trials to detect the appropriate dose ranges was instrumental in causing failures in Phase III. Executives admitted that they had witnessed development programs within their company speed through Phase II to get to Phase III. Interviewees stated that demands and pressures from the investment community contribute to this rush to get to the "next" phase.

Section 5.06 Communication and Interaction in Phase II, III, and the NDA

As one global head of development at a company stated, "Communication leads to increased collaboration, and increased collaboration leads to successful drug development." As a regulatory agency, the FDA is not involved directly in drug development; however, its guidance and mandates can have significant effects on how companies engage in development. Thus, information transparency and reduced information asymmetry are critical in improving the efficiency of development.

To evaluate the hypothesis that "industry believes that communication with the FDA is inadequate during late stage clinical studies," interviewees were asked directly to rate the following set of questions:

- The quality of current communication with the FDA across phases of development
- How valuable additional informal communication would be by phase
- Their willingness to pay additional user fees to increase interactions
- How much they would be willing to pay for these interactions per drug per phase

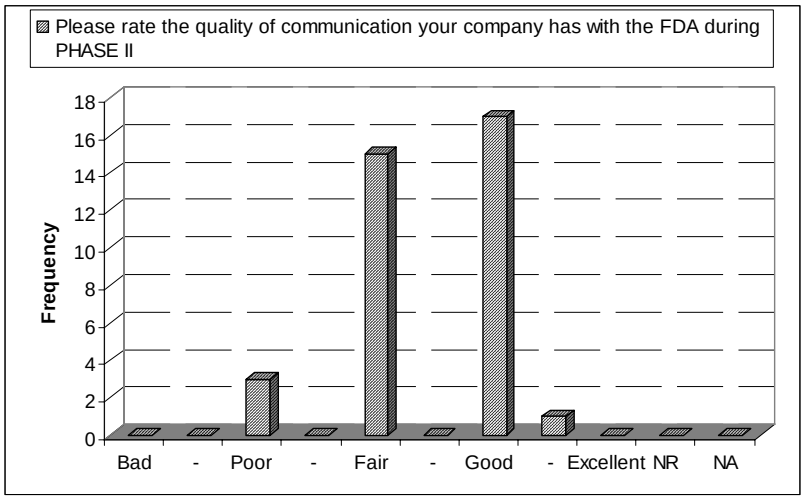
When asked to rate the quality of communication in Phase II, 50% of the interviewees (n =36) gave a "Good" or higher rating (See Figure 5-11). Forty-two percent indicated that communication was "Fair." The consistent theme in rating communication as "Fair" was the variability in communication, ranging from extremely poor to excellent, across therapeutic divisions.

Communication in Phase III rated even higher than Phase II, with 69% percent of respondents indicating "Good" or higher (See Figure 5-12). Sixty-six percent of respondents (n = 35) rated communication during the NDA phase as "Good" or higher (See Figure 5-13). When asked how valuable the meeting was with the FDA between the end of Phase II and beginning of Phase III, 98% rated it "Valuable" or higher. Seventy-four percent rated this meeting as "Very Valuable" (See Figure 5-14).

Interviewees were asked how valuable additional informal communication would be in the various phases. The responses for Phase II (n=35, mean = 4.50, median = 5, mode = 5, stdev = 0.53), Phase II (n=34, mean = 4.71, median = 5, mode = 5, stdev = 0.52), and NDA (n=35, mean = 4.74, median = 5, mode = 5, stdev = 0.51) were overwhelmingly in favor of additional informal communication with 97% of responses rated as "Valuable" or "Very Valuable" (See Figure D-2 in the appendices).

When asked their willingness to pay for additional interaction and assistance in Phase II and Phase III, responses were more variable. However, the mean and median scores for both phases indicate that industry would be willing to pay additional monies to the FDA. In some cases, respondents indicated that they were unwilling to pay additional monies due to concerns about how PDUFA monies were currently being used. Furthermore, respondents indicated that there would need to be mechanisms to gauge incremental quality of personnel, assistance, and the types of issues that would be useful to review.

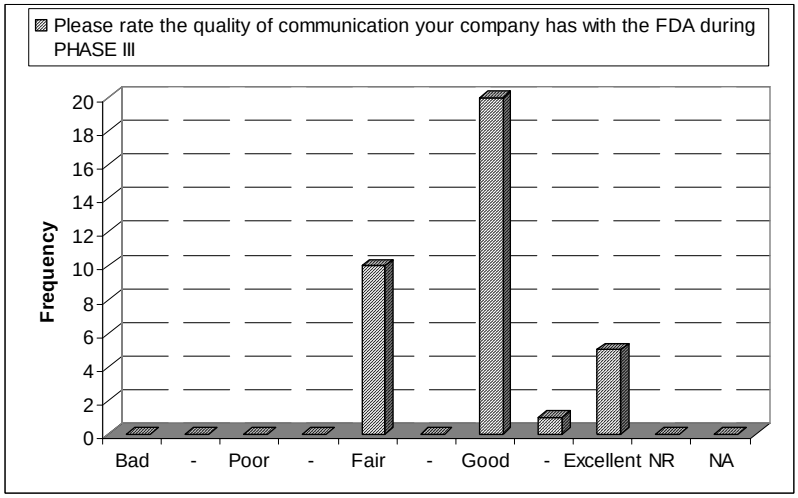
Figure 5-11: Rating - Quality of Communication - Phase II



n = 36
mean = 3.43
median = 3.5
mode = 4
stdev = 0.67

1 = Bad
2 = Poor
3 = Fair
4 = Good
5 = Excellent

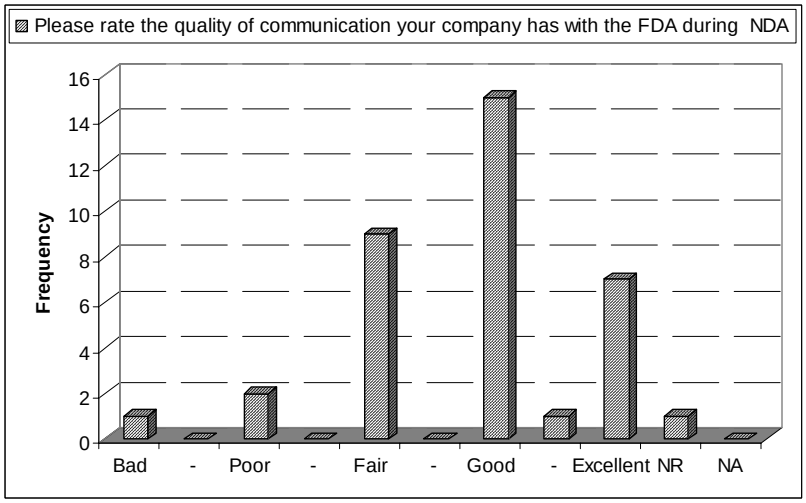
Figure 5-12: Rating - Quality of Communication - Phase III



n = 36
mean = 3.88
median = 4
mode = 4
stdev = 0.65

1 = Bad
2 = Poor
3 = Fair
4 = Good
5 = Excellent

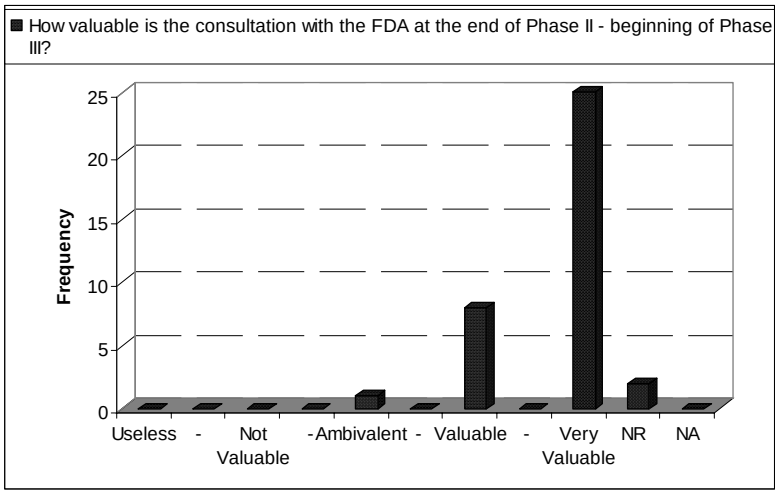
Figure 5-13: Rating - Quality of Communication – NDA



n = 35
mean = 3.76
median = 4
mode = 4
stdev = 0.96

1 = Bad
2 = Poor
3 = Fair
4 = Good
5 = Excellent

Figure 5-14: Rating - Value of End of Phase II Meeting

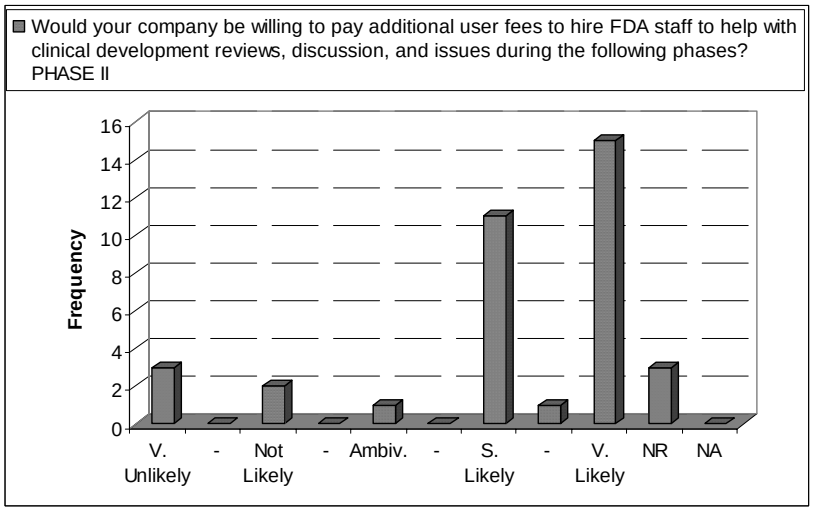


n = 34
mean = 4.71
median = 5
mode = 5
stdev = 0.52

1 = Useless
2 = Not Valuable
3 = Ambivalent
4 = Valuable
5 = Very Valuable

In analyzing the amount interviewees were willing to pay, responses of "Other" with amounts that did not lie in the ranges that were available ($100K to $500K, $500K to $1MM, $1MM to $5MM, and > $5MM) were designated as a no response (NR). Responses of $0 were similarly designated as NR as interviewees indicated they were not willing to pay additional fees but gave a response to the subsequent amount question. Logically, if the interviewee is unwilling to pay additional monies, the quantification of amount is irrelevant.

