

**The Drug Development Process: Evaluation of PDUFA I/II and an Investigation into Reducing Drug Development Times**

by

Matthew W. Strobeck

Ph.D. Cellular and Molecular Biology  
University of Cincinnati, 2001

Submitted to the Sloan School of Management and the Department of Health Sciences and Technology in partial fulfillment of the requirements for the Degrees of

Masters of Science in Management

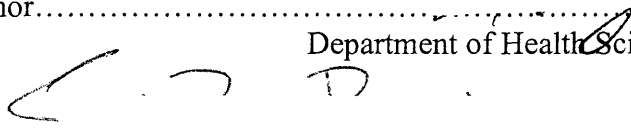
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Masters of Science in Health Sciences and Technology

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Department of Health Sciences and Technology

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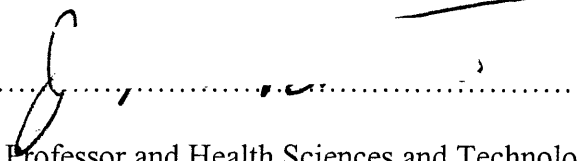
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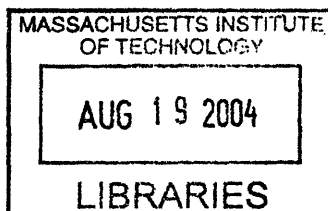
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## **Abstract**

Published findings report that it takes approximately eight years to bring a novel drug to market at an average cost of \$800 million. Over the last ten years, the Food and Drug Administration (FDA) has helped to reduce the time from filing a new drug application (NDA) to granting marketing approval (i.e. the approval phase). However, there has been no alteration in the time required to progress from an investigational new drug application (IND) to an NDA filing (i.e. the clinical phase) over this same period. Since approval times began to decrease upon the initiation of the Prescription Drug User Fee Act (PDUFA), in this thesis I analyze the impact of PDUFA and calculate its benefits to companies. Due to the importance of getting new drugs to the market faster, I also investigate why there has been no significant change in the time required to test a drug clinically, and attempt to identify steps that could be taken to improve the clinical trial process. To investigate this, I evaluated ways in which the FDA and industry can work together to reduce clinical development times, without compromising safety. The results from this study show that PDUFA has had a significant impact on reducing approval times. More importantly, I determined that the direct costs of PDUFA are small in comparison to its benefits. In addition, my analysis of the early clinical phases (pre-clinical to Phase II) of drug

benefits. In addition, my analysis of the early clinical phases (pre-clinical to Phase II) of drug development has revealed potential steps both the FDA and industry can take to facilitate a more efficient process for assessing the safety and efficacy of drugs. Thus, this study represents an important step towards improving the development of medicines for the world.

Thesis Co-supervisor: Dr. Ernst Berndt

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# Chapter I

## Introduction

The mission of the Food and Drug Administration (FDA) is to protect as well as enhance public health (1,2) This important onus brings with it a tremendous amount of responsibility. Over the last twenty-three years, the FDA has approved six hundred and forty nine drugs. During this same period, only eighteen drugs have been removed from the market due to toxicity, suggesting that the FDA selection process for approving drugs has a very high success rate. This accomplishment underscores the importance of the FDA in helping to introduce many useful medicines to society. However, many unmet medical conditions still exist. To meet the demand for new drugs, it is critical that experimental medicines be developed faster. In order for the FDA to continue to uphold its mission statement it will need to work with industry to identify new ways of improving the drug development process.

## The Origin of the Food and Drug Administration

The regulation of pharmaceuticals in the United States began in 1906 under President Theodore Roosevelt, with the passage of the Pure Food and Drug Act (1,2). This Act created the first law that prohibited the mislabeling of medicines to stop the fraudulent marketing of drugs for various illnesses (1). Since the government was not properly staffed to deal with regulating the large number of drug manufacturers at this time, several disasters occurred (1,2). Specifically, during the 1930's a drug called sulfanilamide was developed and marketed without having been examined for toxic side effects (1). After a short period on the market, sulfanilamide killed hundreds of children (1,2). This prompted the passage of the Food, Drug and Cosmetic Act of 1938 by Congress, which required pharmaceutical companies to file a New

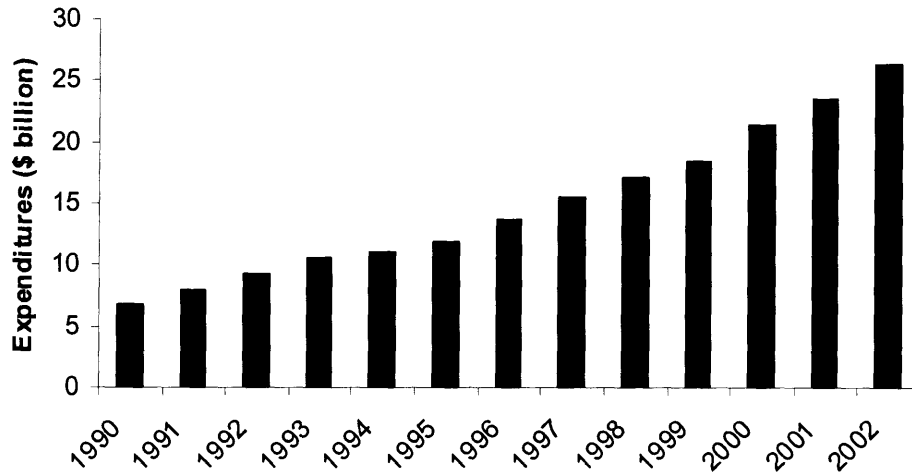


Drug Application (NDA) to the FDA in order to receive marketing approval (1,2). The data submitted in the NDA had to demonstrate that the drug was thoroughly tested for toxicities in the targeted indication. A response to the NDA usually occurred within two months of filing (1). In addition, this Act also mandated that certain drugs be administered to patients only by prescription (1,2). By the end of the 1950's, the number of New Chemical Entities (NCE's) submitted to the FDA was approximately fifty per year, the highest level since 1938. Interestingly, during this time FDA regulatory review times increased to approximately seven months (1,2).

In the early 1960's, a drug called thalidomide, which was approved and marketed in Europe as well as Canada, was shown to cause birth deformities (3). By the time thalidomide was withdrawn from the market, thousands of children had died or were born with severe birth defects (1,2,3). Despite the fact that thalidomide was not approved in the U.S., the devastation thalidomide caused resulted in amendments to the Food, Drug and Cosmetic Act in the U.S in 1962. Specifically, Senator Kefauver and his committee attached two provisions to the Food, Drug and Cosmetic Act that demanded i) a drug must be tested for efficacy in a properly controlled trial, and ii) an Investigational New Drug (IND) application be filed before clinical testing would begin (1,3). This amendment was designed to prevent any future tragedies, such as that seen with thalidomide, by making sure that the drug under investigation was thoroughly studied for safety.

Since the FDA began to hold pharmaceutical companies to high clinical standards, the length of time a drug spent in clinical development steadily increased (1,2,4). It has been documented that after the FDA amendment of 1962, the average time a drug spent in clinical development increased from three and a half to approximately fourteen years (1,2). These larger

and more complicated studies also resulted in an increase in the costs for developing a drug, thus making it more difficult for smaller companies with less money to develop new medicines (5,6).



**Figure 1: US Research and Development Expenditures (3)**

These amendments lengthened clinical development time and made drug trials more complicated. Interestingly, the increased difficulty in clinically testing drugs did not have an adverse effect on the research and development (R&D) of new therapies. Specifically, the amount spent on R&D by pharmaceutical companies has steadily increased over the last ten years (Figure 1.) (7). In addition, the average number of INDs filed per year between 1990 and 2002 was six hundred and eighty. This suggests that despite rigorous clinical testing requirements, many companies continue to enter new drugs into the clinic (7).

In addition to the various clinical trial hurdles, it has also been postulated that governmental regulations around drug development have created disincentives for FDA reviewers to approve drugs. Specifically, if a medical reviewer approves a drug that ultimately causes harm (a Type II error) the patients as well as the reviewer will suffer tremendously (1,8,9). Therefore, it has been argued that FDA personnel will tend to commit Type I errors, in which they reject a drug that is safe and effective. For the reviewer there is little penalty for

committing a Type I error; however, the patients who desperately need new medicines will suffer the most (8,9). Thus, the government has created a number of barriers for drugs to get to the market. Many of these issues will need to be addressed if the government intends on improving current healthcare standards.

In order to be able to identify ways both industry and the FDA can reduce drug development times, it is critical to understand the current structure of the clinical development process.

### The Clinical Trial Process

In order for a drug to obtain FDA approval the therapy must go through four distinct phases of drug development (10). The first step in the drug development process is to identify a candidate molecule (10,11,13). This compound is usually isolated after screening thousands of chemicals/proteins against a specific biological target or in a functional assay. Once lead molecules are identified, toxicity studies are performed in animals (10,11,13). After extensive pharmacokinetic and pharmacodynamic testing in various animal models, the drug is then

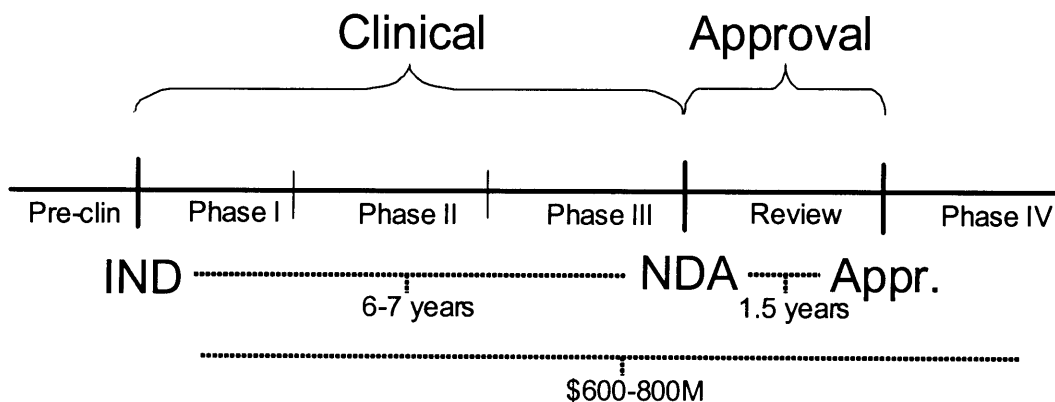


Figure 2: The Clinical Development Process

able to move into human clinical testing. The clinical portion of the drug development process is composed of three distinct phases called Phase I, II and III (Figure 2.) (10,11,13). The Phase I trial is designed to test the safety and tolerability of a drug in roughly twenty to one hundred patients. The Phase I trial is typically performed in healthy volunteers (who are paid a nominal fee) and takes between one week to a few months to complete (11,13). The Phase II trial evaluates the drug's effectiveness in treating a disease within the safe dose range established in Phase I studies. The Phase II trials often involve hundreds of patients and can take from several months to two years to complete (11,13). Phase III trials are designed to evaluate the safety and effectiveness of a drug within a larger and more diverse population. Phase III trials can take on average four years and involve hundreds to several thousand patients (11,13). Phase IV or post marketing studies are performed either as a condition for approval, for approval in a new indication or for marketing purposes (13). Phase IV studies are designed to observe the effects of a drug in a larger often more heterogeneous population. This study can take three to four years on average and can involve thousands of patients (13) .

The approval arm of the clinical development process starts with the filing of the NDA or a Biologic License Application (BLA) and ends with the final response from the FDA (Figure 2). The approval phase takes on average two years and the rate-limiting factor during this stage is FDA review time (11,13).

It has been estimated that the costs of developing a drug from pre-clinical to Phase IV is on average \$800M (12,14,15,16). In order for drug companies to maximize their investment, the therapy being developed needs to generate close to \$1B in sales over its lifetime. However, if drug development times could be reduced, these costs would go down dramatically (half of the cost of drug development involves the time cost of development), and the benefit to society as

well as the pharmaceutical companies would be very significant. Therefore, it is critical to evaluate drug development trends and identify factors that may be useful in getting novel therapies to patients faster without compromising safety.

### Trends in Clinical Development Times

In 2003, Reichert et al. analyzed the mean clinical development and approval times for all drugs approved from 1970 to 2002 (4). Interestingly, between 1990 to 2001, there was an overall decrease in the mean clinical approval phase (NDA filing to market approval) from 32.8 in months in 1992 to 18.5 months in 2001 (4). This 43% decrease could possibly be attributed to a push by both the public and government to speed up the development and approval of AIDS

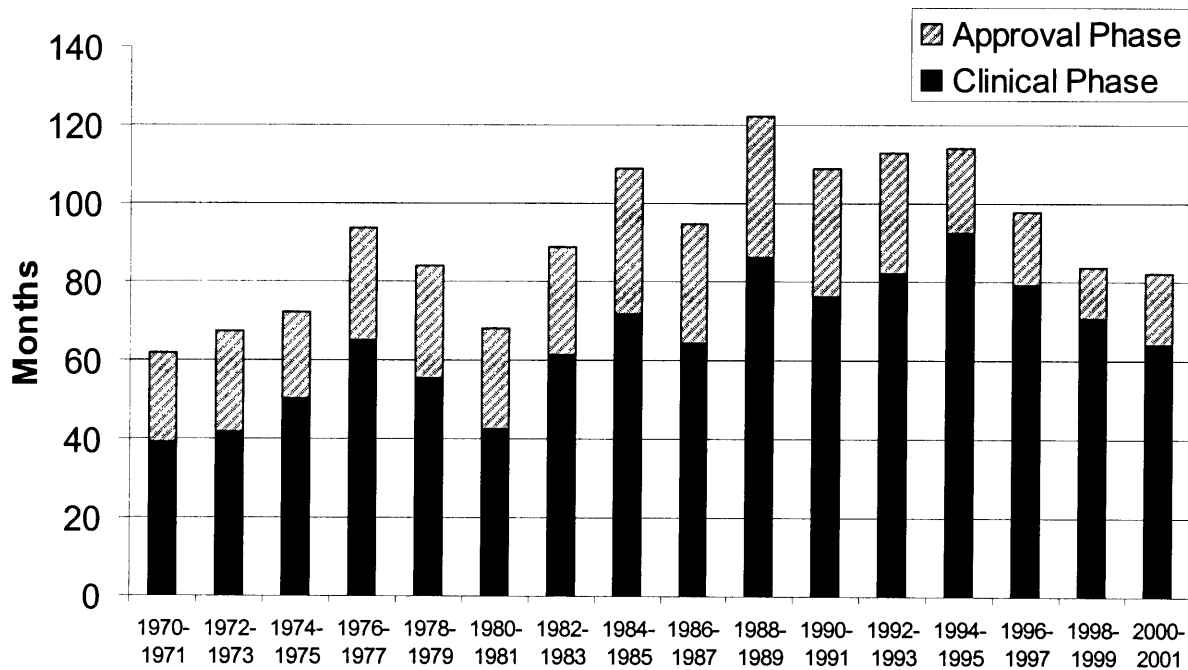


Figure 3: Mean Clinical Approval Times

drugs in the early 1990's to help this large and growing unmet medical condition (4,18). In addition, the Prescription Drug User Fee Act (PDUFA) was enacted during this period and was designed to shorten NDA review times (19,20).