Figure 5-15: Rating - Willingness to Pay for Assistance and Interaction in Phase II

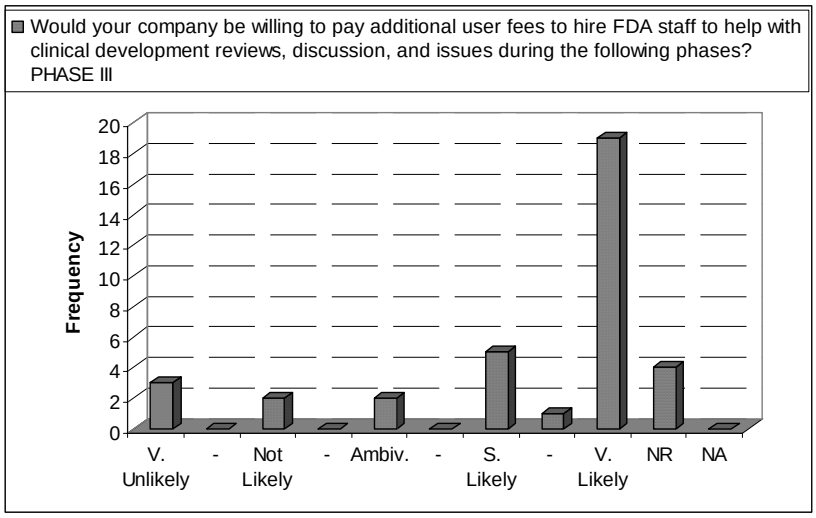


n = 33
mean = 4.05
median = 4
mode = 5
stdev = 1.26

1 = Very Unlikely
2 = Not Likely
3 = Ambivalent
4 = Somewhat Likely
5 = Very Likely

Of the respondents (n = 17) who indicated that they were willing to pay additional monies, 41% indicated they were willing to pay between $100K to $500K on a per drug basis for Phase II. An additional 47% indicated they were willing to pay between $500K to $1MM. For Phase III (n = 16), 31% were willing to pay between $100K to $500K; another 31% were willing to pay $500K to $1MM. In a few cases, respondents indicated their company would be willing to pay in excess of one million dollars per drug for increased Phase II or Phase III interaction with the FDA. Figure 5-17 below gives a comparison of the amounts by phase.

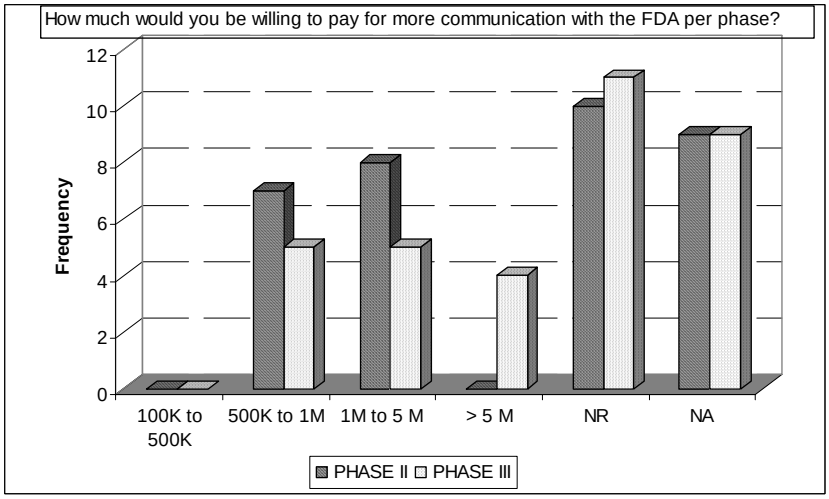
Figure 5-16: Rating - Willingness to Pay for Assistance and Interaction in Phase III



n = 32
mean = 4.14
median = 5
mode = 5
stdev = 1.34

1 = Very Unlikely
2 = Not Likely
3 = Ambivalent
4 = Somewhat Likely
5 = Very Likely

Figure 5-17: Rating – Additional Monies for FDA Interaction – Phase II and Phase III



Interviewees during qualitative discussion placed a premium on appropriate informal and formal communication with the FDA. While interviewees believed that the quality of communication in Phase II and beyond was generally good, they believed additional communication and interaction was critical to reducing drug development times. Consistent with the theme of variability, interviewees indicated that interactions and communication were highly variable from division to division. One company provided an example where development was delayed by half a year. In this particular case, the company was trying to move from Phase II to Phase III. Due to extremely poor communication from the division, what usually took three to four months with other divisions, took over nine months.

Although, interviewees gave high ratings to the current quality of communication with the FDA, the overwhelming response was for additional interaction and communication. Indeed, interviewees indicated that their companies were willing to pay substantial sums of money on a per drug basis for additional communication. Based on the quantitative survey analysis as

discussed above, the hypothesis, that "industry believes that communication with the FDA is inadequate during late stage clinical studies," is substantiated.

Section 5.07 FDA – "Custodian of the Knowledge Base"

The FDA reviews all prescription drug applications in the United States. While this is a completely obvious statement, the implications are significant. De facto, the FDA has knowledge on all classes of compounds and the success or failures of these compounds. This issue was not addressed in the quantitative questionnaire; however, over five interviewees raised this issue during qualitative discussion. An interviewee appropriately termed the FDA the "Custodian of the Knowledge Base."

It is unclear how the vast knowledge accumulated at the FDA has been stored or managed. Given the recent developments in electronic submission of documents, it is likely that much information is paper based or resident with individuals at the FDA.

Respondents indicated that sharing proprietary and confidential information would be rather complicated; however, interviewees indicated a willingness to give the FDA permission to divulge information on drug failures from within their company in exchange for access to information from other companies.

Several interviewees indicated that the FDA often requests certain trials or data points without much explanation. In fact, the FDA issues these seemingly obscure requests based on the agency's experience with similar drugs from other sponsors; however, the agency is unable to discuss specifics or details due to confidentiality requirements and protections afforded to the sponsor companies. In many cases, interviewees indicated that their company pushed back on the FDA's demands due to the lack of explanation. Greater information transparency and reduced information asymmetry in the form of an accessible "knowledge database" would potentially expedite these types of issues and increase the odds of success (or help stop likely failures). Anecdotally, one interviewee pointed out that Phase I clinical trials on a structurally similar drug to that of a previously failed drug that caused toxicities was not in the interest of the public health, and indeed could be viewed as likely inflicting harm on patients.

Reconciling the need for greater information on therapeutics with which the FDA has experience and the need to protect proprietary and competitive information will be challenging. But, companies appear to be willing to discuss the issue. In a recent white paper, the FDA recognizes that this is a significant opportunity to make drug development more efficient.[33] To a more limited extent, CROs also have a pooled knowledge database.

Section 5.08 Surrogate Markers

Surrogate markers, often referred to as biomarkers, are often casually mentioned as being the panacea for drug development. "If only we had a biomarker for X or a biomarker for Y" according to some faculty at Harvard Medical School, drug development would be much easier.

[33] United States Food and Drug Administration. "Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products." US Food and Drug Administration, 2004.

Industry interviewees demonstrated similar enthusiasm for the concept although with much more guarded optimism.

And rightly so, given the complexity of validating that a surrogate marker is indeed highly correlated with clinical benefit. As described by Frank and Hargreaves, surrogate markers fail for five main reasons: 1) treatment effects are reflected in the biomarker but disease pathophysiology is unaffected; 2) biomarker reflects a change in pathophysiology but it is clinically irrelevant; 3) the biomarker reflects clinically relevant changes but does not reflect the treatment mechanism; 4) the biomarker reflects a clinically relevant change but other more relevant changes (toxicity) are not reflected in the marker; and 5) the biomarker may not reflect the "classical" clinical assessment due to patient population, novel mechanism, or novel indication.[34] Interviewees voiced many of the issues stated above. Furthermore, participants indicated that without appropriate guidance from the FDA, use of surrogate markers for primary efficacy endpoints was just too risky.

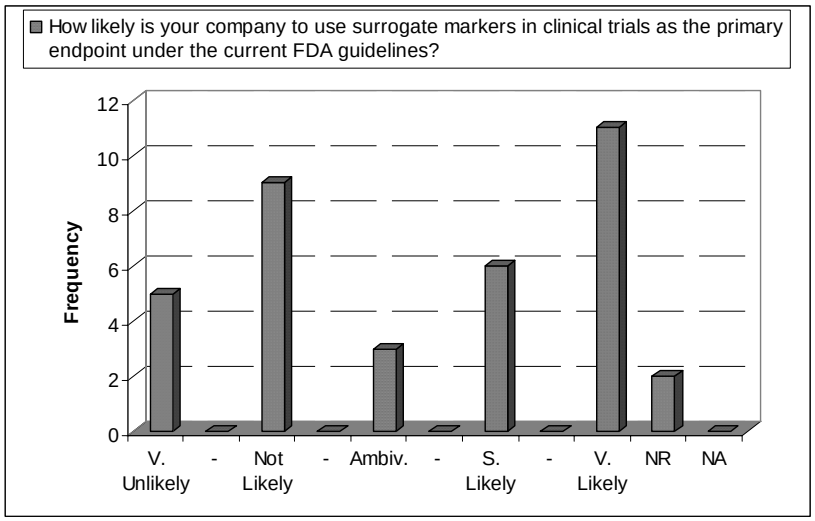
Given the difficulty in validating surrogate markers, the premise of appropriate economic motivation in the form of patent incentives was investigated quantitatively and qualitatively along with the willingness of companies to use surrogate markers as the primary endpoint in clinical trials. Quantitatively, interviewees had a bimodal response to whether their company would be willing to use surrogate markers under current FDA guidelines (See Figure 5-18) with 50% indicating they were "Somewhat Likely" or higher to use them versus 50% that were "Ambivalent" or lower. In the cases where interviewees indicated they were very likely to use the surrogate marker, the interviewee stated that they were trying to validate the marker simultaneously with ongoing clinical trials or were following an approved FDA marker (e.g. CD4+ T-cell level for AIDS).

When asked if their company would be motivated to use surrogate markers if patent opportunities were available on the marker, 62% indicated their company would be "Somewhat Likely" or higher (n =32, mean = 3.98, median = 5, mode = 5, stdev = 1.43). Interestingly, responses were statistically different (p-value = 0.045) based on position within the company. As shown in Figure 5-19 below, executive vice presidents and more senior management believed their company would be less likely to use surrogate markers with patent incentives on the marker as compared to vice presidents and lower management.

During qualitative discussion of surrogate markers, the more senior management indicated that patent incentives would be of significant interest, but not specifically on the marker. Several interviewees stated that it would not be in the interest of the public health or the interest of the company to patent surrogate markers which would be used as tools in research; however, these respondents indicated that extension of patent life on a drug developed using a surrogate marker would be of significant interest. In exchange for the additional patent life, the biomarker would be placed in the public domain and available for use by other drug developers.

[34] Frank, R., Hargreaves, R. "Clinical Biomarkers in Drug Discovery and Development." Nature Reviews Drug Discovery. 2003:2;566-580.

Figure 5-18: Rating - Use of Surrogate Markers as Primary Endpoint

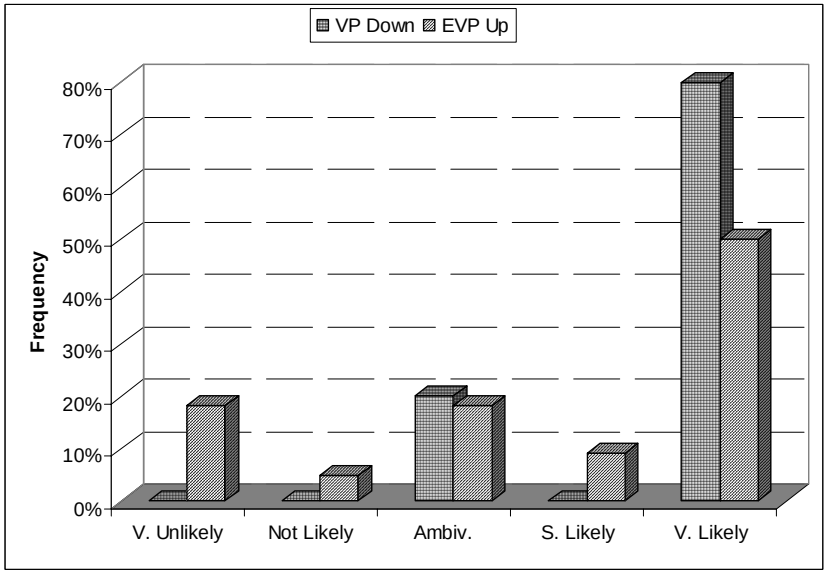


n = 34
mean = 3.26
median = 3.5
mode = 5
stdev = 1.52

1 = Very Unlikely
2 = Not Likely
3 = Ambivalent
4 = Somewhat Likely
5 = Very Likely

Despite the positive quantitative responses, interviewees, during qualitative discussion of surrogate markers, indicated great hesitancy to rely on surrogate markers under current FDA regulations. Many interviewees indicated that biomarkers were used extensively within the company to evaluate safety concerns or to assist in Go/No-Go decisions, but accepted clinical endpoints still trumped biomarkers in most development programs.

Figure 5-19: Rating - Patent Incentives for Surrogate Markers



1 = Very Unlikely
2 = Not Likely
3 = Ambivalent
4 = Somewhat Likely
5 = Very Likely

Section 5.09 FDA Advisory Board Panel

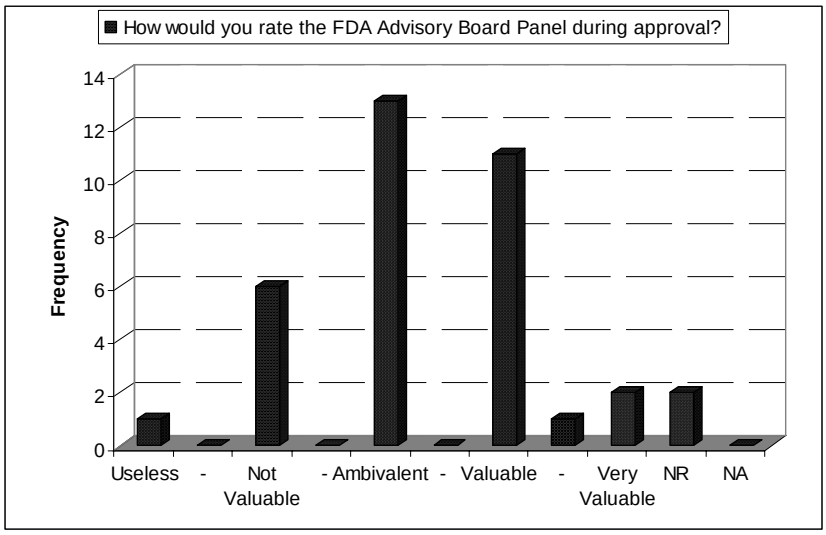
While the FDA advisory board panels are not involved in the clinical development component of drug development, they play a key role in the drug approval process. Interviewees indicated that on average, they were "Ambivalent" about the value of the advisory board panel and process (See Figure 5-20). Individuals who were proponents of the panel indicated that it was a critical

point in the NDA process that allowed the public and outside physicians to evaluate the drug, as well as witness the FDA at work.

Detractors were critical of the advisory board process in no uncertain terms. Several interviewees likened the process to such colorful descriptors as "circus" and "dog and pony show." However, behind the colorful rhetoric, interviewees indicated great concern over the confrontational nature of the hearings. According to several companies that have had very successful approval hearings – and yet are sharply critical - the process is setup with the company on one side, the FDA on the opposing side, and the advisory board as the adjudicator. In some cases, interviewees indicated that FDA personnel were in complete agreement in favor of approval of the drug prior to the hearing and yet had to provide an opposing view during the proceedings.

Interviewees indicated that substantial amounts of money and time are spent preparing for the "show." While respondents agreed that the public must have an opportunity to learn about the drug per Federal regulations, the current process does not do proper service to the sponsor company or to the FDA. According to several interviewees who were high-level FDA personnel prior to joining industry, panel experts are often wholly unprepared for the review and "read the material on the plan ride to the FDA." Given that the review process takes many FDA personnel several months, it seems improbable that a panelist could gain sufficient understanding to make a truly educated decision in just a few hours.

Figure 5-20: Rating - FDA Advisory Board Panel



n = 34
mean = 3.25
median = 3
mode = 3
stdev = 0.94

1 = Useless
2 = Not Valuable
3 = Ambivalent
4 = Valuable
5 = Very Valuable

Interviewees voiced concern over the panel volunteers and indicated that the conflict of interest rules are excessively stringent, preventing more qualified experts to review the drugs. In one anecdotal case, a panel expert, a pediatrician by training, was extremely concerned with pediatric issues, even though the drug was not intended for any pediatric use.

From the perspective of several respondents, the FDA, after reviewing all the safety and efficacy data, is well qualified to make the decision whether to approve the NDA. Given the controversial value of the advisory board panel, dialogue and discussion among the FDA,

industry, and academia should be pursued to develop a better forum for discussing the virtues and faults of new therapeutics. For example, an NIH sponsored discussion with leading experts, even with company affiliations, could be convened to discuss the scientific merits of a variety of therapeutic agents. Given the controversy that sometimes surround advisory panel meetings, the proposed NIH sponsored discussions would at a minimum convene a superset of experts

Section 5.10 FDA Commissioner Vacancy

In the PDUFA analysis in this research, it was not possible to draw any robust statistically significant conclusions from the FDA commissioner vacancy analysis. On many occasions, the issue of an officially appointed FDA commissioner was discussed with interviewees. The general perception from the interviewees was that for the broad range of drugs under review, the absence or presence of the FDA commissioner is immaterial. However, for the few drugs that carry greater political and public baggage, the lack of a commissioner can make progress very challenging given the perceived unwillingness of FDA staff to make politically risky decisions. From an economic perspective, this can be viewed as the FDA commissioner having an effect on NDA review times on the marginal few drugs with major political or social repercussions.

Section 5.11 A Few More Words on PDFUA

The majority of companies agreed that PDUFA has been very successful in reducing NDA review times. However, multiple respondents indicated concern over increasing approval times in the latter part of 2002 and 2003. Over 50% of the interviewees gave examples of the FDA meeting the PDUFA action date with a complete response letter that had a list of questions. In some cases the questions were only a few pages but in many cases they were quite extensive, in one case exceeding twenty pages. Several interviewees suggested that PDUFA has created perverse incentives for certain FDA divisions not to communicate with sponsors for fear of missing the PDUFA date.

While it is completely appropriate for the agency to request more information, companies believed that a vast majority of questions could have been answered in a short time frame during the NDA review process if the agency was able to review the file earlier during the review period. Companies are under the impression that FDA reviewers are overburdened with additional material to review such as supplemental NDAs and clinical trial protocols for drugs under development. As a result, FDA staff does not review NDA packages until shortly before PDUFA action dates. This may or may not be the case, but it is important to recognize that very few drugs are actually approved on a PDUFA action date. As a point of fact, twenty-one NME's were approved in 2003, and according to interviewees none were approved on the PDUFA date.[35]

[35] US Food and Drug Administration. NMEs Approved in Calendar Year 2003. *US Food and Drug Administration*. [online] (cited 30 Apr 204) <http://www.fda.gov/cder/rdmt/NMECY2003.HTM> (2004).

Chapter 6: Discussion and Conclusions

Section 6.01 Summary of Conclusions and Recommendations

The following conclusions can be drawn from the research study:

- R&D and regulatory industry personnel have an overall good opinion of the FDA's ability to regulate drug development.
- Industry believes they are well organized to interact with the FDA but acknowledge that mergers and acquisitions within the industry have resulted in poorer interactions and communication with the FDA, at least in the short run.
- Industry acknowledges that they sometimes run additional clinical trials that are not required for approval; however, these trials are used for internal decisions or for key label requirements that will hopefully allow the company to recoup its investment in the drug.
- Surrogate markers are used extensively for internal decisions within companies but are not used extensively as primary endpoints in clinical trials due to the complexities of validating the markers.
- Industry believes that the FDA advisory panel hearings are of variable value in the approval process.
- Sponsor companies highly value current communication with the FDA but would like additional interactions during all phases of development and are willing to pay substantial amounts to facilitate these interactions.
- PDUFA legislation reduced drug approval times and had a net positive financial impact relative to the direct PDUFA costs paid by companies.
- Inconsistent communication and interactions between FDA therapeutic divisions and sponsors introduce additional volatility into the drug development process.
- Industry believes that the quality, responsiveness, training, and direct leadership of the FDA medical reviewers are highly variable. This leads to inconsistent application of FDA regulations and varied interpretation of scientific data.
- Industry believes that high turnover among FDA medical reviewers and senior officials delay development times due to inefficient communication and understanding of previously accepted decisions.
- The FDA, as the custodian of all drug information, has the ability to inform sponsors of potential safety issues or pitfalls with new drugs; however, due to legal obligations to sponsors, the FDA cannot disclose proprietary information to other drug developers.

Based on the research, I would make the following recommendations, which are discussed in more detail below in Section 6.02 Improving Drug Development for the Future:

- The FDA should strive to decrease the variability of communication practices among its therapeutic divisions by investigating best practices and developing appropriate standards that can be measured and tracked. This will increase information transparency and reduce information asymmetry with industry, leading to more efficient drug development.
- The FDA should establish an automatic dispute escalation and review for key substantive decisions made during formal FDA-Industry meetings that significantly impact the FDA or industry.

- The FDA should establish an official audit and review process that retrospectively analyzes best and worst practices in NDA approval and clinical development each year. The audit should be made publicly available with protections for proprietary information if necessary.
- Industry and the FDA should develop a candid, mutual feedback mechanism to evaluate each other during key milestones of drug development.
- The FDA, as the custodian of the drug knowledge database, should work with industry to provide important safety and efficacy information accrued from previous therapeutic studies. Industry must be willing to help FDA change the confidentiality rules to ensure that the greater public good and safety is served.
- The FDA should establish an "FDA University" where industry and FDA employees can develop greater expertise in the regulatory and review process. A greater understanding of each other's respective challenges will foster communication and collaboration.

Section 6.02 Improving Drug Development for the Future

The FDA is greatly respected for its role in protecting the public health and ensuring the safety and efficacy of therapeutic products. While the industry does not agree with some aspects of how the agency functions, companies, on average, do believe that the agency does a good job given the resources at its disposal. A comment by one interviewee, echoed by many of the respondents, is that "the onus of drug discovery and development falls primarily on industry. The FDA should facilitate, not hinder, the development of good therapeutics and protect the public from unsafe and ineffective drugs." Another interview commented, "There are significant costs to the U.S. public health in the lack of coordination between the FDA and industry. Protecting the U.S. health is achieved when bad drugs are kept off the market, but what about good drugs that are delayed unnecessarily?"