Between 1986 and 2001 (fifteen years), there was only a modest decrease in the mean clinical phase time (IND to NDA filing) (Figure 3.) (4). In 1986, the mean time a drug spent in the clinic was 64.4 months. In 2001, a drug spent on average, 63.9 months in clinical development (4). This 0.7% decrease is much less dramatic when compared to the 43% decrease in mean approval time over the same period (4). Based on these findings, it is key to try to determine what caused this large decrease in mean clinical approval time versus the small change in the time spent in clinic testing.

## **The Prescription Drug User Fee Act**

The Prescription Drug User Fee Act (Public Law 102-571) was established by Congress in 1992 to allow companies developing therapeutics to pay a fee to the FDA for an expedited review of their small molecule or biological product application (19,20). The importance of this Prescription Drug User Fee Act (or PDUFA I) is that it gave the FDA the means to secure resources in order to hire more medical drug reviewers and improve their technology to support the faster approval of drugs (19,20,21,22). Although PDUFA I was designed to expedite the drug review process, the FDA also needed to make sure that safety was not compromised.

To satisfy this, PDUFA requires the FDA to submit two reports to Congress annually (20,21). One report is due at 120 days before the end of the fiscal year, and the second at 60 days before the end of the fiscal year (20,21). These reports allow the government to assess the

performance of the FDA on a yearly basis and gauge whether they were meeting their projected goals while maintaining safety.

The goal of PDUFA I in 1992 was to complete the review of 90% of priority original new drug and biologic applications within six months after the submission date (19,22,23). In addition, PDUFA I also mandated that 90% of standard original new drug applications and efficacy supplements would be reviewed within twelve months after submission (23). Other provisions set forth by this act were to complete the review of 90% of manufacturing supplements as well as resubmitted new drug and biologic applications within six months (22,23). PDUFA I expired in 1997 and during that year PDUFA II was enacted under the FDA Modernization Act (FDAMA) (22,23). The mandates proposed in PDUFA II were similar to PDUFA I except that the review goals were shortened (22,23). Specifically, the goals of the FDA under PDUFA II were to review and act on 90% of new standard small molecule and biological drug applications within ten months after the submission date (23). For priority drug applications, the FDA's goal was to review and act on 90% within six months of submission (23). Other provisions included in PDUFA II were that 90% of manufacturing supplements must be reviewed in four months and complete review of 90% of Class I resubmitted efficacy supplements in two months and Class II supplements in six months (22,23).

PDUFA III was renewed in 2002 under the Public Health and Security and Bioterrorism Preparedness and Response Act (23). Under PDUFA III, the current requirements are for complete review of 90% of standard NDA/BLA's within ten months, and 90% of priority NDA/BLA's within six months similar to PDUFA II (23). Other changes made under PDUFA III were to the response time for the resubmitted efficacy supplements and discipline review letters on "reviewable units" (23).

The PDUFA fees charged to companies for applications, supplements, establishment and product fees have increased steadily from 1993 (Figure 5) (24). In 2002, the total collection realized by the FDA for PDUFA was approximately \$143M. The PDUFA collections realized by the FDA have been growing at a 30% cumulative annual growth rate from 1993 (24). Under PDUFA III, the cost for an NDA review was increased to approximately \$573,000, representing a 7.5% increase from 2003 (24). Based on the amount of funds pharmaceutical companies have been spending to expedite the review of their drug applications, it still remains to be determined what the impact of PDUFA has been on drug approval times controlling for confounders (26). In addition, if PDUFA has had a significant effect on reducing approval times it will be important to determine the benefit, in terms of present value of sales, realized by companies paying the user fees.

<b>Actual Fees Charged Each Year</b>					
	APPLICATIONS	APPLICATIONS	SUPPLEMENTS	ESTABLISHMENT	PRODUCT
Year	WITH	WITH NO	WITH	FEE	FEE
	CLINICAL	CLINICAL	CLINICAL		
	DATA	DATA	DATA		
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

**Figure 4. Actual Fees Charged Per Year (24).**



## Issues in Clinical Development

In contrast to the approval phase, there has been no significant decrease in clinical development times over the last twenty years (Figure 3.) (4). One reason for this trend could be due to the reluctance on behalf of the FDA to alter existing clinical trial guidelines (27). This is supported by the fact that few regulations or changes have been made to dramatically shorten clinical trials over the last decade (27,28) The future of medicine is dependent on innovation in both the therapies being developed as well as the ability to expeditiously get drugs to patients. Currently, it takes at least six or seven years on average to bring a drug to market. As a result, many patients will die or their condition will worsen over this period. When Dr. Mark McClellan became commissioner of the FDA, he recognized this problem and stated that he would try to determine ways in which clinical timelines could be shortened. The importance of this idea was underscored in 2003, when based on Phase II data and within three months of receiving the application, the FDA approved a drug called bortozemib (Velcade) for the treatment of multiple myeloma, a rare blood cancer (29). This quick turnaround by the FDA fueled excitement within the biotechnology and pharmaceutical industries as well as in general the medical field. Most importantly, this rapid approval allowed the 45,000 multiple myeloma patients in the US to have immediate access to this life saving drug (29).

The focus of this study is to understand factors associated with the significant decrease in drug approval times over the last decade. In this thesis, I also investigate why clinical development times have not changed over this same period, and attempt to identify ways in which this part of the drug development process could be shortened. The results of this study not only provide insight into the benefit of PDUFA but also identify steps both the industry and FDA can take to reduce drug development times. These findings will help provide the framework for

future changes in improving the development of new medicines and the treatment of patients.

# Chapter II

## Methods

### New Molecular Entity Data Set

In order to perform the analysis of PDUFA, I obtained a New Molecular Entity (NME) Data Set from the FDA. This data set contained a list of all NME's from 1965-2003. In addition, this data set also included important biologics approved from 1/1/65 through 7/31/2003. The list included the generic name, a descriptor, the developing company and country, the FDA approval date and the therapeutic significance rating (at time of approval). The year and country of first world marketing, the US Trade Name (at time of approval - a few are different from marketed trade name), the IND submission date, the NDA clock date, the IND number, the elapsed approval time (months), years in IND Phase (IND submission thru NDA submission), total development years (IND submission thru NDA approval), the NDA/BLA number, the sponsoring company (at time of approval), foreign/US developer, an Orphan Drug designator and the US marketing date (year and month) were also included. The generic name (NME - generic) column includes a few notes (safety withdrawals, etc.), the descriptor (DES) identifies characteristics of the drug according to the following codes: N – (NDA), B - (BLA) Biologic, V – Vaccine, D – Diagnostic, R – Radiopharmaceutical, O - Orphan drug, T - Therapeutic (in the case of several nuclear products). The Therapeutic Significance (TS) codes reflect the current Priority/Standard review system for post PDUFA and the old A, B, C system for pre-PDUFA submissions. The year of first worldwide marketing is two digit until 2000. Then 100 00, 101 01, etc. The country codes are three letters. Certain trade names were changed after approval of

the drug. Thus, some are simply the name provided to FDA prior to approval and are not the name of the drug as marketed. The Sponsor name is the name of the firm at the time of approval. Several are currently different due to mergers. The US/Foreign developer codes are U=US, F=foreign and UN=unknown while the Orphan drug code is "O" in the descriptor column.

## **Descriptive Statistics**

The drugs approved between 1979-2002 were separated based on either PDUFA or non-PDUFA review as well as by therapeutic class. Next, the average time (in months) the drugs spent in the IND to NDA phase as well as the NDA to approval phase was evaluated. Descriptive statistics (e.g. mean, median....) were then determined using Excel.

Kaplan Meier curves for NDA approval times were also constructed to measure the percentage of approval remaining over time in months. To calculate the survival curve, the number of drugs approved over different times was determined from the NME data set. Next, the ratio of drugs approved over the total number of drugs was estimated. To plot the data I then took the inverse of these various data points.

## **Multivariate Linear Regression Analyses**

A multivariate regression analyses was performed to evaluate the effects of PDUFA on approval times controlling for confounders. To investigate this, the following explanatory variables were used:

- Time Trend

- Measures progression of time (proxy for improvements in information technology, medical advances)
- Priority Binary
  - Is the NDA review a standard review or a priority review
- PDUFA1 Binary x Time Trend
  - Is time period during PDUFA 1
- PDUFA2 Binary x Time Trend
  - Is time period during PDUFA 2
- Orphan Binary
  - Is the drug filed for an orphan drug indication
- Nation Binary
  - Is the sponsoring drug developer foreign
- IND-NDA Time (months)
  - Natural log of the IND to NDA time
- Therapeutic Class
  - Four major therapeutic areas and biologics evaluated (omitted class is “all other”)

The equation used for the regression was:  $\text{Ln}(\text{time}) = \alpha + \beta_1 \cdot \text{timetrend} + \beta_2 \cdot \text{timetrend} \cdot \text{PDUFA1} + \beta_3 \cdot \text{PRIORITY} + \beta_4 \cdot \text{timetrend} \cdot \text{PDUFA2} + \beta_5 \cdot \text{FOREIGN} + \beta_6 \cdot \text{ORPHAN} + \beta_7 \cdot \ln(\text{IND-TO-NDA}) + \beta_x \cdot \text{THERAPEUTIC AREA} + \text{random disturbance term}$ .

The hypotheses for the coefficients were:  $\beta_1 < 0$ ,  $\beta_2$ ,  $\beta_4$  ??,  $\beta_3 < 0$ ,  $\beta_5 < 0$ ,  $\beta_6 < 0$ ,  $\beta_7$  ??,  $\beta_x$  varies. Adrian Gottschalk engineered the NME dataset to perform the regressions in Excel.

The natural log of approval months was converted into relative NDA months using the following equation:  $NDA(\text{time}) = e^{(\ln \text{ app months} + 0.5 * (\text{standard error of regression})^2)}$ . The standard error of regression correction factor used was 0.575. The ln approval months was a predicted value based on regression equation estimates.

## Net Present Value of Sales

In order to examine the benefit of PDUFA on the net present value of drug sales, I first calculated the present value of sales by using 1) the NME data set that listed actual approval dates and 2) the counterfactual where the PDUFA variable was turned off in the linear regression equation. Next, I determined the present value of the difference between PDUFA approvals and the counterfactual. I used the following equation to determine the present value of sales for PDUFA NDA:  $PV = [1 / (1+r)^{(\alpha_i + \tau_i + \mu_i)}] [CF / (1+r)^t]$ . In this PV equation,  $\alpha_i$  equates to the time between the enactment of PDUFA and the NDA start date,  $\tau_i$  equals the time between the NDA start date and final approval date,  $\mu_i$  is the time interval between approval and market launch, discount rate ( $r$ ) is 5% and time ( $t$ ) is 15. For the counterfactual I used the following PV calculation:  $PV = [1 / (1+r)^{(\alpha_i + \tau_i + \mu_i + \delta_{NDA})}] [CF / (1+r)^t]$ . In this counterfactual equation the NDA approval time ( $\tau_i$ ) is shifted by ( $\delta_{NDA}$ ) the predicted counterfactual NDA approval time. For the PV calculations, I also separated the drugs by therapeutic class. The final NPV of PDUFA vs. the counterfactual was calculated by subtracting the total user fees from the present value calculations.

Next, sales for each drug were forecasted using IMS data to approximately year 15 with sales peaking in year 13. First, I annualized sales to determine first year of full sales after launch

based on the IMS data (7). I then divided the sales for the various therapeutics by the corresponding percentage of peak year sales that correlates to the number of years after market launch. With the peak sales in year 13, we used the IMS average NME sales curve to construct the 15-year forecast.

Next, I used the GDP deflator to convert all 1998-2002 data to 1992 dollars. This was replicated for PDUFA fees. Thus, the discount rates used were real, not nominal. The baseline year (1.00) is 2000. To adjust for inflation I first took Annualized Sales Year and divided by IMS Health percentage of peak to get peak sales. Next, I took peak sales and divided by the GDP deflator for the corresponding year of first annualized sale year = 2000 basis of sales. Finally, I multiplied the 2000 basis of sales by the 1992 GDP deflator to derive the 1992 basis of peak sales.

## **Questionnaire Development**

The questionnaire was constructed based on discussions with Professor Fiona Murray, Ernst Berndt, and Joseph Bonventre as well as reviews of the literature (30,31). I refined the questionnaire after two company visits. In addition to this qualitative questionnaire, I assembled a quantitative questionnaire focusing on some of the critical issues outlined in the qualitative questionnaire. Both questionnaires are reproduced in the appendix. Together with Professor Berndt and Adrian Gottschalk, I interviewed executive vice presidents, senior vice presidents, chief medical officers as well as other senior regulatory personnel and management of various biotechnology, contract research organizations (CRO's), and pharmaceutical companies. In total, we interviewed 50 people from 17 companies. The breakdown of the companies interviewed were three CRO's, seven biotechnology companies and seven pharmaceutical companies. The

positions of the personnel interviewed were twenty two from biotech (seven global heads, three executive vice presidents, nine vice presidents, three directors), twenty two from pharma (four global heads, nine executive vice presidents, seven vice presidents, two directors), and six from CROs (two executive vice presidents, two vice presidents, two directors).