As demonstrated in the PDUFA analysis in this thesis, creation of metrics with accountability to sponsors has significantly accelerated drug approval from averages exceeding thirty months in the 1980's to roughly over one and a half years during PDUFA I and II. The benefit to companies in terms of increase in profitability and innovative returns has been significant. The PDUFA fees, while not insignificant amounts of money, have yielded definite returns for companies. While concerns do exist regarding the current use of PDUFA fees and what appears to be slightly increasing approval times[36], the legislation has been very successful. Finally, PDUFA has increased the transparency and predictability of the NDA review process.

The consistent theme stated by respondents throughout the quantitative and qualitative interviews was the high degree of variability in communication, interaction, and organization within the FDA. The clinical development process can benefit from the precedence of PDUFA and the implementation of performance measurements that focused the agency on efficiency. The primary hypothesis in this thesis attempted to assess the premise that communication and interaction between the FDA and industry is inadequate. This hypothesis is supported as assessed through the quantitative questionnaire. While companies consider the current level of

[36] US Food and Drug Administration. Approval Times for Priority and Standard NDAs Calendar Years 1993-2003. *US Food and Drug Administration*. [online] (cited 30 Apr 2004) <http://www.fda.gov/cder/rdmt/NDAapps93-03.htm> (2004).

communication to be on average "Good," interviewees strongly indicated the desire for additional informal communication and were willing to pay substantial amounts of money for additional interactions with the FDA across all phases of development.

Interviewees consistently stated that increased communication and interaction would substantially increase information transparency and reduce information asymmetry between the FDA and industry. In turn, this would lead to an overall reduction in risk and increase in predictability. However, these actions must be coupled with standard performance metrics and best practices across the therapeutic divisions in order to be effective. Industry "wants as many interactions as possible" with the FDA to develop mutually respectful and collegial relationships.

But, there will be a "constant balance between a company wanting to know what is going on and the agency's need to safeguard its decision making process." The agency has been burned as in the case of ImClone where company management sold shares on insider information that the FDA was going to reject the company's NDA. The pressure from the investment community is substantial. The FDA is rightly concerned with how much information to divulge to companies during the development and NDA process given the past negative experiences.

In many cases, communication between the FDA and industry is imperfect. When industry does not agree with a specific medical reviewer or staff member, industry attempts to resolve the issue through informal communication with the reviewer or their superior. In some cases, critical issues, such as protocol agreements, are more difficult to resolve. While the agency encourages the use of the Ombudsman's office, no company or interviewee in the sample surveyed in this research has ever used the office. Industry indicated that using the Ombudsman was not a viable method for dispute resolution. Their reasoning was that regardless of the outcome via the Ombudsman, the reviewer would feel threatened. This would damage the ongoing relationship for the current review, not to mention future reviews by the same individual or division. A possible way to handle the more difficult disputes would be a mandatory review of controversial decisions or disputes via automatic escalation to an appropriately staffed review committee. This would potentially eliminate any hard feelings that would be harbored by the reviewer and would ease the fears of industry. However, this process would have to be carefully crafted to prevent unnecessary escalations that would exacerbate delays in development and increase burdens on FDA personnel.

Interviewees expressed concern as to whether "the FDA [is] prepared for the new paradigm in molecular medicine." Given the greater emphasis on molecular biology and the conservation of basic molecular mechanisms across therapeutic areas, interviewees believe that the FDA, with the current strict divisional separation, is ill-prepared to handle complex combination products (e.g. Drug Eluting Stents) and NDAs with applications in several diseases (e.g. immune therapies that treat rheumatoid arthritis, psoriasis, and Crohn's).

In order to keep pace with the rapid changes in science and medicine, the FDA needs a more rigorous training and development program. The industry consistently raised the issue of the variability of quality, training, and accountability among FDA medical reviewers. Interviewees acknowledged that there are some very good training classes within the FDA but not enough.

An interviewee gave the novel suggestion of creating an "FDA University" which would grant degrees and/or certifications across the broad spectrum of activities in which reviewers and staff are involved. A current best practice is the invitation of industry to present a lecture to the agency on the drug development process. Furthermore, industry participation will ensure that FDA staff is cognizant of the great time and cost involved in drug development. According to interviewees, many FDA staff are not well-informed regarding how much additional clinical trials and studies cost. Often reviewers will request studies without understanding the difficulties of recruiting patients and the associated financial costs. Inclusion of industry and academia in such a university would ensure a consistent level of training and education. Additionally, enhancement and extension of relationships with the National Institute of Health (NIH) and academic institutions across the country will ensure that FDA staff has access to the latest research and experts.

Industry has made significant use of information technology (IT) to assist in streamlining processes. From the respondents' perspective, the FDA has not exploited IT. For example, more and more companies are using electronic data capture during clinical trials. This provides real time monitoring. In theory, the FDA could be provided access to the records and could better monitor any safety concerns. PDUFA mandated specific response times from the agency and as a result the agency developed systems to monitor and track performance. Similar IT systems can be developed to measure other aspects of communication and interaction with industry. FDA staff could be rewarded with appropriate incentives for improving performance, perhaps via performance bonuses provided in the form of graduated fees from industry. Implementation of additional IT systems also will enable the FDA to provide more accurate feedback and reporting to the industry, ensuring better and more frequent communication.

During discussions with industry employees, we discovered that there is no true audit and review of the FDA with the exception of Congress. Audit reviews, either independent or internal, that measure division performance and best practice implementation would provide the FDA with the means to evaluate itself. Additionally, retrospective sampling of some portion of successful and unsuccessful applications would allow the agency to provide feedback to the industry and to its staff on best and worst practices. In one case, a company initiated a meeting with FDA medical reviewers and team leads to receive feedback on their application process and NDA post approval. Formal feedback from the agency on what activities industry should start, stop, and continue would help industry improve. Likewise, feedback and involvement of industry on a regular basis would provide similar benefits to the agency.

The cornerstone of the FDA is the protection of the public health. The concern with Type I errors is understandable, but the public, FDA, and industry need to evaluate continually the appropriate level of risk that will be tolerated in our medical products. Certainly, the FDA can reduce pre-market requirements and allow products to market sooner. Academics and industry suggest earlier approval with the understanding that a drug will have restricted use for the first year or few years until appropriate safety data is accumulated in the market. For example, a drug could theoretically be approved for prescription by certain centers or physicians. Marketing of the product would be severely restricted. In the case where safety parameters are exceeded, the FDA can exercise its power and withdraw approval. It is important to bear in mind that

companies do not want product failures in the market place, for several reasons. First, they are potentially exposed to legal recourse from consumers. Second, their reputation within the market and among physicians will suffer. The trend of increasing safety requirements will likely increase as science reveals additional ways to measure toxicities and effects. However, designing very large studies to assess these issues in patient populations will become increasingly difficult as drug naïve patient segments dwindle. Development of pharmacogenomics and patient enrichment studies will be critical in accommodating the increasing safety demands.

"The FDA is like the IRS, you only hear from them when there are problems" and "No news is *very* bad news" are not the statements that one wants to hear from industry regarding the FDA. Rather the agency should strive for comments such as "the agency is a top-notch organization" with "lots of excellent talent and people." Indeed, industry as a whole has a high opinion of the FDA; however companies take issue with the interaction and communication breakdowns within the agency and between the agency and their company. Clearly, industry is willing to have more interaction with the FDA and will put their money where their mouth is. Improving the predictability of interactions with the FDA and ensuring appropriate mechanisms to track and measure performance, as evidenced by PDUFA, can help ensure that the agency moves smoothly into the 21st century of drug development. Simultaneously, industry must and does appear to recognize that the burden of discovery and drug development falls squarely on their shoulders. The FDA can facilitate development, provide and receive feedback, and implement systems to reduce information asymmetry and confusion, but ultimately the pharmaceutical and biotech companies must prove that they have safe and effective products.

Section 6.03 Study Enhancements and Limitations

In retrospect, the quantitative questionnaire could have been enhanced to delve deeper into some of the key issues that were investigated. More pointed questions would have been extremely valuable in elucidating distinctions when the interviewee did respond or gave a weighted average response. For example, interviewees often responded with the answer "fair" or "variable" to the questions regarding medical reviewers. Refinement of these questions to solicit feedback on a per division basis or with percentage estimates might have been more useful.

The sample of companies interviewed during this research was not chosen at random from a listing of biotech, pharmaceutical, and CRO companies. It was important for the purpose of the research to interview personnel at companies that had considerable experience with the FDA and drug development. A random sampling of companies engaged in drug development would not have ensured coverage of companies with significant development experience. While not proven, we believe that the sample is representative of the major stakeholders of drug development within industry.

Virtually all the interviewees were engaged in R&D or regulatory activities. General management and senior executives (e.g. chief executive officer, chief financial officer) were not interviewed. Their opinions on interactions with the FDA might be very different given the greater pressure they face from the investment community and shareholders.

It is my intent in conjunction with Professor Ernst Berndt of MIT Sloan and Dr. Matthew Strobeck to interview a number of division directors at the FDA using a similar quantitative instrument to the one used with industry respondents. A white paper document providing a comprehensive overview of all findings of this research is forthcoming during May or June of 2004.

REFERENCES

- Bernard, H. Russell. *Social Research Methods: Qualitative and Quantitative Approaches*. 3rd ed. California: Sage Publications Inc., 2000.

- Chapman, Ian. "Evolving with Contemporary Contract Research." Nature Reviews Drug Discovery. 2003: 2; 597.

- Dimasi, Joseph A. "The Value of Improving the Productivity of the Drug Development Process." Pharmacoeconomics. 2002; 20(S3): 1-10.

- Dimasi, Joseph A., Hansen, Ronald W., Grabowski, Henry G. "The Price of Innovation: New Estimates of Drug Development Costs." Journal of Health Economics, 2003: 22; 51-185.

- "Food, Drugs, and Economics." Economist, Aug. 21, 2003.

- Frank, R., Hargreaves, R. "Clinical Biomarkers in Drug Discovery and Development." Nature Reviews Drug Discovery. 2003:2;566-580.

- Gilbert, Jim, et al. "Rebuilding Big Pharma's Business Model." In Vivo, 2003; 21(10).

- Grabowski, H Vernon, et al. "Returns on research and development for 1990s new drug introductions: The cost and value of new medicines in an era of change". Pharmacoeconomics. 2002;20(Suppl 3):11-29.

- Kaitin, K., Cairns, C. "The New Drug Approvals of 1999, 2000, and 2001: Drug Development Trends a Decade after Passage of the Prescription User Fee Act of 1992." Drug Information Journal. 2003; 37(1): 357-371.

- Mathieu, M.P., ed. *PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2003/2004*. Massachusetts: PAREXEL International Corp., 2003.

- Miller, Henry I. "A Proposal for FDA Reform." Nature Reviews Drug Discovery. Aug. 2002: 1; 642-648.

- Olson, Mary K. "Pharmaceutical Regulation." *The New Palgrave Dictionary of Economics and the Law*. Ed. Peter Newman. New York: Stockton Press, 1998. 40-45.

- Peltzman, Sam. *Regulation of Pharmaceutical Innovation: The 1962 Amendments*. Washington, D.C.: American Enterprise Institute for Public Policy Research, 1974.