A letter from the FDA endorsing the study was sent to the companies prior to the interview (see appendix). In order to perform the interview, we were required to apply and obtain Institutional Review Board (IRB) approval at MIT as well as COUHES certification. Forty-four out of the fifty interviews were conducted at the company. The qualitative results were organized by company and incorporated into one master document. The quantitative questionnaire results were tabulated and the descriptive statistics were determined using Excel. No questionnaire was excluded from the final analysis. During the company visit, the quantitative questionnaire was administered first, followed by the qualitative questionnaire.



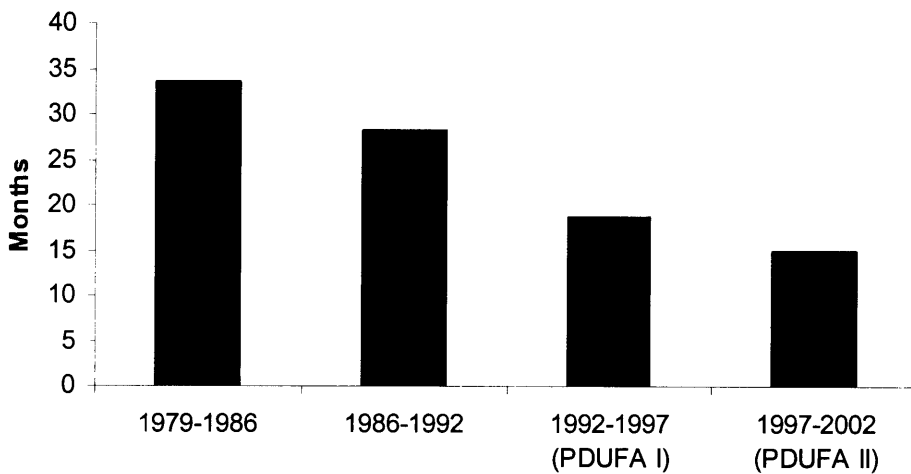
# Chapter III

## Results

### The Effect of PDUFA on Approval Times

Since mean drug approval times have been decreasing over the last decade (Figure 4), I sought to understand what has contributed to this decline (4). The approval of PDUFA I coincided with a large decrease in approval times (19,20). This downward trend continued through the passing of PDUFA II in 1997 (4). Based on these observations, I *hypothesized* that after controlling for confounders, PDUFA I and II have reduced approval times relative to the prior time trend.

In order to correlate the enactment of PDUFA with approval times, I first evaluated

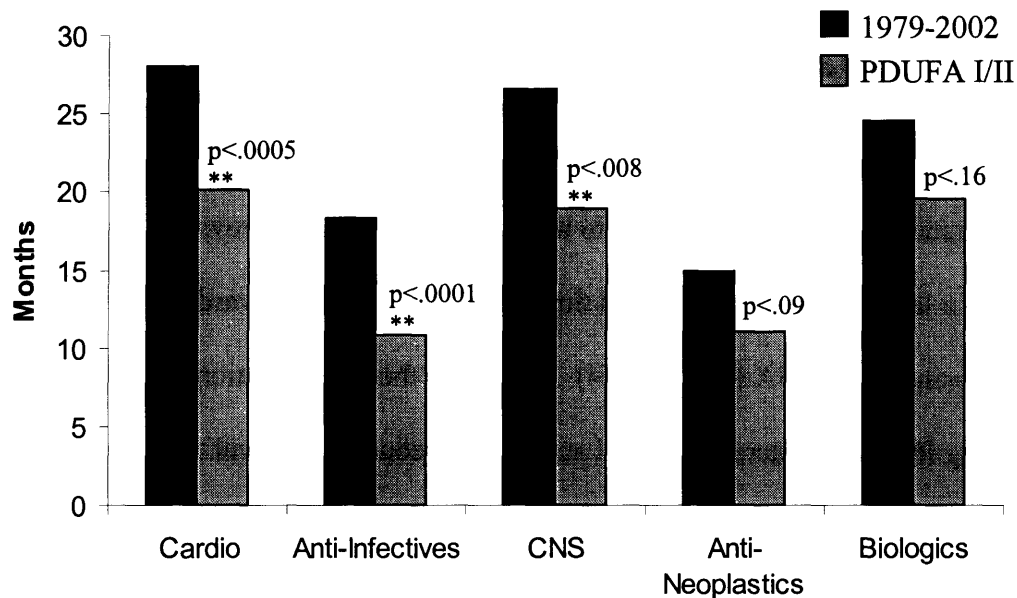


**Figure 5. Mean NDA approval times**

the mean approval times from 1979-2002 (Figure 5). Approval times during PDUFA I and II were substantially less than pre-PDUFA times. Specifically, I determined that average approval times went from 28.19 months between 1986-1992, to 18.65 months between 1992-1997

(PDUFA I) (Figure 6.). Strikingly, approval times decreased even further between 1997 and 2002 to 14.85 months.

Analysis of the drugs in specific therapeutic classes demonstrate that PDUFA I and



**Figure 6. Mean Approval Times by Therapeutic Class**

II are associated with a significant decrease in clinical approval times among cardiovascular, anti-infectives and CNS drugs (p-value = .005, .001 and .008 respectively (Figure 6).

Interestingly, the approval time for anti-neoplastics and biologics from 1979-2002 were not significantly different from the same class of drugs approved under PDUFA (p-value = .09 and .16 respectively) (Figure 6).

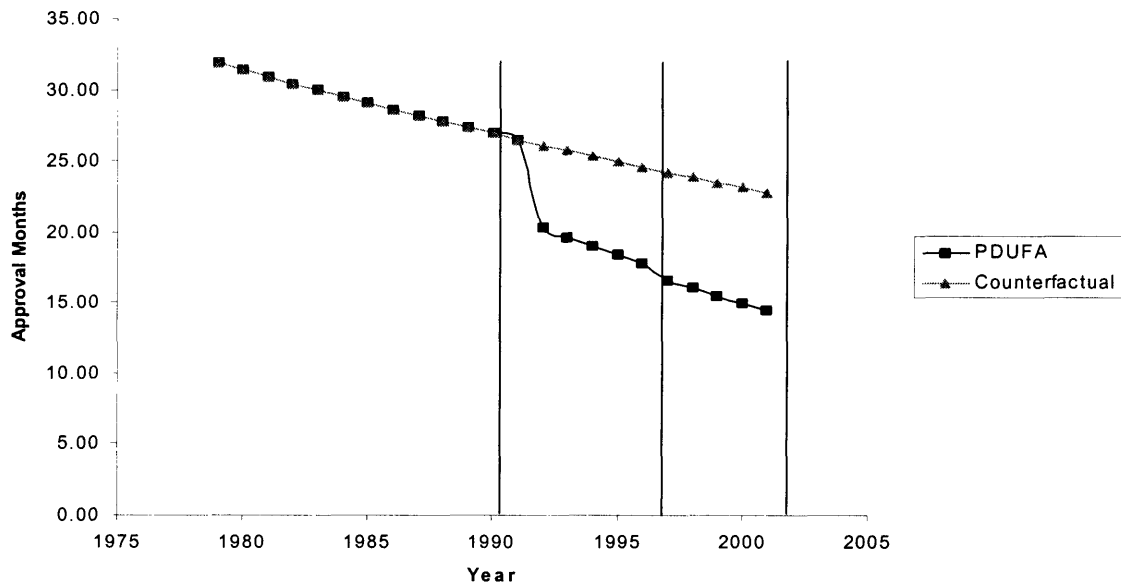
Thus, these data suggest that PDUFA I and II may have been associated with significant decreases in drug approval times. In addition, this significant decrease in approval times occurred for most therapeutic classes. Although these results are suggestive of PDUFA reducing NDA review times, additional analyses that control for potential confounding variables such as therapeutic class etc. were performed.

To evaluate the direct impact of PDUFA on drug approval times I performed multivariate linear regressions comparing PDUFA versus the counterfactual.

$$\text{Ln}(\text{time}) = \alpha + \beta_1 \cdot \text{timetrend} + \beta_2 \cdot \text{timetrend} \cdot \text{PDUFA1} + \beta_3 \cdot \text{PRIORITY} + \beta_4 \cdot \text{timetrend} \cdot \text{PDUFA2} + \beta_5 \cdot \text{FOREIGN} + \beta_6 \cdot \text{ORPHAN} + \beta_7 \cdot \text{IND-TO-NDA} + \beta_x \cdot \text{THERAPEUTIC AREA} + \text{random disturbance term}$$

**Figure 7. Multivariate Linear Regression Equation**

To assess this empirically, the parameters in the multivariate regression equation with the aforementioned explanatory variables were used (Figure 7). All of the drugs approved between October 10, 1979 and September 30, 2002 were used for this regression. PDUFA variables were



**Figure 8. PDUFA Multivariate Linear Regression**

multiplied by the time trend. Since the time trend increases this gives greater weight to the PDUFA binary variable. The therapeutic classes were evaluated at their sample means. The

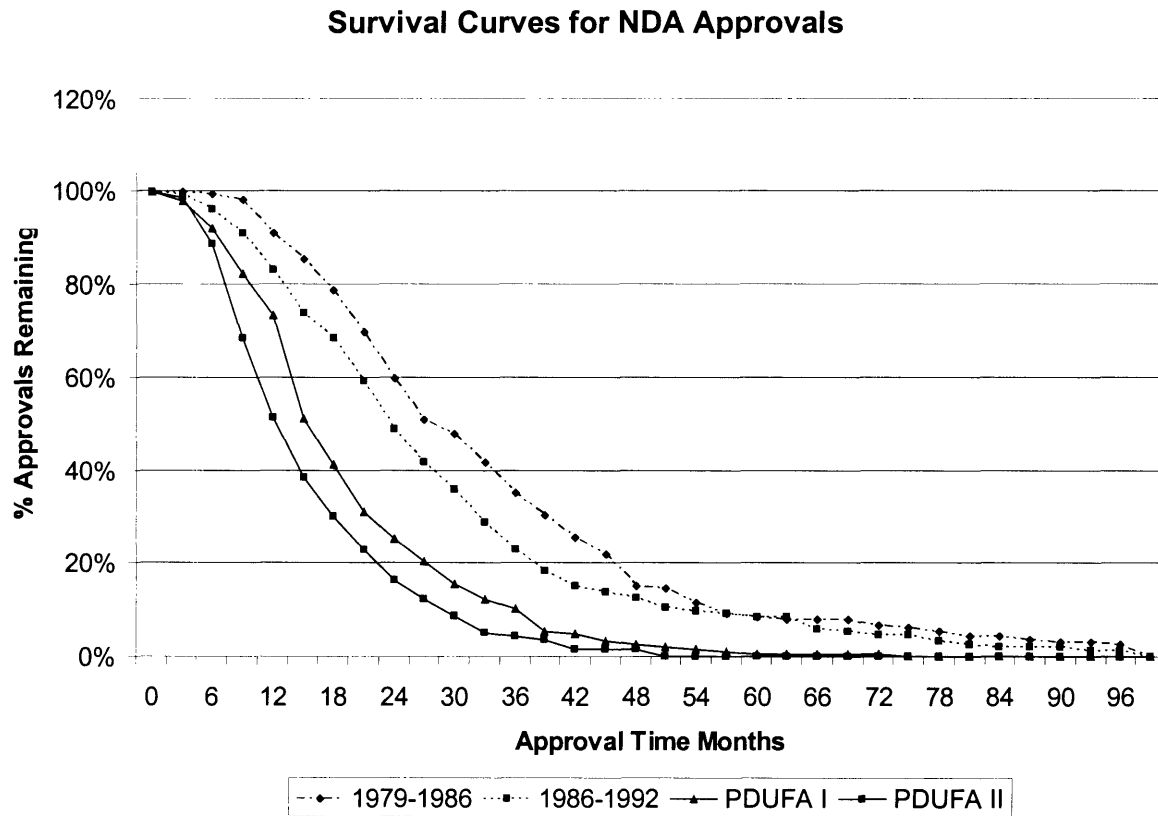
results of the regression show that PDUFA I is associated with a significant decrease (p value = .0015) in approval times relative to pre-PDUFA (Figure 8). This decrease in NDA review times occurred during 1992 and continued through 1997 when compared to the counterfactual. PDUFA II also associated with a further decrease in approval times (p value = .0013), and these results had an even larger divergence from the counterfactual (Figure 8).

In addition to PDUFA, I also determined the effect of PDUFA on the approval times of drugs that had priority status. The analysis reveals that priority review also caused a significant reduction in approval times (p value = .0001). Evaluation of orphan drug status or country where application was filed did not have a significant effect on altering approval times (p value = 0.14 and 0.27, respectively). Next, I investigated the impact of disparate therapeutic classes that were approved either under PDUFA or via standard review. Interestingly, anti-neoplastic as well as anti-infective drugs approved during this period had a significant contribution to the overall decrease in approval time relative to all other categories (p value = .001 and .009, respectively). The anti-infective drugs analyzed did not include drugs for Acquired Immunodeficiency Syndrome (AIDS). A separate analysis of AIDS drugs revealed that this class also had a significant decrease in approval time under PDUFA (p value = .0001). However, cardiovascular, central nervous system and biologics did not have a statistically significant effect on approval times (p value = .089, .417 and .0336, respectively) relative to all other classes.

In summary, this analysis reveals that both PDUFA I and II have had a significant effect on reducing approval times. Interestingly, this dramatic result was observed independent of therapeutic class. Furthermore, the priority review times implemented under PDUFA had a significant reduction in approval times. This finding supports the belief that higher priority

diseases get new drugs approved quicker. This data also supports the hypothesis, which shows PDUFA to have a major impact on expediting the review of novel therapeutics.

To display the progress that has been made since 1979, a survival curve analysis was performed. For this investigation, the number of approvals remaining were plotted out over 90+

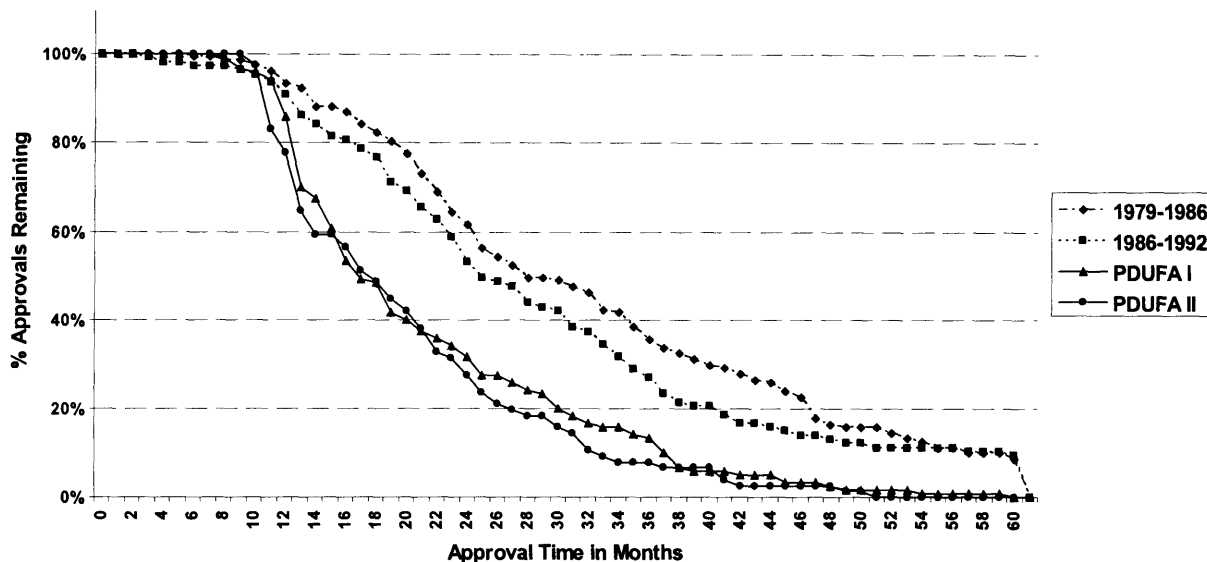


**Figure 9. Survival Analysis of NDA Approvals.**

months. The survival curve illustrates that under PDUFA I approximately 50% of drugs under review by the FDA were approved in less than 18 months (Figure 9). Strikingly, under PDUFA II, 50% of drugs were approved in less than 13 months and 90% by 30 months. These findings suggest that PDUFA I and II have helped to expedite drug approval times when compared to pre-PDUFA trends.

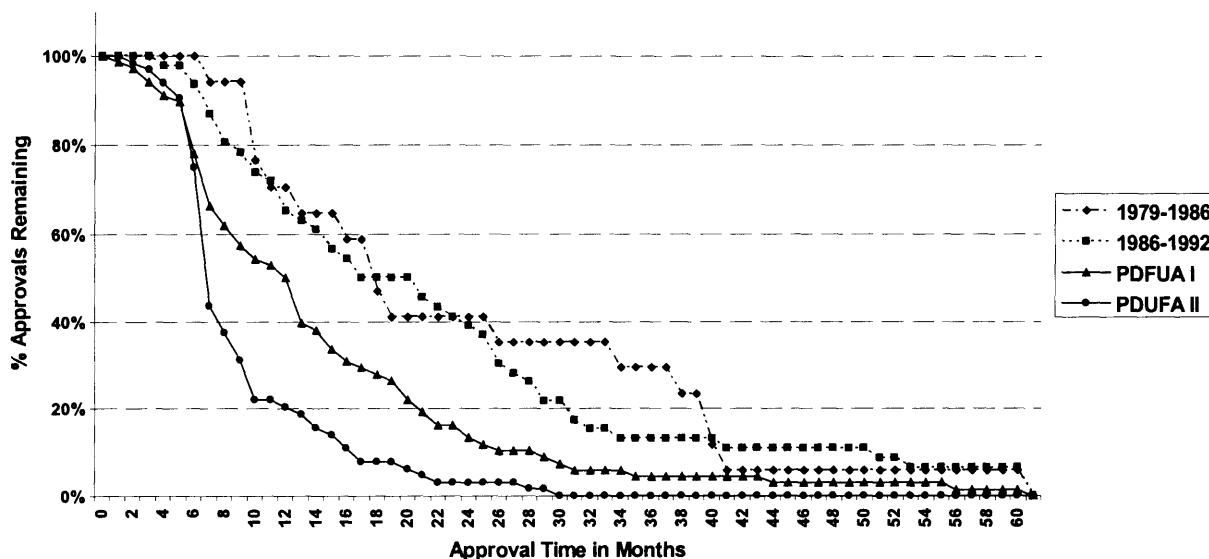
A survival analysis of drugs approved under PDUFA via standard review showed that approximately 60% of the drugs were accepted by 20 months. This was significantly less than the non-PDUFA trend, which was around 40 months (Figure 10).

**Approvals - Standard Designation**



**Figure 10. NDA Survival Analysis for Standard Approvals**

**Approvals - Priority Designation**



**Figure 11. NDA Survival Analysis for Priority Review**

These results indicate that PDUFA I and II have had a substantial impact on shortening the approval times for drugs under standard review. Next, the impact of PDUFA on drugs that had priority review was assessed. The results from this investigation revealed that 80% of drugs with priority status under PDUFA I were approved by 20 months. Consistent with the goals for PDUFA II, approximately 80% of drugs under review were approved within 10 months. When compared to the pre-PDUFA historical average for priority review (~35months) these results were quite substantial (Figure 11). In summary, these findings support PDUFA's positive role in reducing drug approval times. This data also indicates that both drugs under either standard or priority review benefited from PDUFA.

It should be noted that this analysis does not include data on drugs reviewed under PDUFA that were ultimately rejected. Data on review times from disapproved drugs may have influenced the downward trend in approval times determined for drugs approved under PDUFA. Thus, the results reported in this thesis are predicated on the assumption that disapproval rates are not changing over the different PDUFA time periods. Hopefully, in the future the FDA will reveal this information so this caveat can be addressed.

Although approving drugs more rapidly has the perceived benefit of helping patients earlier, it is still unclear as to what benefit PDUFA has had on society or on the companies developing these drugs.

## **The Commercial Benefit of PDUFA**

Since PDUFA has had a dramatic impact on reducing drug approval time, I *hypothesized* that the value of PDUFA to both the public and pharmaceutical companies exceeded its fees and

appropriations. To investigate this, I estimated the value of PDUFA to sponsors by taking the difference in the present value of sales for drugs approved under PDUFA vs. the counterfactual.

This analysis was performed on drugs grouped by therapeutic class. Since anti-infective and anti-neoplastic drugs have experienced the greatest decrease in approval times, their benefit was calculated. To do this, anti-infective and anti-neoplastic drugs were separated and sales forecasts were generated based on IMS data. Sales of the various drugs were forecasted assuming that the sales life of the drug would peak at approximately 13 years and have a sales life of approximately 15 years, due to patent life (7). Sales for drugs in these two classes were

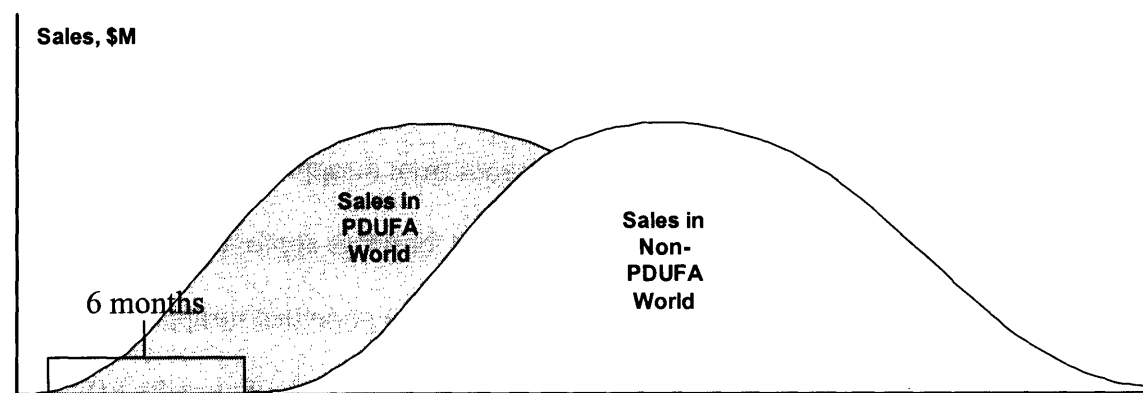


Figure 12. Regression for World +/- PDUFA

forecasted using IMS study results on the lifecycle profile of annual sales. The regression equation was modified to account for a delay in approval if PDUFA was not an option (Figure 12). This delay equated on average to approximately 6 months. Although, the anti-infective and anti-neoplastic drugs make up a small fraction of drugs approved under PDUFA, their overall significance is quite large. Since getting drugs to the market faster is inherently beneficial, the approximate value in terms of returns to pharmaceutical companies remains equivocal.

To determine the present value (PV) of sales with and without PDUFA I forecasted revenues out to year 15, adjusted for inflation and then discounted them back at a discount rate of 5%. Next, I calculated the user fees for PDUFA by assigning 100% of the establishment fee for



each drug. Additional assumptions were that each drug approved had two supplemental NDA's in year two following the initial approval.

I estimated the present value of sales for anti-infective drugs approved under PDUFA to equal \$85.3B but if the approval occurred 6 months later (i.e. without PDUFA) the PV of sales is around \$83.8B (Figure 13). The difference between PDUFA and non-PDUFA sales is approximately \$1.5B or roughly 1.8%. For anti-neoplastics, I estimated the PV of sales after

*(\$ Millions)*

<b>Anti-Infectives</b>	PV PDUFA	\$ 85,352.58	PV PDUFA FEE	FEE % of Diff.
	Counterfactual	\$ 83,860.08	\$ 83.50	5.6%
	Difference	\$ 1,492.50		
<b>Neoplastics</b>	PV PDUFA	\$ 36,103.60	PV PDUFA FEE	FEE % of Diff.
	Counterfactual	\$ 35,429.69	\$ 50.70	7.5%
	Difference	\$ 673.90		
<b>TOTAL Difference</b>		\$ 2,166.41	<b>Total fees as a % of Total Difference</b>	
<b>TOTAL Fees</b>		\$ 134.20	6.2%	
<b>NPV</b>		\$ 2,032.21		

**Figure 13. NPV Analysis of PDUFA.**

approval under PDUFA to be \$36.1B and without PDUFA to be \$35.4B, with the difference equaling \$673M or 2% (Figure 13). The PDUFA fee for anti-infective and anti-neoplastic applications were estimated to be \$83.5M and \$50.7M respectively. The differences were added to get a total of \$2.166B. To determine the Net Present Value (NPV), the total fees for PDUFA (\$134.2M) were subtracted from the total difference in PV of sales (\$2.166B). This calculation yielded an NPV of \$2.03B (Figure 13).

Next, I calculated the effects of PDUFA on the profitability of companies developing anti-infective and anti-neoplastic drugs, assuming that the ratio of i) sales, general and administrative expenses (SG&A), ii) cost of goods sold (COGS) and iii) research and

development (R&D) expenses were constant and unaffected by PDUFA. To estimate the profits, I took the PV of PDUFA sales for a specific class of drug minus the PDUFA fees minus the PV of counterfactual sales divided by the PV of the counterfactual or [profit = PV PDUFA sales – PV PDUFA fees – PV counterfactual sales / PV counterfactual]. At a 5% real discount rate, the companies that developed anti-infective drugs had a 1.68% increase in profitability due to PDUFA (Figure 14). This increase in profitability was similar to anti-neoplastics, which had a 1.76% increase in profitability (Figure 14). At a 10% real rate, these increases in the NPV of profits for anti-infective and anti-neoplastic drugs were 3.35% and 3.49% respectively. These results show that PDUFA had a positive effect on the net income earned by companies developing drugs in these two therapeutic areas.

Real Discount	Anti-Infectives	Anti-Neoplastics
1%	0.27%	0.26%
2%	0.63%	0.64%
3%	0.98%	1.02%
4%	1.33%	1.39%
5%	1.68%	1.76%
6%	2.02%	2.12%
7%	2.36%	2.47%
8%	2.69%	2.82%
9%	3.02%	3.16%
10%	3.35%	3.49%

**Figure 14. Percentage Increase in Profitability**

These data support my hypothesis for they show that the value of PDUFA has exceeded its costs and appropriations. This substantive return to industry also suggests that the public is benefiting from the approval of novel therapeutics. The PDUFA fees for anti-infective and anti-neoplastic drugs were only 6.5% of the total difference in PV of sales. This suggests that the total fees were relatively small when compared to the PV of sales.