- Reichert, Janice M. "Trend in Development and Approval Times for New Therapeutics in the United States." Nature Reviews Drug Discovery. Sept. 2003; 2: 695-702.

- Singleton, Royce Jr., et al. *Approaches to Social Research*. New York, Oxford University Press, 1988.

- United States Food and Drug Administration. "Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products." US Food and Drug Administration, 2004.

- United States Food and Drug Administration. [online] <http://www.fda.gov> (2004).

APPENDICES

Appendix A: PDUFA Data and Information

Figure A-1: Data Fields Provided in NME List[37]

Field Name	Field Description	Coded Values
NME Name	Generic Name of the NME with any Withdrawal Information	
Des	Descriptive Characteristics of Drug	N = NDA; B = Biologic; V = Vaccine; D = Diagnostic; R = Radiopharmaceutical; O = Orphan drug; T = Therapeutic (nuclear related products)
Dev Co	Developing Company	
DC	Developing Country	
USA App	FDA Approval Date	
TS	Therapeutic Significance Rating	A, B, C - Pre-PDUFA; P = Priority; S = Standard
1st MKT	Year of 1st World Marketing	
1st YR	County of 1st World Marketing	
USA Trade	US Trade Name at the time of approval	
IND Sub	IND Submission Date	
NDA Clock	NDA/BLA Clock Date	
IND #	IND Number	
App Mo	Elapsed Approval Time in Months	
IND Yrs	Years in the IND Phase (IND through NDA/BLA submission)	
Dev Yrs	Total development years (IND through NDA/BLA approval)	
NDA #	NDA/BLA Number	
Sponsor	Name of the Sponsoring Company	
USDev?	US/Foreign Developer Code	US = USA; F = Foreign; UN = unknown
Orp?	Orphan Drug Code	O = Orphan; N = Non-orphan
MK_DT	US Marketing Date (Year and Month)	

[37] Compliments of Ed Hass, Office of Policy and Planning, Food and Drug Administration

Figure A-2: Major Therapeutic Code

Description	Major Class Code
ANESTHESIA	604
ANTIBIOTICS/SYSTEMIC	401
ANTIBIOTICS/SYSTEMIC	701
ANTI-HYPERTENSIVES/RENAL	102
ANTI-INFECTIVES/SYSTEMIC	403
ANTI-INFECTIVES/SYSTEMIC	703
ANTI-INFLAMMATORY	503
BIOLOGIC	B
CARDIAC DRUGS	101
CARDIAC DRUGS	801
DENTAL	603
DERMATOLOGICS	402
DRUG ABUSE	203
FERTILITY/ANTIFERTILITY	301
GASTRO-INTESTINAL	803
IMMUNOSTIMULATORY AGENTS	702
METABOLIC/ENDOCRINE I	302
METABOLIC/ENDOCRINE II	303
METABOLIC/ENDOCRINE III	304
NEUROLOGY	201
NO THERAPEUTIC CLASS ENTERED	0
ONCOLOGY	501
OPHTHALMICS	404
PSYCHO-PHARMACOLOGY	202
RADIOPHARMACEUTICALS	502
RENAL	605
RESPIRATORY	601
SURGICAL	602
TROPICAL	405
VAGINAL AND RELATED PRODUCTS	406

Figure A-3: Super Major Therapeutic Code

Super Major Category (SMC) Code	Description
1	Cardiovascular
2	Anti-Infectives
3	Neoplastic
4	CNS
5	Other
6	AIDS
7	Reproduction
8	Biologic
9	[Reserved for future use]
10	None

Figure A-4: Cross-reference of Super Major Therapeutic Code to Major Therapeutic Code

Major Class Code	Description	SMC Code
0	NO THERAPEUTIC CLASS ENTERED	10
101	CARDIAC DRUGS	1
102	ANTI-HYPERTENSIVES/RENAL	1
201	NEUROLOGY	4
202	PSYCHO-PHARMACOLOGY	4
203	DRUG ABUSE	4
301	FERTILITY/ANTIFERTILITY	5
302	METABOLIC/ENDOCRINE I	5
303	METABOLIC/ENDOCRINE II	5
304	METABOLIC/ENDOCRINE III	5
401	ANTIBIOTICS/SYSTEMIC	2
402	DERMATOLOGICS	5
403	ANTI-INFECTIVES/SYSTEMIC	2
404	OPHTHALMICS	5
405	TROPICAL	2
406	VAGINAL AND RELATED PRODUCTS	5
501	ONCOLOGY	3
502	RADIOPHARMACEUTICALS	5
503	ANTI-INFLAMMATORY	5
601	RESPIRATORY	5
602	SURGICAL	5
603	DENTAL	5
604	ANESTHESIA	5
605	RENAL	5
701	ANTIBIOTICS/SYSTEMIC	2
702	IMMUNOSTIMULATORY AGENTS	2
703	ANTI-INFECTIVES/SYSTEMIC	2
801	CARDIAC DRUGS	1
803	GASTRO-INTESTINAL	5
A70	AIDS DRUGS	6
B	BIOLOGIC	8

Figure A-5: GDP Deflation Table[38]

Year	GDP (Chained) Price Index
1990	0.8125
1991	0.8430
1992	0.8642
1993	0.8838
1994	0.9028
1995	0.9218
1996	0.9395
1997	0.9559
1998	0.9675
1999	0.9802
2000	1.0000
2001	1.0234
2002	1.0415
2003	1.0585
2004	1.0724

Figure A-6: Published FDA PDUFA Fees for 1993 to 2004

Year	APPLICATIONS WITH CLINICAL DATA	APPLICATIONS WITH NO CLINICAL DATA	SUPPLEMENTS WITH CLINICAL DATA	ESTABLISHMENT FEE	PRODUCT FEE
1993	$100,000	$50,000	$50,000	$60,000	$6,000
1994	$162,000	$81,000	$81,000	$93,800	$9,400
1995	$208,000	$104,000	$104,000	$129,000	$12,200
1996	$204,000	$102,000	$102,000	$135,300	$12,600
1997	$205,000	$102,500	$102,500	$115,700	$13,200
1998	$256,846	$128,423	$128,423	$141,966	$18,591
1999	$272,282	$136,141	$136,141	$128,435	$18,364
2000	$285,740	$142,870	$142,870	$141,971	$19,959
2001	$309,647	$154,823	$154,823	$145,989	$21,892
2002	$313,320	$156,660	$156,660	$140,109	$21,630
2003	$533,400	$266,700	$266,700	$209,900	$32,400
2004	$573,500	$286,750	$286,750	$226,800	$36,080

[38] Reference GDP Deflator Tables

Figure A-7: GDP Deflated PDUFA Fees - Forecast to 2017

GDP Deflator	*Year*	APPLICATIONS WITH CLINICAL DATA	Growth Rate	APPLICATIONS WITH NO CLINICAL DATA	Growth Rate	SUPPLEMENTS WITH CLINICAL DATA	Growth Rate	ESTABLISHMENT FEE	Growth Rate	PRODUCT FEE	Growth Rate
0.864	1992	$97,782		$48,891		$48,891		$58,669		$5,867	
0.884	1993	$97,782		$48,891		$48,891		$58,669		$5,867	
0.903	1994	$155,074	59%	$77,537	59%	$77,537	59%	$89,789	53%	$8,998	53%
0.922	1995	$195,003	26%	$97,501	26%	$97,501	26%	$120,939	35%	$11,438	27%
0.940	1996	$187,650	-4%	$93,825	-4%	$93,825	-4%	$124,456	3%	$11,590	1%
0.956	1997	$185,334	-1%	$92,667	-1%	$92,667	-1%	$104,601	-16%	$11,934	3%
0.968	1998	$229,423	24%	$114,711	24%	$114,711	24%	$126,808	21%	$16,606	39%
0.980	1999	$240,059	5%	$120,030	5%	$120,030	5%	$113,236	-11%	$16,191	-3%
1.000	2000	$246,937	3%	$123,468	3%	$123,468	3%	$122,691	8%	$17,249	7%
1.023	2001	$261,478	6%	$130,739	6%	$130,739	6%	$123,279	0%	$18,486	7%
1.042	2002	$259,982	-1%	$129,991	-1%	$129,991	-1%	$116,258	-6%	$17,948	-3%
1.059	2003	$435,488	68%	$217,744	68%	$217,744	68%	$171,370	47%	$26,453	47%
1.072	2004	$462,158	6%	$231,079	6%	$231,079	6%	$182,768	7%	$29,075	10%
N/A	2005	$ 485,266	5%	$ 242,633	5%	$ 242,633	5%	$ 191,907	5%	$ 30,529	5%
N/A	2006	$ 509,530	5%	$ 254,765	5%	$ 254,765	5%	$ 201,502	5%	$ 32,056	5%
N/A	2007	$ 535,006	5%	$ 267,503	5%	$ 267,503	5%	$ 211,577	5%	$ 33,658	5%
N/A	2008	$ 909,510	70%	$ 454,755	70%	$ 454,755	70%	$ 359,681	70%	$ 57,219	70%
N/A	2009	$ 1,000,462	10%	$ 500,231	10%	$ 500,231	10%	$ 395,649	10%	$ 62,941	10%
N/A	2010	$ 1,050,485	5%	$ 525,242	5%	$ 525,242	5%	$ 415,431	5%	$ 66,088	5%
N/A	2011	$ 1,103,009	5%	$ 551,504	5%	$ 551,504	5%	$ 436,203	5%	$ 69,392	5%
N/A	2012	$ 1,158,159	5%	$ 579,080	5%	$ 579,080	5%	$ 458,013	5%	$ 72,862	5%
N/A	2013	$ 1,968,871	70%	$ 984,435	70%	$ 984,435	70%	$ 778,622	70%	$ 123,865	70%
N/A	2014	$ 2,165,758	10%	$ 1,082,879	10%	$ 1,082,879	10%	$ 856,485	10%	$ 136,252	10%
N/A	2015	$ 2,274,046	5%	$ 1,137,023	5%	$ 1,137,023	5%	$ 899,309	5%	$ 143,065	5%
N/A	2016	$ 2,387,748	5%	$ 1,193,874	5%	$ 1,193,874	5%	$ 944,274	5%	$ 150,218	5%
N/A	2017	$ 2,507,135	5%	$ 1,253,568	5%	$ 1,253,568	5%	$ 991,488	5%	$ 157,729	5%

Appendix B: Interview Questionnaires

Figure B-1: Official COUHES Approval

MASSACHUSETTS INSTITUTE of TECHNOLOGY
77 Massachusetts Avenue
Cambridge, MA 02139

Committee On The Use of Humans as Experimental Subjects

Building E32-335
(617) 253-6787

APPROVAL TO CONDUCT RESEARCH

DATE: 01/27/2004

TO: Ernst R. Berndt, Ph.D.
E52-452

FROM: Leigh Firn., M.D.
Chairman

COUHES NO.: 3172 (use this number in all correspondence with COUHES)

TITLE: Reducing Drug Development Time

OSP NO:

APPROVAL DATE: 01/27/2004

Your application to the Committee on the Use of Humans as Experimental Subjects has been approved. Please note the following:

1. This approval is for one year from the above approval date, when your study will be subject to continuing review. Failure to renew your study before the renewal date will result in termination of the study and suspension of related research grants.