Next, I investigated the NPV distribution across both the anti-infective and anti-neoplastic class of drugs. Interestingly, only two of the twenty-two (9%) anti-neoplastic drugs had a negative PV (Figure 15). Two of the drugs broke even after subtracting the user fees the remaining eighteen had positive present values. The chemotherapeutic Eloxatin had the highest present value of \$297M (Figure 15). Analysis of the NPV distribution for anti-infective drugs

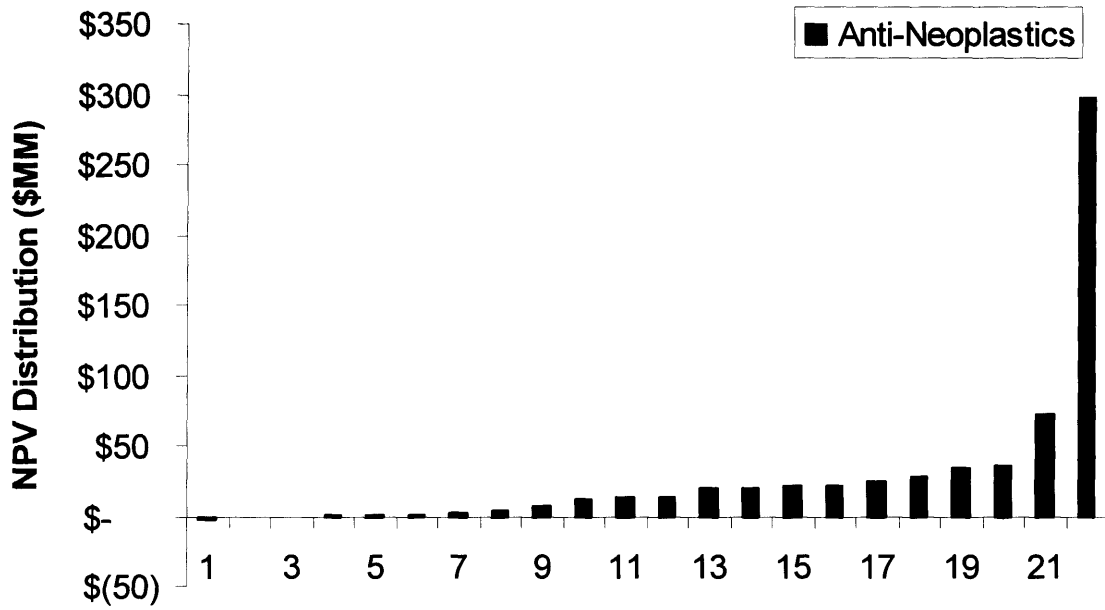


Figure 15. NPV Distribution for Anti-Neoplastic Drugs

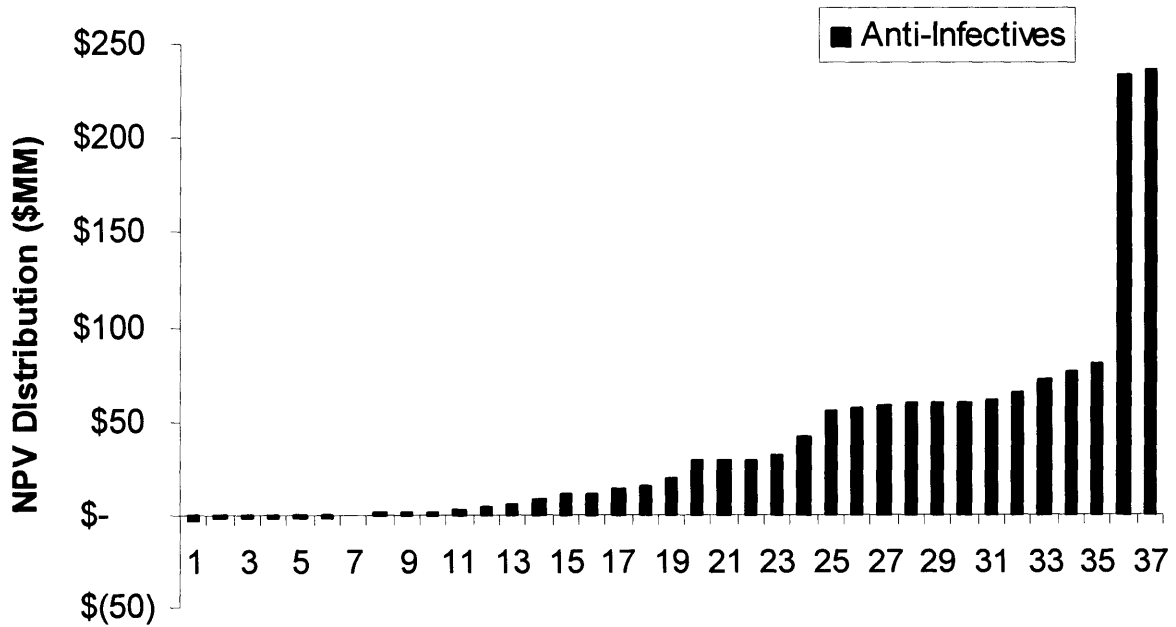


Figure 16. NPV Distribution for Anti-Infective Drugs

revealed that seven out of the thirty-seven drugs (18%) did not recoup their fees (Figure 16).

The anti-infective, Trovan, had the highest present value of \$236M.

In addition to anti-infective and anti-neoplastic therapies, the NPV benefits of drugs in other therapeutic classes were investigated. Interestingly, I found that the distribution across other therapeutic areas (e.g. cardiovascular, CNS...) were positive. In fact, if cardiovascular and CNS drugs were included with the anti-infective and anti-neoplastic drugs the benefit would total approximately \$7B (see Adrian Gottschalk's thesis, HST '04, *Improving the Efficiency of the Later stages of the Drug Development Process: Survey Results from the Industry, Academia and the FDA*). Hence, companies developing drugs in these therapeutic areas recouped their PDUFA user fee costs and this expense only represented 6.2% of the total difference. Thus, PDUFA has provided a substantial return to companies while providing the public with new drugs faster.

To determine if drugs getting to market faster were having an adverse effect on patient safety, a number of studies have investigated withdrawal rates for all drugs pre and post PDUFA. A report by the General Accounting Office (GAO) evaluated the rate of safety withdrawals

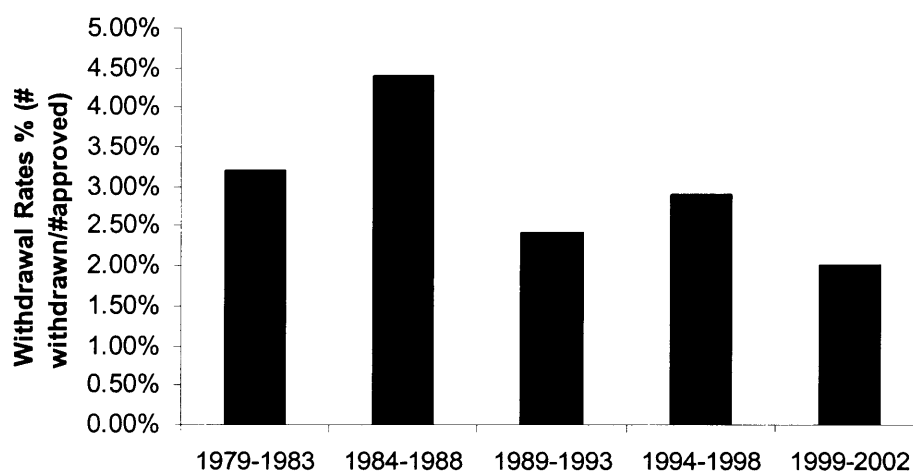


Figure 17. Safety Withdrawal Rates (7)

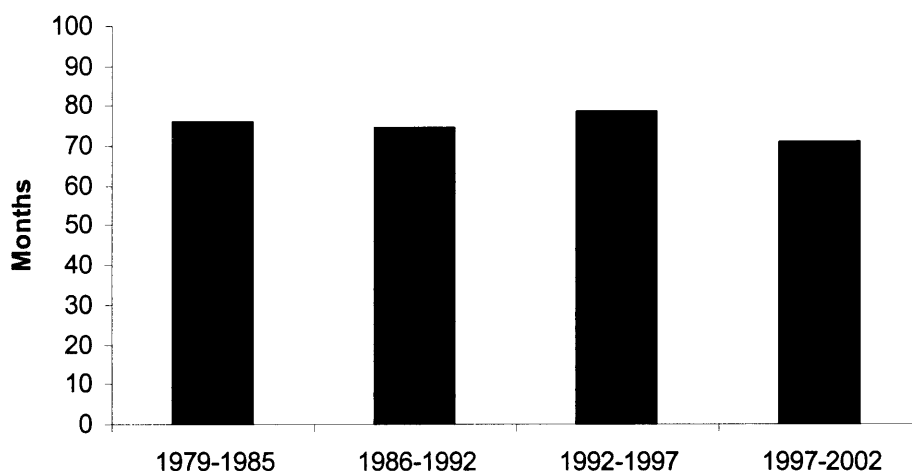
between 1985-1992 (pre-PDUFA) and 1992-2000 (post-PDUFA) (32,7). The report found that six of the one hundred ninety three (3.1%) NME's approved between 1985 and 1992 were withdrawn (See Appendix, Figure 40). From 1992-2002, nine out of the two hundred and fifty nine (3.47%) NME's approved eventually were pulled from the market. This analysis suggests that there may be a slight increase (.37%) in the withdrawal rates during PDUFA years.

However, GAO analysis is flawed since it does not take into account drugs withdrawn that were specifically reviewed under PDUFA guidelines. An analysis by the FDA demonstrated that at four-year intervals from 1979, the FDA withdrawal rates are decreasing (Figure 17) (7). In summary, the data suggests that despite PDUFA significantly reducing drug approval times it apparently has not had an adverse effect on patient safety. In fact, the benefit as determined by the NPV analysis suggests that patients as well as companies have significantly benefited from the enactment of PDUFA.

## **Reducing Clinical Development Time**

Despite the drop in NDA approval times over the last decade, there has been no material change in the clinical development time or more specifically the time between when an IND is filed to the submission of the NDA (Figure 18) (4). This clinical phase on average takes 6.2 years and has a relatively low (approximately 25-35%) chance of success (Figure 2). Since a drug in development spends approximately 77% of its time in clinical testing, it is important to try to identify steps that can shorten this timeframe. The clinical phase consists mainly of human drug trials that are often difficult to run and require large numbers of patients, particularly in

their final stages. The planning, design and initiation of these various clinical trials are well established and many large companies have regulatory departments solely dedicated to managing



**Figure 18. Months from IND to NDA (1979-2002)**

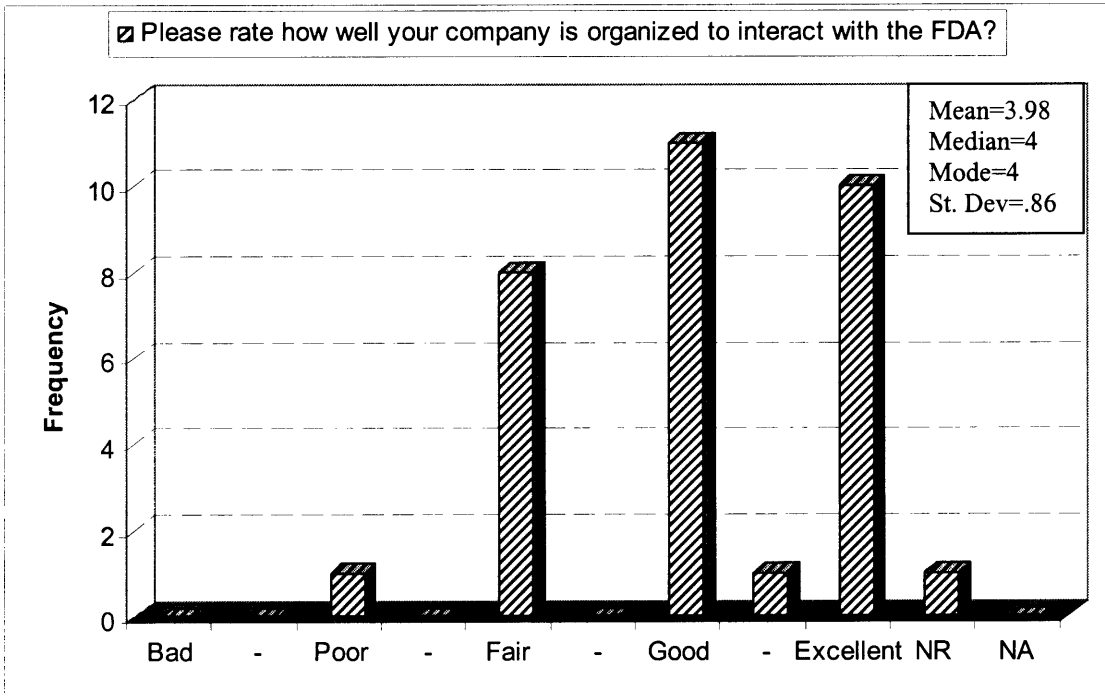
this side of the business. Over the last few years, certain FDA mandated provisions such as “fast track” status have provided select companies with the ability to have more frequent interaction with the FDA during clinical studies (33). Despite this, no other major changes have been initiated to enhance communication or facilitate clinical development. Therefore, I *hypothesized* that communication between the FDA and industry during the early stages of drug development (i.e. pre-clinical, Phase I and Phase II) viewed from an industry perspective is inadequate. In addition, I hypothesized that companies would be willing to pay for more communication with the FDA during these stages, with the hope of reducing drug development times.

To investigate ways in which the industry and FDA can work collectively to expedite drug development, together with Mr. Adrian Gottschalk and Professor Ernst Berndt, I interviewed regulatory personnel from biotechnology and pharmaceutical companies as well as contract research organizations. Between January 6<sup>th</sup>, 2004 and April 23<sup>rd</sup>, 2004, we interviewed fifty people from seventeen companies (three CRO’s, seven biotechnology and seven

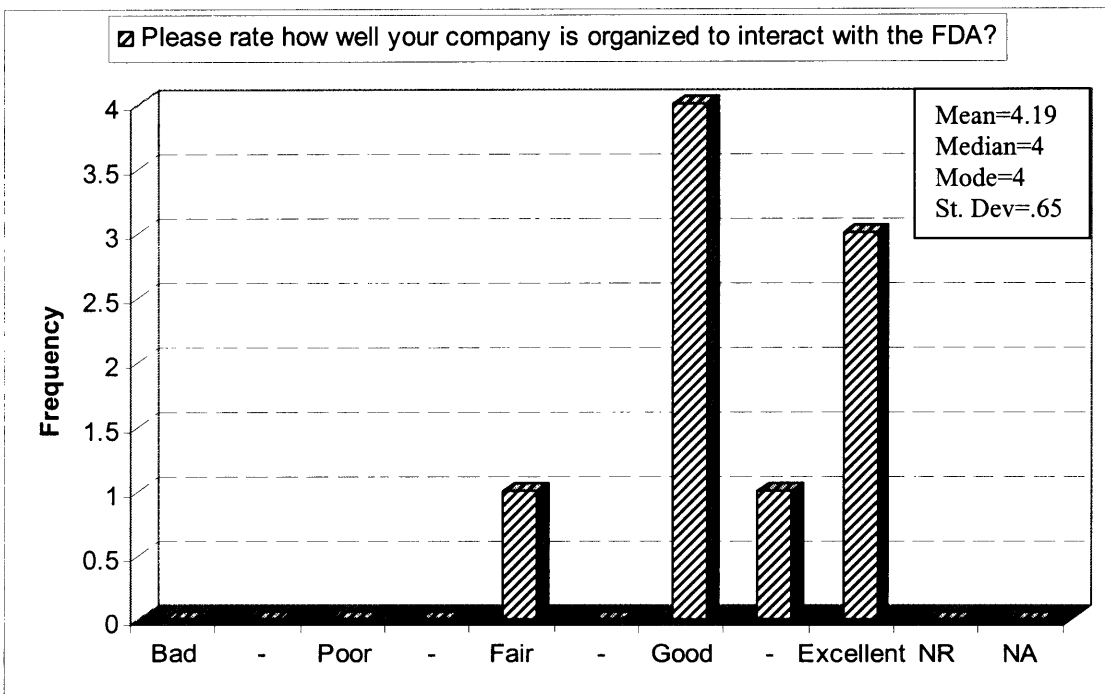
pharmaceutical companies). The breakdown and positions of the personnel interviewed were twenty two from biotech (seven global heads, three executive vice presidents, nine vice presidents three directors), twenty two from pharma (four global heads, nine executive vice presidents, seven vice presidents, two directors), and six from CRO's (two executive vice presidents, two vice presidents, two directors). For the interviews, I assembled both a qualitative as well as a quantitative questionnaire (Appendix: Figure 38). These questionnaires were designed to examine the relationship between the FDA and industry focusing on critical issues such as communication, trial designs, use of biomarkers, information gathering technology etc..