2. Any serious or unexpected adverse event must be reported to COUHES within 48 hours. All other adverse events should be reported in writing within 10 working days

3. Any change to the protocol that impacts human subjects, including change in experimental design, equipment, personnel or funding, must be approved by COUHES before they can be initiated.

4. You must maintain a research file for at least 3 years after completion of the study. This file should include, all correspondence with COUHES, original signed consent forms, and study data.

5. Prospective new study personnel must, where applicable, complete training in human subjects research and in the HIPAA Privacy Rule before participating in the study.

cc: OSP

Figure B-2: Quantitative Questionnaire Page

1	2	3	4	5		
Bad	*Poor*	*Fair*	*Good*	*Excellent*	*N/R*	***Question***
☐	☐	☐	☐	☐	☐	What is your overall perception of the FDA in regards to regulating drug development and appropriately weighing the risk/benefits of new drugs?
☐	☐	☐	☐	☐	☐	How would you rate the FDA's effectiveness of keeping unsafe drugs from the market?
☐	☐	☐	☐	☐	☐	Please rate how well your company is organized to interact with the FDA?
☐	☐	☐	☐	☐	☐	Please rate the progress your company has made in reducing clinical development times on issues that your company can control.
☐	☐	☐	☐	☐	☐	How would you rate your company's experience with Contract Research Organizations?
						Please rate the quality of communication your company has with the FDA during the following phases
☐	☐	☐	☐	☐	☐	Pre-Clinical
☐	☐	☐	☐	☐	☐	Phase I
☐	☐	☐	☐	☐	☐	Phase II
☐	☐	☐	☐	☐	☐	Phase III
☐	☐	☐	☐	☐	☐	NDA
						Please rate the following in regards to the FDA reviewers.
☐	☐	☐	☐	☐	☐	The quality of FDA reviewers is:
☐	☐	☐	☐	☐	☐	Accountability of FDA reviewers is:
☐	☐	☐	☐	☐	☐	Training for FDA reviewers is:
☐	☐	☐	☐	☐	☐	Direct Leadership of FDA reviewers is:
☐	☐	☐	☐	☐	☐	The clinical protocols my company submits to the FDA are on average:
☐	☐	☐	☐	☐	☐	When responding to FDA inquiries or questions, your company responds effectively and efficiently.

1	2	3	4	5		
Very Unlikely	*Not Likely*	*Ambivalent*	*Somewhat L.*	*Very Likely*	*N/R*	***Question***
						Would your company be willing to pay additional user fees to hire FDA staff to help with clinical development reviews, discussion, and issues during the following phases?
☐	☐	☐	☐	☐	☐	Phase I
☐	☐	☐	☐	☐	☐	Phase II
☐	☐	☐	☐	☐	☐	Phase III
						How much would you be willing to pay for more communication with the FDA per phase?
100-500K	500k-1M	1M-5M	>5M	Other		Phase I
100-500K	500k-1M	1M-5M	>5M	Other		Phase II
100-500K	500k-1M	1M-5M	>5M	Other		Phase III
☐	☐	☐	☐	☐	☐	How likely is your company to use surrogate markers in clinical trials as the primary endpoint under the current FDA guidelines?
☐	☐	☐	☐	☐	☐	How likely is your company to use surrogate markers if patent opportunities and incentives were available on the surrogate marker?

1	2	3	4	5		
Useless	*Not Valuable*	*Ambivalent*	*Valuable*	*Very Valuable*	*N/R*	***Question***
☐	☐	☐	☐	☐	☐	How valuable is the consultation with the FDA at the end of Phase II - beginning of Phase III?
						Please rate how valuable additional informal communication would be with the FDA during the following phases.
☐	☐	☐	☐	☐	☐	Pre-Clinical/IND
☐	☐	☐	☐	☐	☐	Phase I
☐	☐	☐	☐	☐	☐	Phase II
☐	☐	☐	☐	☐	☐	Phase III
☐	☐	☐	☐	☐	☐	NDA
						How valuable has information gathering technology (e.g. proteomics, genomics, imaging - MRI, CT, etc.) been in helping reduce clinical development times in the following phases?
☐	☐	☐	☐	☐	☐	Pre-Clinical/IND
☐	☐	☐	☐	☐	☐	Phase I
☐	☐	☐	☐	☐	☐	Phase II
☐	☐	☐	☐	☐	☐	Phase III
☐	☐	☐	☐	☐	☐	NDA
☐	☐	☐	☐	☐	☐	How useful has electronic submission been to your company in the clinical development process?
☐	☐	☐	☐	☐	☐	How would you rate the FDA Advisory Board Panel during approval?

1	2	3	4	5		
Strongly Dis.	*Disagree*	*Neutral*	*Agree*	*Strongly Agree*	*N/R*	***Question***
☐	☐	☐	☐	☐	☐	In interacting with the FDA, my company's regulatory group is afraid to push back on many protocols or requirments demanded by the agency?
☐	☐	☐	☐	☐	☐	In interacting with the FDA, my company runs trials that are not often required by the FDA, but in anticipation of some future question they may ask.
☐	☐	☐	☐	☐	☐	In interacting with the FDA, my company runs additional tests in pre-clinical that are not required by the FDA.
☐	☐	☐	☐	☐	☐	Your company strongly takes into consideration FDA feedback on clinical protocols.
☐	☐	☐	☐	☐	☐	When your company ignores FDA advice on clinical protocols, drug development costs and times are increased.
☐	☐	☐	☐	☐	☐	The EMEA is more efficient than the FDA in approving drugs?
☐	☐	☐	☐	☐	☐	Biologics fail in Phase III more often that small molecules fail in phase III
☐	☐	☐	☐	☐	☐	The FDA has made significant efforts to reduce clinical development times
☐	☐	☐	☐	☐	☐	The FDA has made significant efforts to reduce approval times

Figure B-3: FDA Letter Endorsing Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

January 8, 2004

Dear Pharma and Biotechnology Company Representative:

The Food and Drug Administration, Office of the Commissioner, Office of Policy and Planning, has initiated a collaborative research effort with the MIT Sloan School of Management and the Harvard-MIT Division of Health Sciences and Technology. The goal of this project is to identify ways in which the FDA and industry can reduce the time interval between the filing of the initial Investigational New Drug application and the submission of the New Drug Application/Biologics License Application, without compromising safety and patient welfare.

This research effort will be supervised by Ernst R. Berndt, Ph.D., Louis B. Seley Professor of Applied Economics, MIT Sloan School of Management, and Joseph B. Bonventre, M.D., Ph.D., Co-Director of the Biomedical Enterprise Program. The FDA Project Manager for this research effort is Tomas Philipson, Ph.D., Senior Economic Advisor to the Commissioner, Office of Policy and Planning, Office of the Commissioner. Initially two MIT/Harvard graduate students will be working with Professors Berndt and Bonventre on this research effort. They are Adrian Gottschalk, M.B.A., and Matthew Strobeck, Ph.D.; brief bios of each are attached. As part of this research effort, team members will seek to interview appropriate senior management officials in industry and at the FDA on ways in which Phases I, II and III of the clinical development process can be carried out more efficiently and expeditiously, without compromising safety and patient welfare.

A final written report from this research project will be presented to the FDA in late Spring 2004; a copy will also be sent to each interviewer participant in the study. Although the content of the interviews with industry and FDA officials will form a portion of the basis of the students' masters theses, great care will be taken to assure confidentiality of interviewees' comments and feedback. In particular, specific sources of information from the interviews will not be shared with either the FDA or any industry officials.

The FDA would greatly appreciate your cooperation with and assistance to the MIT/Harvard research team on this very important research project. Feel free to contact Dr. Tomas Philipson at the Office of Policy and Planning at the FDA (Tomas.Philipson@fda.gov, 301-827-9253) if you have any concerns or questions regarding this collaborative project.

Tomas Philipson, Ph.D.
Senior Economic Advisor to the Commissioner
Food and Drug Administration

Appendix C: PDUFA Analysis Additional Results

Figure C-1: Descriptive Statistics for All Approved NMEs (10/01/1979 - 09/30/2002)

All Drugs (1979-2002)	
Mean	23.58
Standard Error	0.69
Median	19.19
Mode	11.99
Standard Deviation	17.67
Sample Variance	312.19
Kurtosis	6.08
Skewness	2.03
Range	132.11
Minimum	0.59
Maximum	132.70
Sum	15306.61
Count	649

All Drugs (1979-1986)	
Mean	33.09
Standard Error	1.64
Median	26.68
Mode	19.32
Standard Deviation	21.26
Sample Variance	452.20
Kurtosis	4.59
Skewness	1.83
Range	127.38
Minimum	5.32
Maximum	132.70
Sum	5558.67
Count	168

All Drugs (1986-1992)	
Mean	27.79
Standard Error	1.53
Median	23.49
Mode	29.90
Standard Deviation	18.94
Sample Variance	358.61
Kurtosis	2.80
Skewness	1.58
Range	97.45
Minimum	2.86
Maximum	100.30
Sum	4251.43
Count	153

All Drugs (PDUFA I)	
Mean	18.34
Standard Error	0.85
Median	14.97
Mode	11.99
Standard Deviation	11.62
Sample Variance	134.91
Kurtosis	2.77
Skewness	1.46
Range	70.87
Minimum	0.59
Maximum	71.46
Sum	3447.82
Count	188

All Drugs (PDUFA II)	
Mean	14.63
Standard Error	0.81
Median	11.93
Mode	5.95
Standard Deviation	9.59
Sample Variance	91.98
Kurtosis	1.72
Skewness	1.33
Range	48.46
Minimum	1.51
Maximum	49.97
Sum	2048.69
Count	140

Figure C-2: Descriptive Statistics for Cardio Approved NMEs (10/01/1979 -09/30/2002)

Cardiovascular Drugs (1979-2002)	
Mean	27.70
Standard Error	1.55
Median	23.72
Mode	23.72
Standard Deviation	16.48
Sample Variance	271.75
Kurtosis	4.69
Skewness	1.72
Range	94.39
Minimum	5.91
Maximum	100.30
Sum	3130.58
Count	113

Cardiovascular Drugs (1979-1986)	
Mean	36.11
Standard Error	2.81
Median	33.38
Mode	#N/A
Standard Deviation	17.12
Sample Variance	292.96
Kurtosis	3.04
Skewness	1.42
Range	82.92
Minimum	13.08
Maximum	96.00
Sum	1335.89
Count	37

Cardiovascular Drugs (1986-1992)	
Mean	30.28
Standard Error	3.49
Median	26.97
Mode	17.28
Standard Deviation	18.11
Sample Variance	328.06
Kurtosis	8.01
Skewness	2.36
Range	90.87
Minimum	9.43
Maximum	100.30
Sum	817.54
Count	27

Cardiovascular Drugs (PDUFA I)	
Mean	21.61
Standard Error	1.95
Median	18.23
Mode	13.14
Standard Deviation	11.06
Sample Variance	122.24
Kurtosis	1.08
Skewness	1.19
Range	46.52
Minimum	6.67
Maximum	53.19
Sum	691.55
Count	32