In order to better understand the critical issues around communication between industry and the FDA, the interviewer first asked the study participants how well their company is organized to interact with the FDA. The scale used for this question was 1=bad, 2=poor, 3=fair, 4=good, 5=excellent and N/R= no response. The frequency of the response was plotted on the y-axis and the responses on the x-axis. The hash marks on the x-axis represent those interviewed personnel who answered between the choices given on the form (i.e. between good (4) and excellent (5) = 4.5). The results of this question revealed that both pharmaceutical and biotechnology companies felt good on average (mean = 3.98) about how well their company is organized to interact with the FDA (Figure 19). Interestingly, biotechnology companies on average felt better than pharmaceutical companies about how well they are organized to interact with the FDA, as evidenced by a mean of 4.2 for biotechnology and 3.8 for pharmaceutical companies (p value = 0.123)(Figures 20 and 21). These results suggest that both pharmaceutical and biotechnology companies have carefully organized their regulatory group to interact with the FDA.

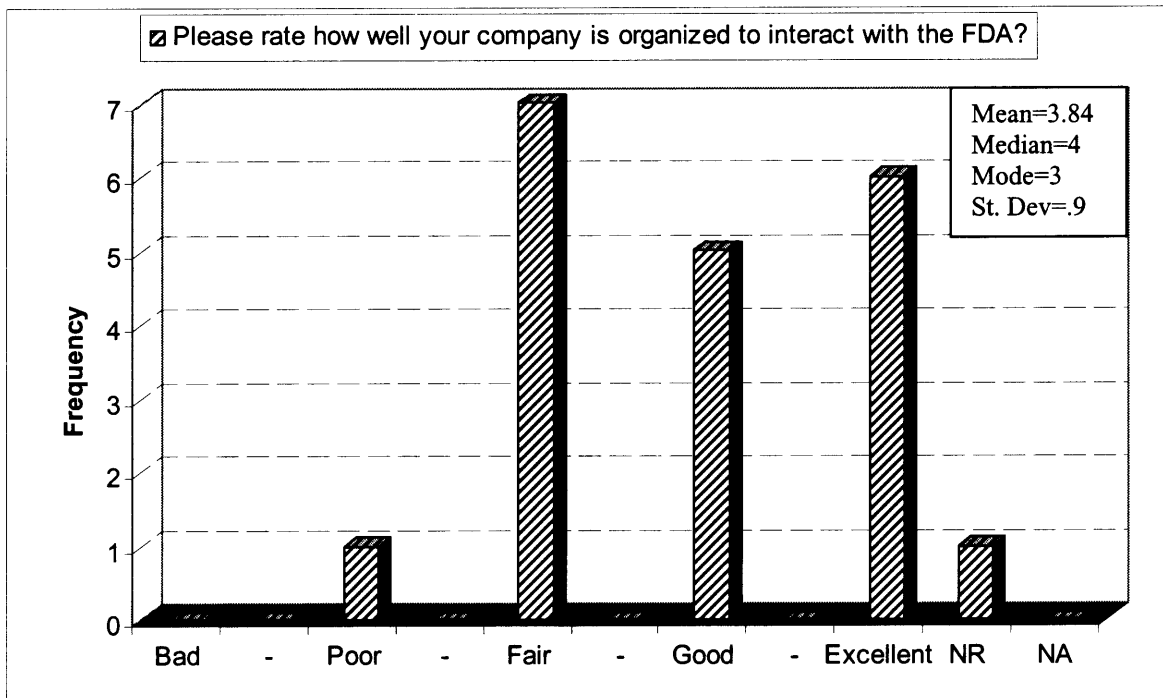




**Figure 19. Both Pharmaceutical and Biotechnology Companies: Interaction**



**Figure 20. Biotechnology Companies: Interaction**

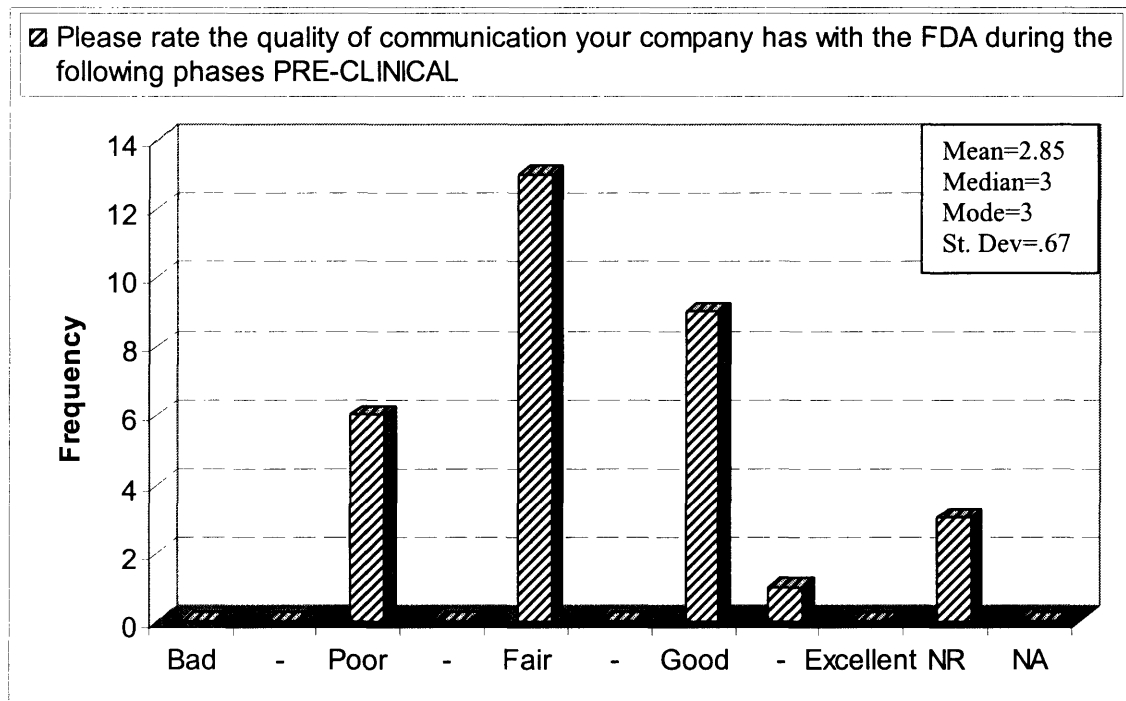


**Figure 21. Pharmaceutical Companies: Interaction**

From the qualitative analysis, I gleaned that the ability of a company to effectively interact with the FDA is vital to the development of their therapeutics. In fact, some of the regulatory groups that we talked with actually recruited folks away from the FDA in order to manage this interaction. In addition, some examples of disorganization were described by interviewers that led to months/years delay of a therapeutic. Thus, companies recognize the value of having the ability to effectively interact with the FDA.

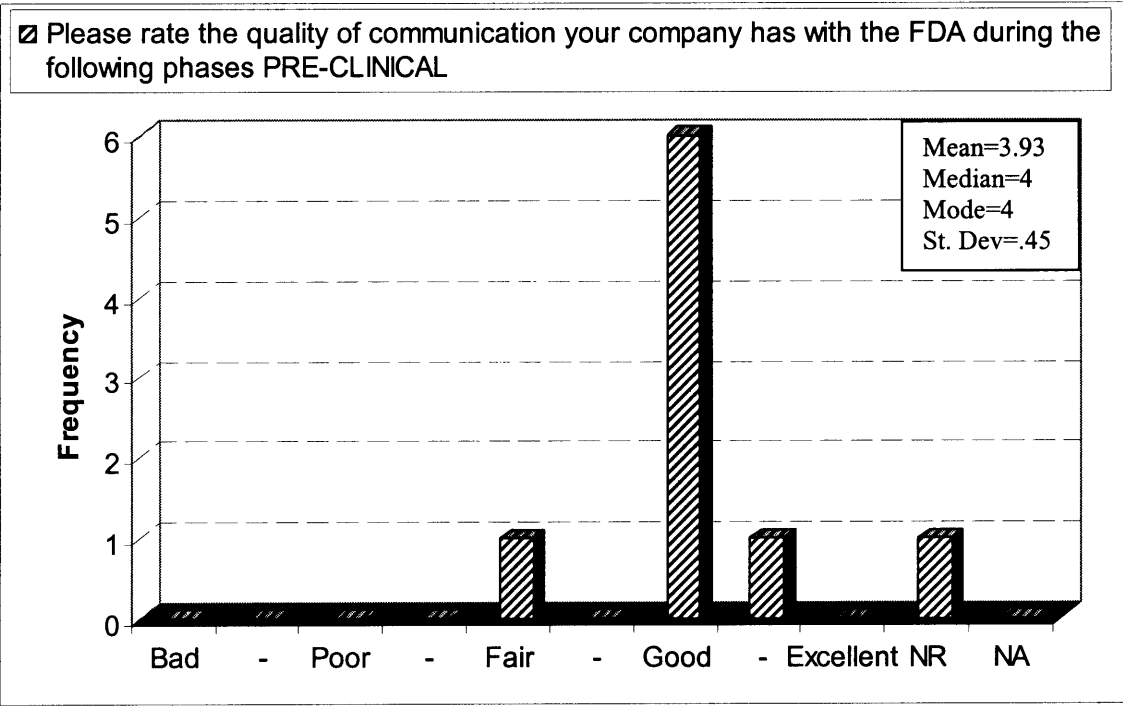
Next, the quality of communication between industry and the FDA during pre-clinical, Phase I and Phase III was investigated. Specifically we asked both pharmaceutical and biotechnology companies to rate the quality of communication they have with the FDA during these early stages. The same rating scale (1=bad, 2=poor, 3=fair, 4=good, 5=excellent and N/R=

no response) was used. During pre-clinical studies, both pharmaceutical and biotechnology companies believe on average that the quality of communication with the FDA was fair (mean =

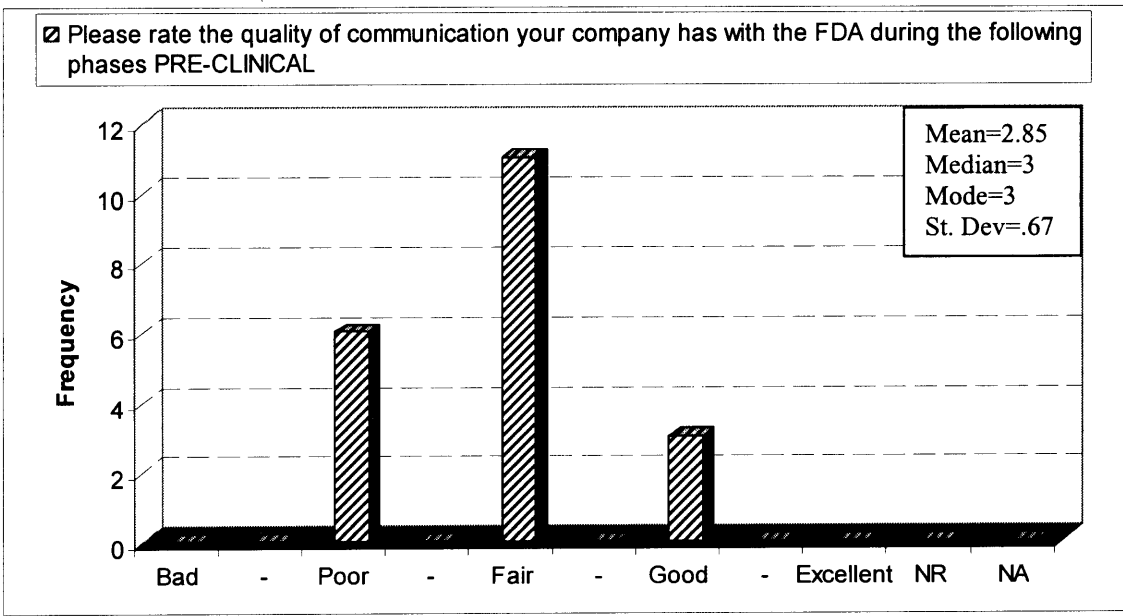


**Figure 22. Both Biotechnology and Pharmaceutical Companies: Quality of Communication**

2.85). Interestingly, biotech companies believed that on average (mean = 3.93) that they had good quality communication with the FDA during pre-clinical studies. This was in contrast to pharmaceutical companies who believed on average (mean = 2.85) that their interaction was poor to fair (p value = <.0001) (Figures 23 and 24).

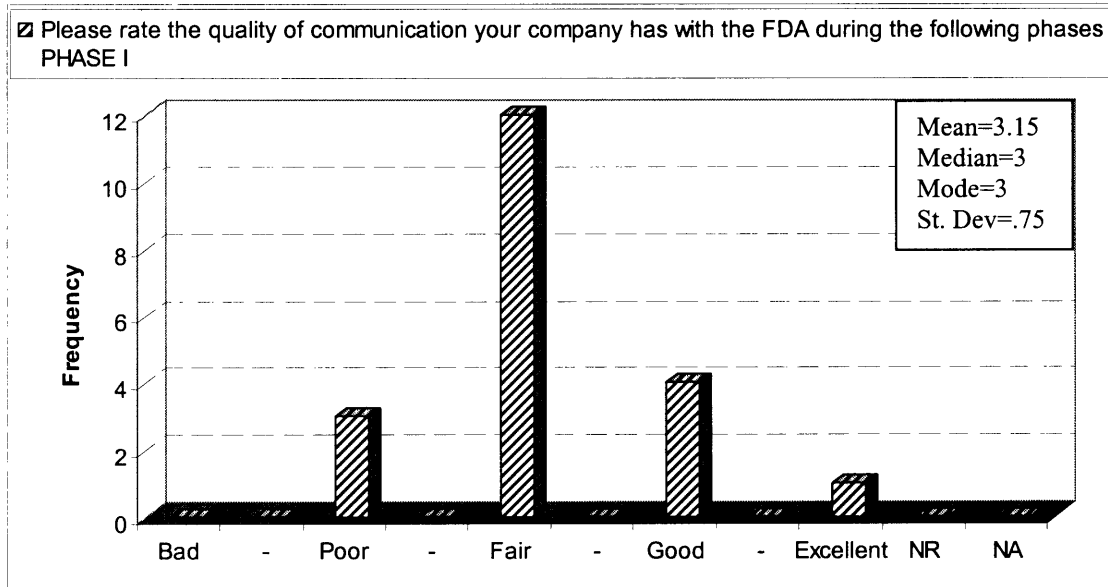


**Figure 23. Biotechnology Companies: Quality of Communication Pre-Clinical**

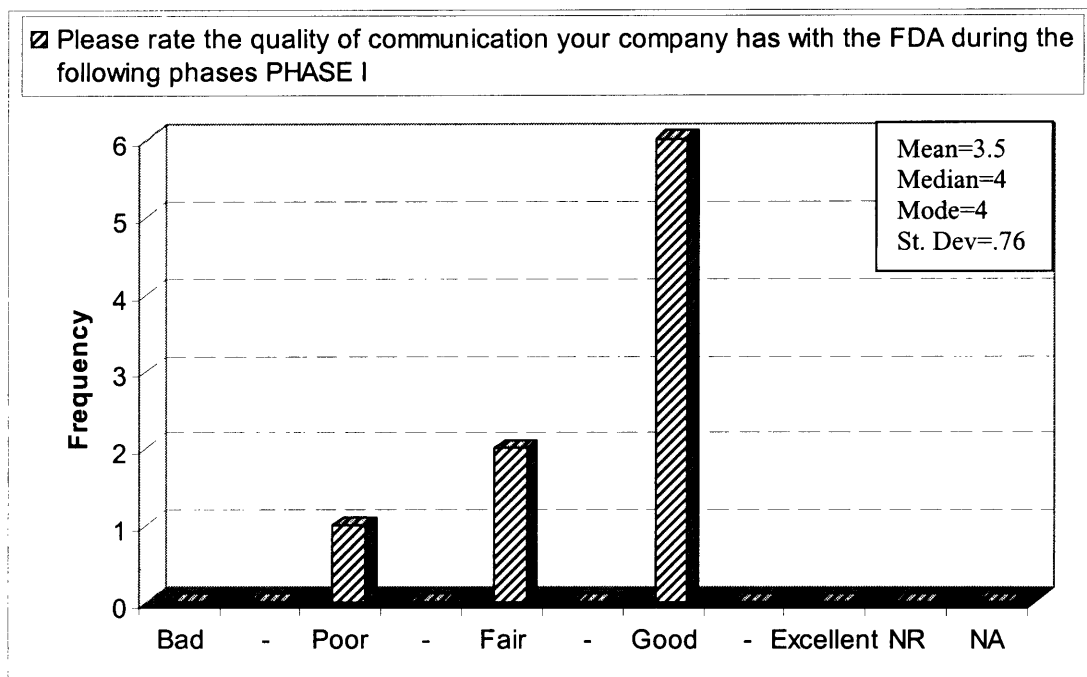


**Figure 24. Pharmaceutical Companies: Quality of Communication Pre-Clinical**

Next, the quality of communication in Phase I was evaluated. Pharmaceutical companies felt on average that the quality of communication during Phase I is fair (mean = 3.15)(Figure 25). However, biotechnology companies rated the quality of communication during Phase I to be



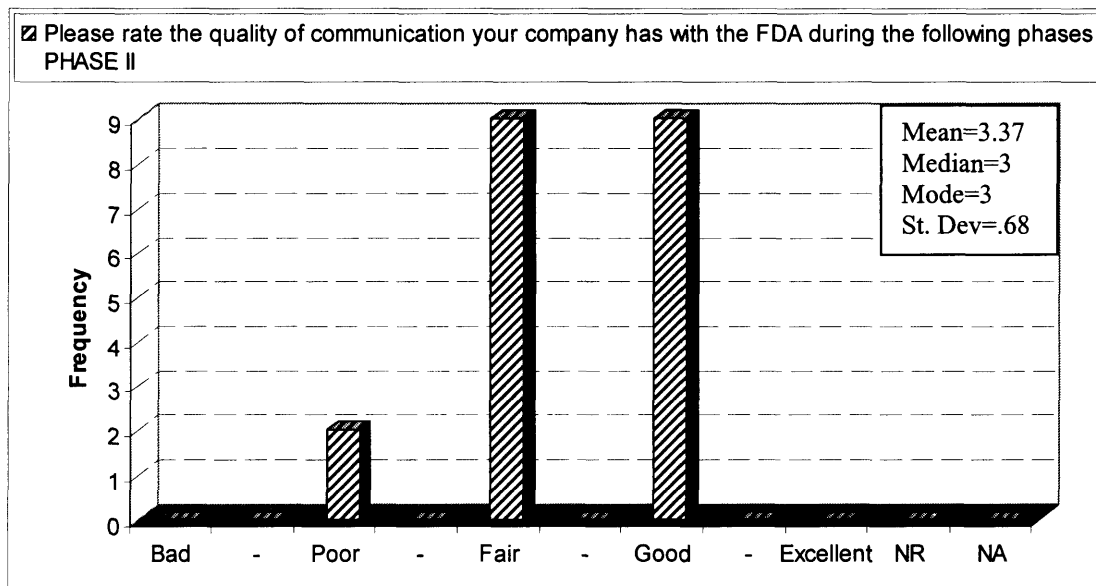
**Figure 25. Pharmaceutical Companies: Quality of Communication Phase I**



**Figure 26. Biotechnology Companies: Quality of Communication Phase I**

generally good (mean = 4.0) (Figure 26). These results for biotechnology companies were significantly different from pharmaceutical companies (p value = .038).

Next, the quality of communication during Phase II was assessed. Both pharmaceutical and biotechnology companies believed that communication during Phase II was on average between fair and good (mean = 3.37) (Figure 27). This result was consistent when both types of

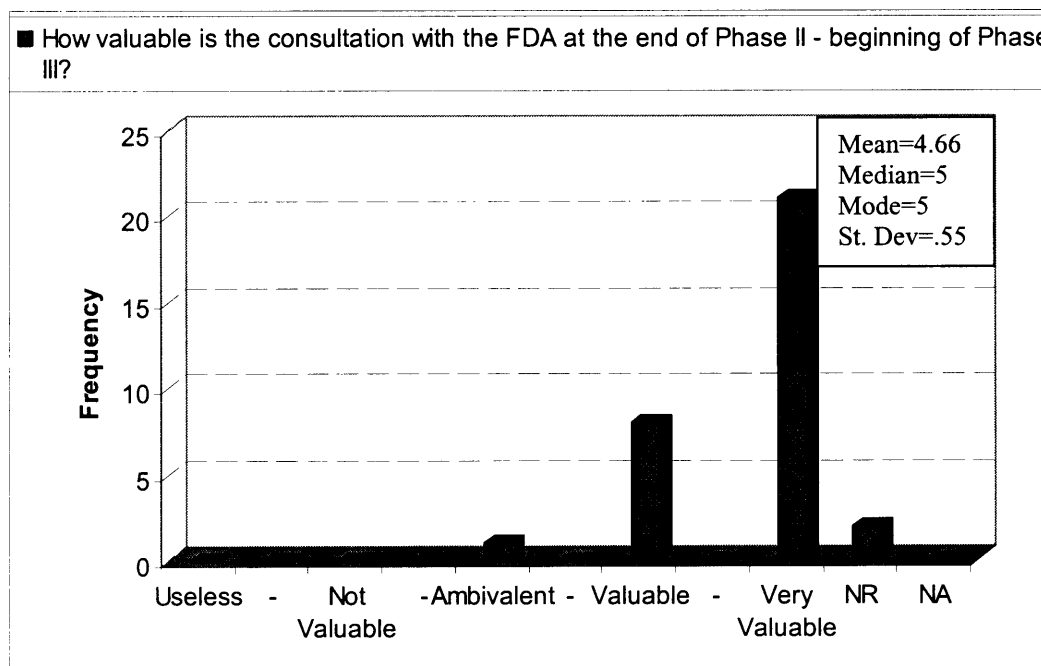


**Figure 27. Pharmaceutical and Biotechnology Companies: Quality of Communication Phase II**

companies were looked at individually (data not shown).

The results from this question indicate that biotechnology companies perceive they have better quality communication with the FDA during earlier stages of clinical development (pre-clinical and Phase I) than is perceived by pharmaceutical companies. However, during Phase II trials the quality of communication for both types of companies was gleaned to be between fair and good. This result is surprising since Phase II trials are more complicated and generally more critical than the earlier phases.

To examine the importance of communication after Phase II trials, companies were asked to rate the value of the consultation at the end of this phase. The rating scale used for this question was; 1=useless, 2=not valuable, 3=ambivalent, 4=valuable, 5=very valuable and N/R=no response. The results of the analysis revealed that on average both biotechnology and



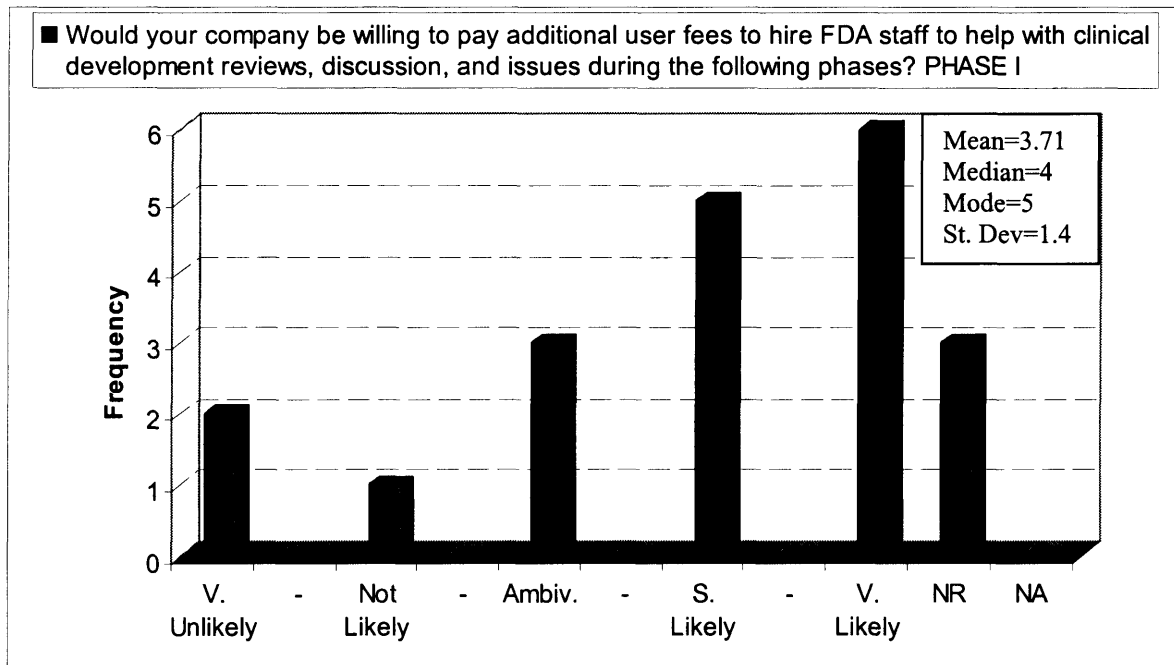
**Figure 28. Pharmaceutical and Biotechnology Companies: Value of End of Phase II Meeting**

pharmaceutical companies believe that the value of the consultation at the end of Phase II prior to phase III is very valuable (mean = 4.66) (Figure 28).

Thus, both pharmaceutical and biotechnology companies find the end of Phase II meeting to be very valuable; however, the quality of the interaction during this Phase is on average fair. These findings suggest that there are opportunities for the FDA and industry to engage in higher quality communication during this key phase. Based on the impact of PDUFA in reducing drug approval time, instituting a user fee program analogous to PDUFA for early clinical studies may

be useful. If a user fee program was enacted, not for profit organizations should be exempt from having to pay the FDA.