Cardiovascular Drugs (PDUFA II)	
Mean	16.80
Standard Error	2.40
Median	13.63
Mode	#N/A
Standard Deviation	9.91
Sample Variance	98.19
Kurtosis	0.68
Skewness	1.17
Range	33.54
Minimum	5.91
Maximum	39.46
Sum	285.60
Count	17

Figure C-3: Descriptive Statistics for CNS Approved NMEs (10/01/1979 - 09/30/2002)

CNS Drugs (1979-2002)	
Mean	26.22
Standard Error	2.14
Median	21.01
Mode	11.96
Standard Deviation	17.43
Sample Variance	303.63
Kurtosis	2.03
Skewness	1.40
Range	83.65
Minimum	0.59
Maximum	84.24
Sum	1730.56
Count	66

CNS Drugs (1979-1986)	
Mean	41.53
Standard Error	6.23
Median	39.56
Mode	#N/A
Standard Deviation	24.13
Sample Variance	582.07
Kurtosis	-0.99
Skewness	0.48
Range	73.66
Minimum	10.58
Maximum	84.24
Sum	622.95
Count	15

CNS Drugs (1986-1992)	
Mean	30.37
Standard Error	3.05
Median	32.10
Mode	#N/A
Standard Deviation	11.01
Sample Variance	121.20
Kurtosis	0.44
Skewness	-0.56
Range	40.08
Minimum	6.44
Maximum	46.52
Sum	394.84
Count	13

CNS Drugs (PDUFA I)	
Mean	18.09
Standard Error	2.10
Median	14.88
Mode	11.96
Standard Deviation	10.68
Sample Variance	114.17
Kurtosis	1.08
Skewness	1.07
Range	46.09
Minimum	0.59
Maximum	46.69
Sum	470.28
Count	26

CNS Drugs (PDUFA II)	
Mean	20.21
Standard Error	3.24
Median	16.79
Mode	#N/A
Standard Deviation	11.22
Sample Variance	125.93
Kurtosis	4.28
Skewness	2.01
Range	40.05
Minimum	9.92
Maximum	49.97
Sum	242.50
Count	12

Figure C-4: Pooled Regression with All NDAs (10/01/1979 - 09/30/2002)

Regression Statistics	
Multiple R	0.6215
R Square	0.3862
Adjusted R Square	0.3736
Standard Error	0.5754
Observations	649

ANOVA

	df	SS	MS	F	Significance F
Regression	13	132.277	10.175	30.734351	5.77706E-59
Residual	635	210.228	0.331		
Total	648	342.504			

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0%	Upper 95.0%
INTERCEPT	3.4047	0.1273	26.7429	0.000	3.1547	3.6547	3.1547	3.6547
LNINDNDAMONTHS	0.0247	0.0239	1.0338	0.302	-0.0222	0.0715	-0.0222	0.0715
TIMETREND	-0.0154	0.0087	-1.7605	0.079	-0.0325	0.0018	-0.0325	0.0018
PRIORITY	**-0.4955**	0.0562	-8.8097	**< 0.001**	-0.6059	-0.3850	-0.6059	-0.3850
TREND_PDUFA1	**-0.0180**	0.0056	-3.1830	**0.002**	-0.0291	-0.0069	-0.0291	-0.0069
TREND_PDUFA2	**-0.0198**	0.0061	-3.2262	**0.001**	-0.0319	-0.0078	-0.0319	-0.0078
ORPHAN	0.0945	0.0647	1.4609	0.145	-0.0325	0.2216	-0.0325	0.2216
NATION	-0.0495	0.0452	-1.0948	0.274	-0.1383	0.0393	-0.1383	0.0393
DRG_CARDIO	0.1131	0.0665	1.7004	0.090	-0.0175	0.2437	-0.0175	0.2437
DRG_ANTIINFECT	**-0.2833**	0.0707	-4.0067	**< 0.001**	-0.4222	-0.1445	-0.4222	-0.1445
DRG_NEOPLASTIC	**-0.2608**	0.1002	-2.6020	**0.009**	-0.4576	-0.0640	-0.4576	-0.0640
DRG_CNS	0.0655	0.0808	0.8108	0.418	-0.0932	0.2242	-0.0932	0.2242
DRG_BIO	0.0336	0.0764	0.4400	0.660	-0.1164	0.1836	-0.1164	0.1836
DRG_AIDS	**-0.8568**	0.1686	-5.0823	**< 0.001**	-1.1878	-0.5257	-1.1878	-0.5257

Figure C-5: Sensitivity to Real Discount Rate of NPVs for CNS and Cardiovascular

CNS						
Real Discount Rate	NPV ($B)	PV PDUFA Sales ($ B)	PV Counterfactual Sales ($ B)	Benefit ($ B)	PV Fee ($ B)	Fee % of Benefit
0.5%	$ 0.48	$ 184.12	$ 183.47	$ 0.65	$ 0.17	25.8%
1.0%	$ 1.04	$ 170.03	$ 168.84	$ 1.19	$ 0.15	13.0%
1.5%	$ 1.50	$ 157.15	$ 155.51	$ 1.64	$ 0.14	8.7%
2.0%	$ 1.88	$ 145.37	$ 143.36	$ 2.02	$ 0.13	6.6%
2.5%	$ 2.20	$ 134.59	$ 132.27	$ 2.32	$ 0.12	5.3%
3.0%	$ 2.45	$ 124.70	$ 122.14	$ 2.57	$ 0.11	4.4%
3.5%	$ 2.66	$ 115.64	$ 112.87	$ 2.76	$ 0.11	3.8%
4.0%	$ 2.82	$ 107.32	$ 104.40	$ 2.92	$ 0.10	3.3%
4.5%	$ 2.94	$ 99.68	$ 96.64	$ 3.03	$ 0.09	3.0%
5.0%	$ 3.03	$ 92.65	$ 89.54	$ 3.12	$ 0.08	2.7%
5.5%	$ 3.09	$ 86.19	$ 83.01	$ 3.17	$ 0.08	2.5%
6.0%	$ 3.13	$ 80.23	$ 77.03	$ 3.21	$ 0.07	2.3%
6.5%	$ 3.15	$ 74.75	$ 71.53	$ 3.22	$ 0.07	2.1%
7.0%	$ 3.15	$ 69.69	$ 66.48	$ 3.22	$ 0.06	2.0%
7.5%	$ 3.14	$ 65.03	$ 61.83	$ 3.20	$ 0.06	1.9%
8.0%	$ 3.11	$ 60.72	$ 57.54	$ 3.17	$ 0.06	1.8%
8.5%	$ 3.08	$ 56.73	$ 53.60	$ 3.13	$ 0.05	1.7%
9.0%	$ 3.04	$ 53.05	$ 49.96	$ 3.09	$ 0.05	1.6%
9.5%	$ 2.99	$ 49.64	$ 46.60	$ 3.03	$ 0.05	1.5%
10.0%	$ 2.93	$ 46.48	$ 43.50	$ 2.98	$ 0.04	1.5%

Cardiovascular						
Real Discount Rate	NPV ($B)	PV PDUFA Sales ($ B)	PV Counterfactual Sales ($ B)	Benefit ($ B)	Fee ($ B)	Fee % of Benefit
0.5%	$ 0.36	$ 161.38	$ 160.83	$ 0.54	$ 0.19	34.7%
1.0%	$ 0.83	$ 149.63	$ 148.63	$ 1.00	$ 0.17	17.3%
1.5%	$ 1.23	$ 138.85	$ 137.46	$ 1.39	$ 0.16	11.6%
2.0%	$ 1.56	$ 128.94	$ 127.23	$ 1.71	$ 0.15	8.7%
2.5%	$ 1.84	$ 119.84	$ 117.86	$ 1.98	$ 0.14	7.0%
3.0%	$ 2.07	$ 111.47	$ 109.27	$ 2.20	$ 0.13	5.8%
3.5%	$ 2.26	$ 103.76	$ 101.38	$ 2.38	$ 0.12	5.0%
4.0%	$ 2.41	$ 96.65	$ 94.13	$ 2.52	$ 0.11	4.4%
4.5%	$ 2.53	$ 90.10	$ 87.48	$ 2.63	$ 0.10	3.9%
5.0%	$ 2.62	$ 84.06	$ 81.35	$ 2.71	$ 0.10	3.5%
5.5%	$ 2.68	$ 78.48	$ 75.71	$ 2.77	$ 0.09	3.2%
6.0%	$ 2.73	$ 73.33	$ 70.51	$ 2.81	$ 0.08	2.9%
6.5%	$ 2.76	$ 68.56	$ 65.72	$ 2.84	$ 0.08	2.7%
7.0%	$ 2.77	$ 64.15	$ 61.30	$ 2.84	$ 0.07	2.5%
7.5%	$ 2.77	$ 60.06	$ 57.22	$ 2.84	$ 0.07	2.4%
8.0%	$ 2.76	$ 56.28	$ 53.45	$ 2.82	$ 0.06	2.2%
8.5%	$ 2.74	$ 52.76	$ 49.96	$ 2.80	$ 0.06	2.1%
9.0%	$ 2.71	$ 49.51	$ 46.74	$ 2.77	$ 0.06	2.0%
9.5%	$ 2.68	$ 46.48	$ 43.75	$ 2.73	$ 0.05	1.9%
10.0%	$ 2.64	$ 43.67	$ 40.98	$ 2.69	$ 0.05	1.8%

Appendix D: Quantitative Survey Results

Figure D-1: Descriptive Statistics of Quantitative Survey

1 = BAD / 2 = POOR / 3 = FAIR / 4 = GOOD / 5 = EXCELLENT	n =	Mean	Median	Mode	Std. Dev	NR	NA	Biotech vs. Pharma (p-value for t-test)	EVP Up vs. VP Down (p-value for t-test)
What is your overall perception of the FDA in regards to regulating drug development and appropriately weighing the risk/benefits of new drugs?	36	3.57	4	4	0.66	0	0	0.248	0.561
How would you rate the FDA's effectiveness of keeping unsafe drugs from the market?	36	4.07	4	4	0.60	0	0	0.233	0.827
Please rate how well your company is organized to interact with the FDA?	35	4.07	4	4	0.84	1	0	0.082	0.724
Please rate the progress your company has made in reducing clinical development times on issues that your company can control.	33	3.67	4	3	0.78	3	0	0.272	0.868
How would you rate your company's experience with Contract Research Organizations?	31	3.39	3	3	0.80	5	0	0.313	0.287
Please rate the quality of communication your company has with the FDA during the following phases PRE-CLINICAL	32	3.23	3	3	0.81	4	0	**> 0.000**	0.737
Please rate the quality of communication your company has with the FDA during the following phases PHASE I	34	3.35	3	3	0.77	2	0	0.053	0.773
Please rate the quality of communication your company has with the FDA during the following phases PHASE II	36	3.43	3.5	4	0.67	0	0	0.549	0.836
Please rate the quality of communication your company has with the FDA during the following phases PHASE III	36	3.88	4	4	0.65	0	0	0.136	0.407
Please rate the quality of communication your company has with the FDA during the following phases NDA	35	3.76	4	4	0.96	1	0	0.561	0.722
Please rate the following in regards to the FDA reviewers. The quality of FDA reviewers is:	32	3.33	3	3	0.70	4	0	0.481	0.959
Please rate the following in regards to the FDA reviewers. Accountability of FDA reviewers is:	33	3.06	3	3	0.76	3	0	0.411	0.777
Please rate the following in regards to the FDA reviewers. Training for FDA reviewers is:	22	2.86	3	3	0.82	14	0	0.515	0.279
Please rate the following in regards to the FDA reviewers. Direct Leadership of FDA reviewers is:	32	3.45	3.5	4	0.65	4	0	0.292	0.589
The clinical protocols my company submits to the FDA are on average:	25	4.24	4	4	0.52	2	9	0.626	0.894
When responding to FDA inquiries or questions, your company responds effectively and efficiently.	27	4.20	4	4	0.71	0	9	0.265	0.253

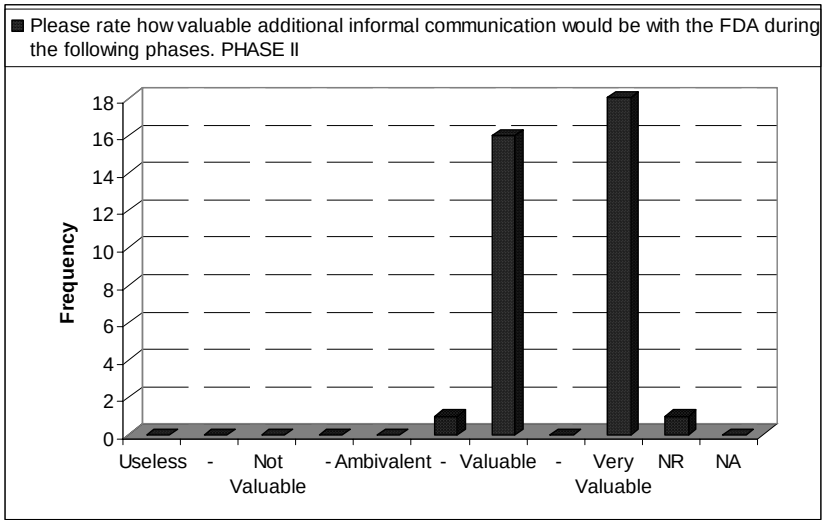
1 = VERY LIKELY / 2 = NOT LIKELY / 3 = AMBIVALENT / 4 = SOMEWHAT LIKELY / 5 = VERY LIKELY	n =	Mean	Median	Mode	Std. Dev	NR	NA	Biotech vs. Pharma (p-value for t-test)	EVP Up vs. VP Down (p-value for t-test)
Would your company be willing to pay additional user fees to hire FDA staff to help with clinical development reviews, discussion, and issues during the following phases? PHASE I	33	3.86	4	5	1.26	3	0	0.600	0.888
Would your company be willing to pay additional user fees to hire FDA staff to help with clinical development reviews, discussion, and issues during the following phases? PHASE II	33	4.05	4	5	1.26	3	0	0.529	0.880
Would your company be willing to pay additional user fees to hire FDA staff to help with clinical development reviews, discussion, and issues during the following phases? PHASE III	32	4.14	5	5	1.34	4	0	0.807	0.645
How much would you be willing to pay for more communication with the FDA per phase? PHASE I	17	1.29	1.00	1.00	1.00	10	9	0.761	0.607
How much would you be willing to pay for more communication with the FDA per phase? PHASE II	17	1.82	2.00	2.00	2.00	10	9	0.622	0.693
How much would you be willing to pay for more communication with the FDA per phase? PHASE III	16	2.19	2.00	1.00	1.00	11	9	0.106	0.345
How likely is your company to use surrogate markers in clinical trials as the primary endpoint under the current FDA guidelines?	34	3.26	3.5	5	1.52	2	0	0.338	0.149
How likely is your company to use surrogate markers if patent opportunities and incentives were available on the surrogate marker?	32	3.98	5	5	1.43	4	0	0.690	**0.045**

** Note that the responses for the questions related to how much industry would be willing to pay for more interaction were scaled so that responses of "Other – 5 " were rated as NR in order to prevent the actual dollar estimates from being skewed by the scale. Thus, this scale is set from one to four with one being $100K to $500K, two being $500k to $1MM, three being $1MM to $5MM, and four being greater than $5MM.

1 = USELESS / 2 = NOT VALUABLE / 3 = AMBIVALENT / 4 = VALUABLE / 5 = VERY VALUABLE	n =	Mean	Median	Mode	Std. Dev	NR	NA	Biotech vs. Pharma (p-value for t-test)	EVP Up vs. VP Down (p-value for t-test)
How valuable is the consultation with the FDA at the end of Phase II - beginning of Phase III?	34	4.71	5	5	0.52	2	0	0.895	0.745
Please rate how valuable additional informal communication would be with the FDA during the following phases. PRE-CLINICAL/IND	33	4.42	5	5	0.79	3	0	0.529	0.971
Please rate how valuable additional informal communication would be with the FDA during the following phases. PHASE I	35	4.11	4	5	0.90	1	0	0.331	0.542
Please rate how valuable additional informal communication would be with the FDA during the following phases. PHASE II	35	4.50	5	5	0.53	1	0	0.800	1.000
Please rate how valuable additional informal communication would be with the FDA during the following phases. PHASE III	34	4.71	5	5	0.52	2	0	0.195	0.864
Please rate how valuable additional informal communication would be with the FDA during the following phases. NDA	35	4.74	5	5	0.51	1	0	0.596	0.402
How valuable has information gathering technology been in helping reduce clinical development times in the following phases? PRE-CLINICAL/IND	33	3.30	3	3	0.95	3	0	0.516	0.497
How valuable has information gathering technology been in helping reduce clinical development times in the following phases? PHASE I	31	3.27	3	3	0.95	5	0	0.552	0.098
How valuable has information gathering technology been in helping reduce clinical development times in the following phases? PHASE II	31	3.35	3	3	0.98	5	0	0.790	0.182
How valuable has information gathering technology been in helping reduce clinical development times in the following phases? PHASE III	30	3.35	3	3	1.11	6	0	0.212	0.207
How valuable has information gathering technology been in helping reduce clinical development times in the following phases? NDA	30	3.28	3	2	1.22	6	0	0.150	0.300
How useful has electronic submission been to your company in the clinical development process?	34	3.99	4	5	1.08	2	0	0.096	0.832
How would you rate the FDA Advisory Board Panel during approval?	34	3.25	3	3	0.94	2	0	0.973	0.485

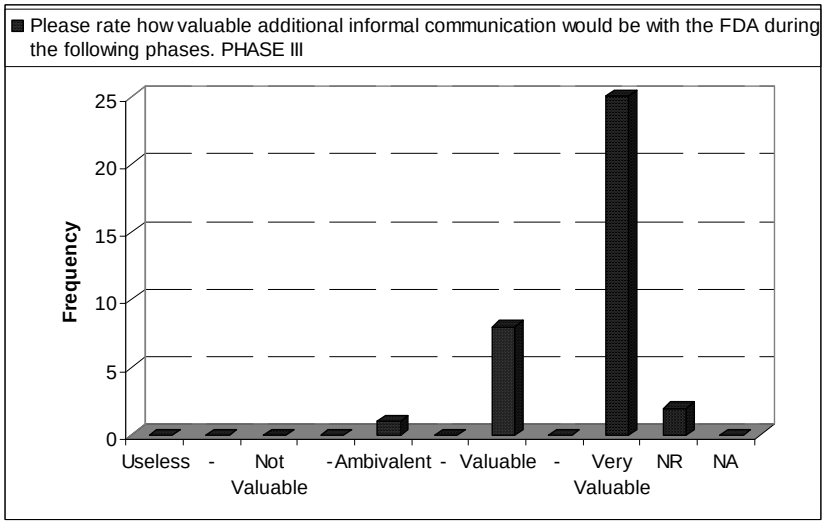
1 = STRONGLY DISAGREE / 2 = DISAGREE / 3 = NEUTRAL / 4 = AGREE / 5 = STRONGLY AGREE	n =	Mean	Median	Mode	Std. Dev	NR	NA		
In interacting with the FDA, my company's regulatory group is afraid to push back on many protocols or requirments demanded by the agency?	36	3.00	2	2	1.45	0	0	0.095	0.614
In interacting with the FDA, my company runs trials that are not often required by the FDA, but in anticipation of some future question they may ask.	36	3.13	3	2	1.35	0	0	**0.006**	0.291
In interacting with the FDA, my company runs additional tests in pre-clinical that are not required by the FDA.	34	3.38	4	2	1.26	2	0	0.227	0.321
Your company strongly takes into consideration FDA feedback on clinical protocols.	25	4.68	5	5	0.48	2	9	0.906	0.438
When your company ignores FDA advice on clinical protocols, drug development costs and times are increased.	23	4.04	4.5	5	1.16	4	9	0.913	0.414
The EMEA is more efficient than the FDA in approving drugs?	34	2.15	2	1	1.10	2	0	0.128	0.436
Biologics fail in Phase III more often that small molecules fail in phase III	24	2.54	2	2	1.14	12	0	**0.050**	0.905
The FDA has made significant efforts to reduce clinical development times	34	2.12	2	2	0.91	2	0	0.471	0.594
The FDA has made significant efforts to reduce approval times	34	3.53	4	4	0.99	2	0	0.870	0.057

Figure D-2: Rating - Additional Informal Communication Value - Phase II, III, and NDA



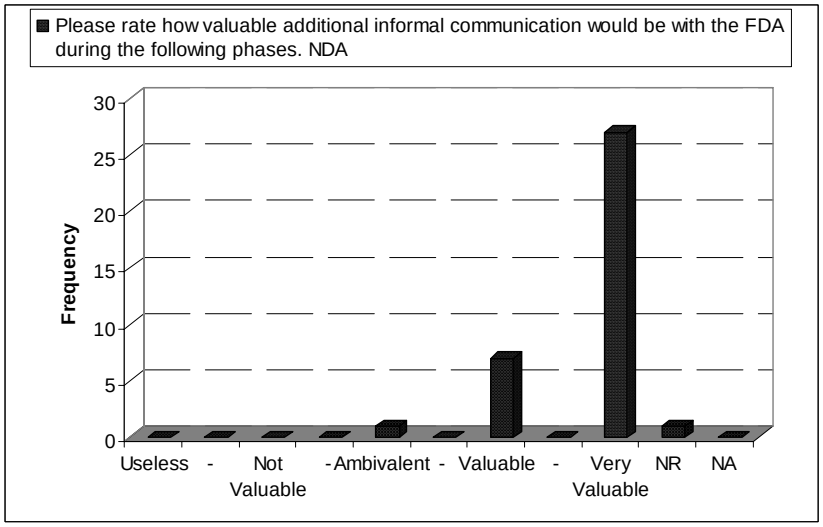
n = 35
mean = 4.50
median = 5
mode = 5
stdev = 0.53

1 = Useless
2 = Not Valuable
3 = Ambivalent
4 = Valuable
5 = Very Valuable



n = 34
mean = 4.71
median = 5
mode = 5
stdev = 0.52

1 = Useless
2 = Not Valuable
3 = Ambivalent
4 = Valuable
5 = Very Valuable



n = 35
mean = 4.74
median = 5
mode = 5
stdev = 0.51

1 = Useless
2 = Not Valuable
3 = Ambivalent
4 = Valuable
5 = Very Valuable