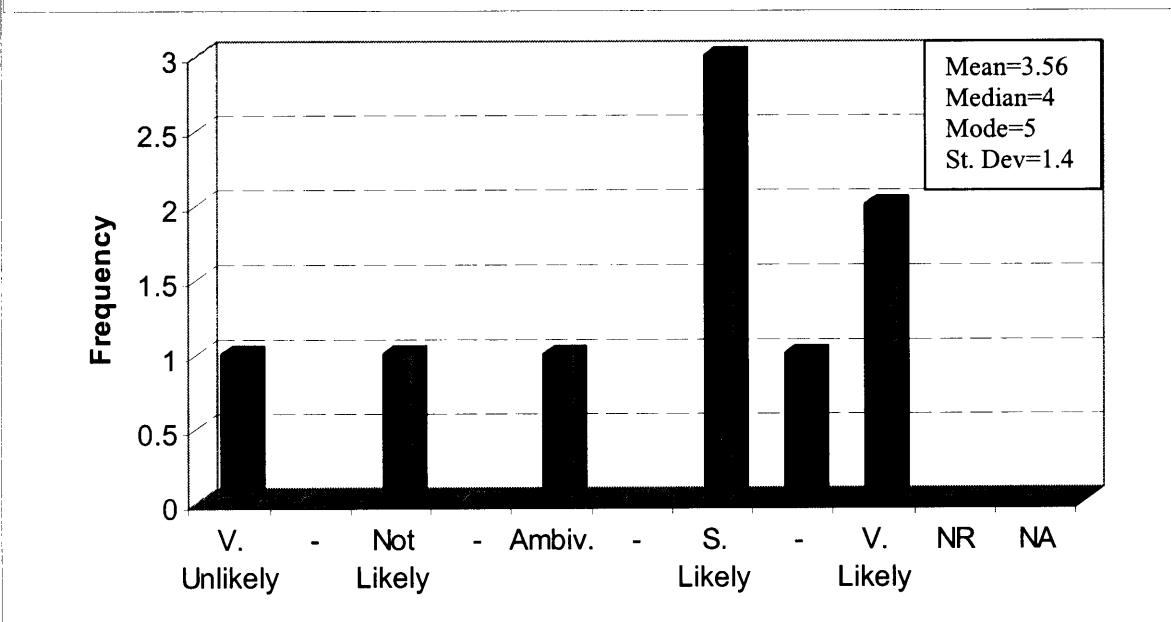
Since the lack of quality communication with the FDA is a concern among biotechnology and pharmaceutical companies, I investigated whether these companies would be willing to pay more for communication with the FDA during Phase I and II to help with clinical development reviews, and discussion on various regulatory issues. Due to the importance of these early clinical studies, it was hypothesized that companies would be willing to pay for more communication with the FDA.



**Figure 29. Pharmaceutical Companies: Phase I User Fees**



■ 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



**Figure 30. Biotechnology Companies: Phase I User Fees**

The rating scale used for this question was 1 = very unlikely, 2 = not likely, 3 = ambivalent, 4 = somewhat likely, 5 = very likely and N/R = no response. The analysis revealed that during Phase I, pharmaceutical companies would be somewhat likely (mean = 3.71) to pay user fees for more communication with the FDA (Figure 29). These results were similar to biotechnology companies who also believed on average (mean = 3.56) they were somewhat likely to pay additional user fees for more communication during Phase I (Figure 30).

The same question of paying additional fees for more communication was asked in regards to Phase II. Both pharmaceutical and biotechnology companies responded similarly in that they would be somewhat likely to pay user fees for more phase II interactions (mean = 3.88 and 3.81, respectively) (p value = 0.62). These findings suggest that industry believes more communication with the FDA is important and that they would be willing to pay for it.

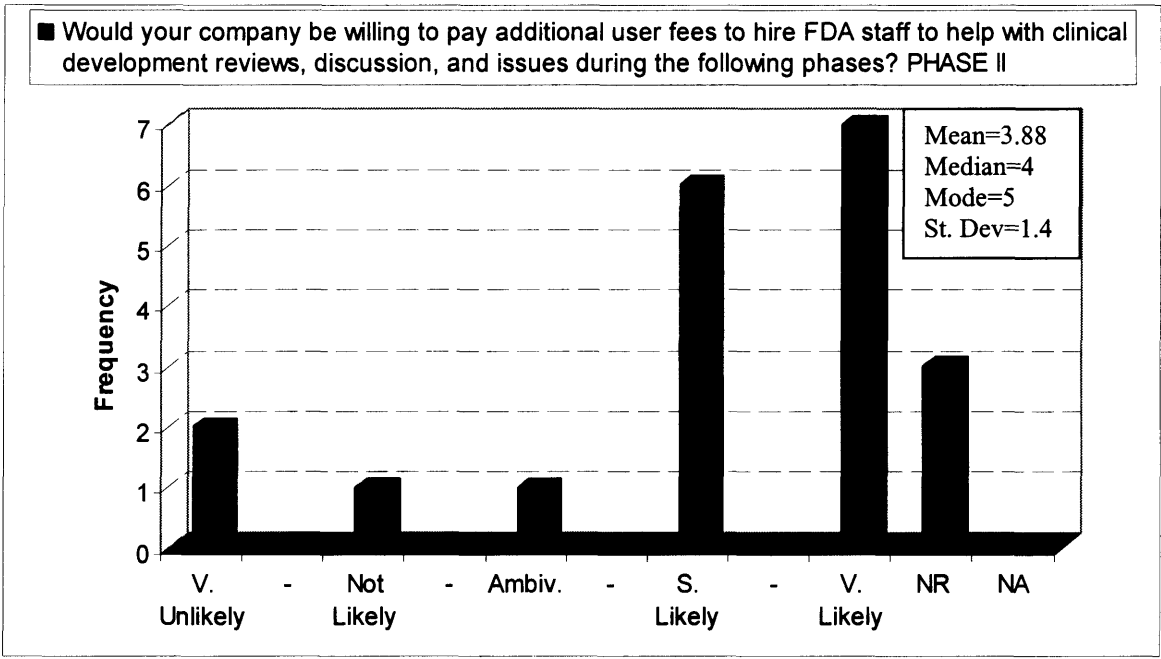


Figure 31. Pharmaceutical Companies: Phase II User Fees

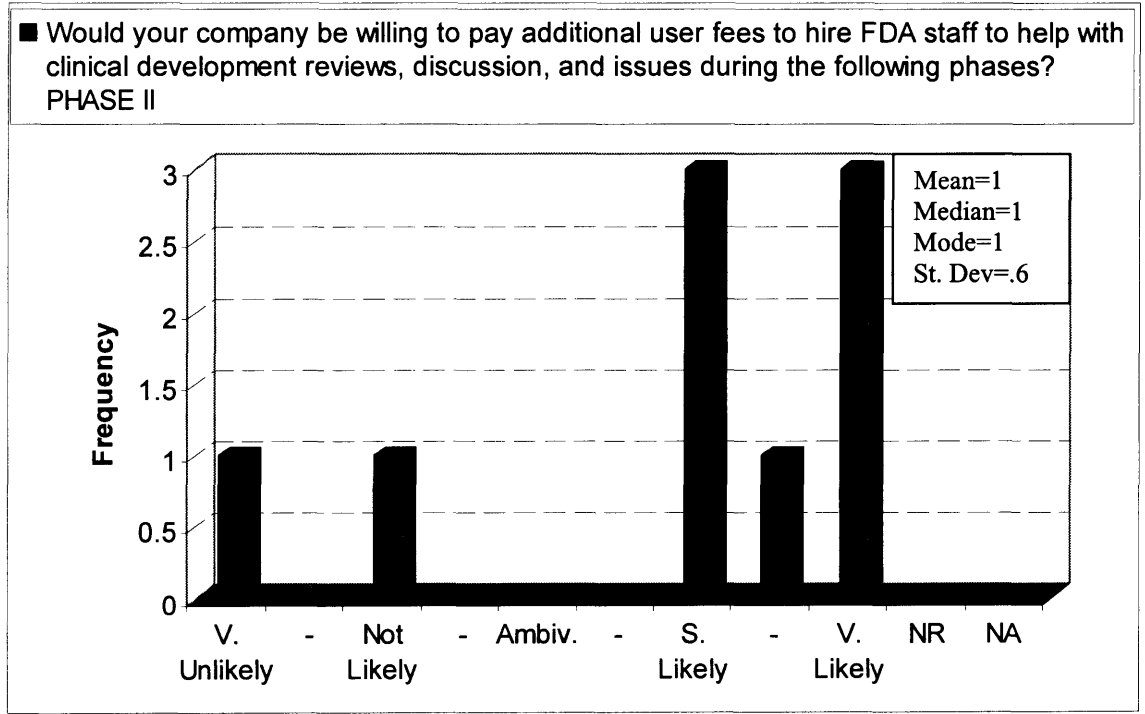
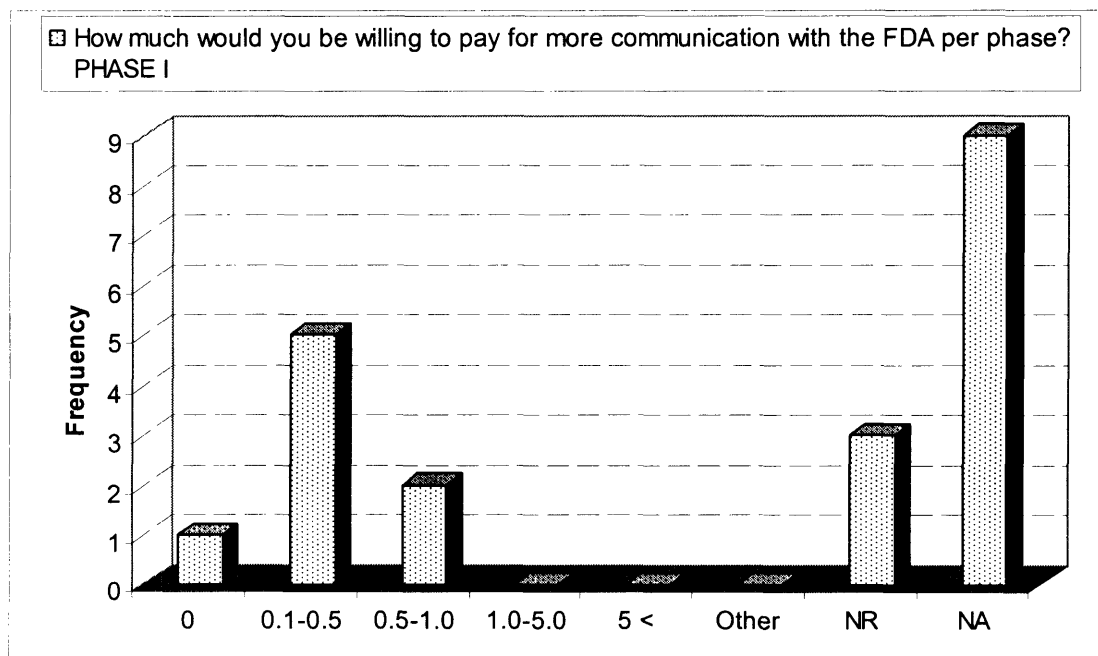


Figure 32. Biotechnology Companies: Phase II User Fees

Since both pharmaceutical and biotechnology companies are somewhat likely to pay for more communication during Phase I and II, I wanted to quantify this by determining how much they would be willing to pay. For this question we gave the options of paying \$100K-500K, \$500K-1M, \$1M-5M, >5M, were given per drug. To determine the descriptive statistics for the various ranges, I used the following key: \$100K-500K = 1, \$500K-1M = 2, \$1M-5M = 3, >5M = 4, or other = 5, NA = test not administered and NR = no response. Of the pharmaceutical companies that responded, on average most were willing to pay between \$100K to \$500K for more communication with the FDA during Phase I (mean = 1)(Figure 33). Of the biotechnology companies surveyed, most would be willing to pay \$100,000 to \$500,000 for more interaction with the FDA during Phase I (mean = 1)(p-value = 1)(Figure 34). The finding that pharmaceutical companies would be willing to pay the same as biotech companies is somewhat surprising since the pharmaceutical companies we interviewed had more financial resources than the biotechs (Figure 34). Regardless, both pharmaceutical and biotechnology companies on



**Figure 33. Pharmaceutical Companies: Projected Phase I User Fees**

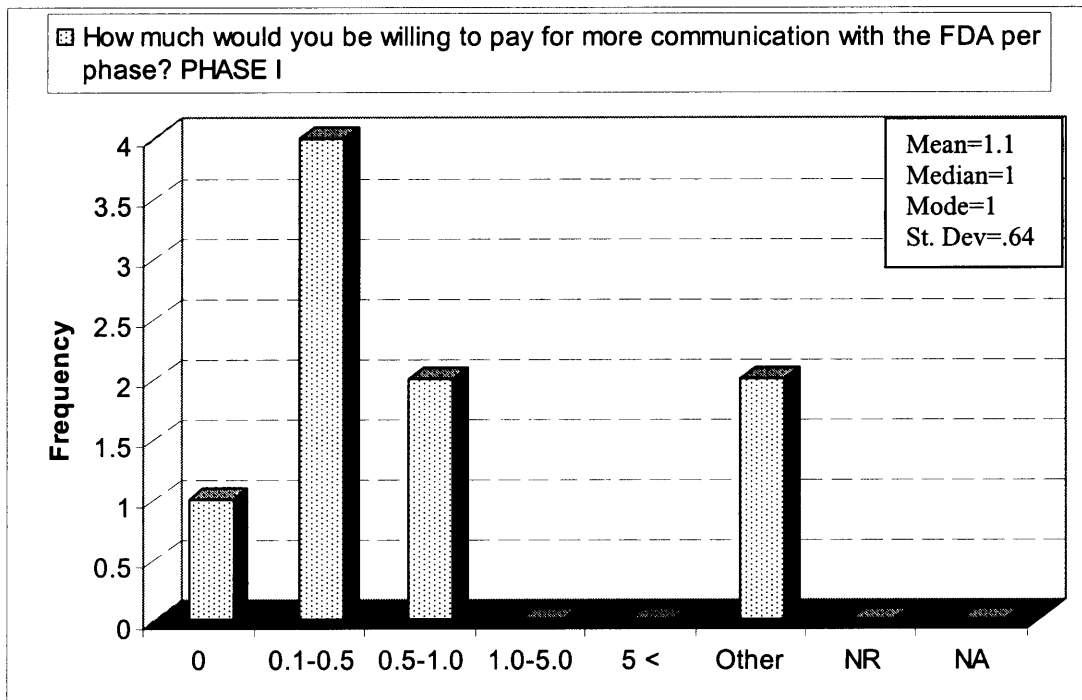


Figure 34. Biotechnology Companies: Projected Phase I User Fees

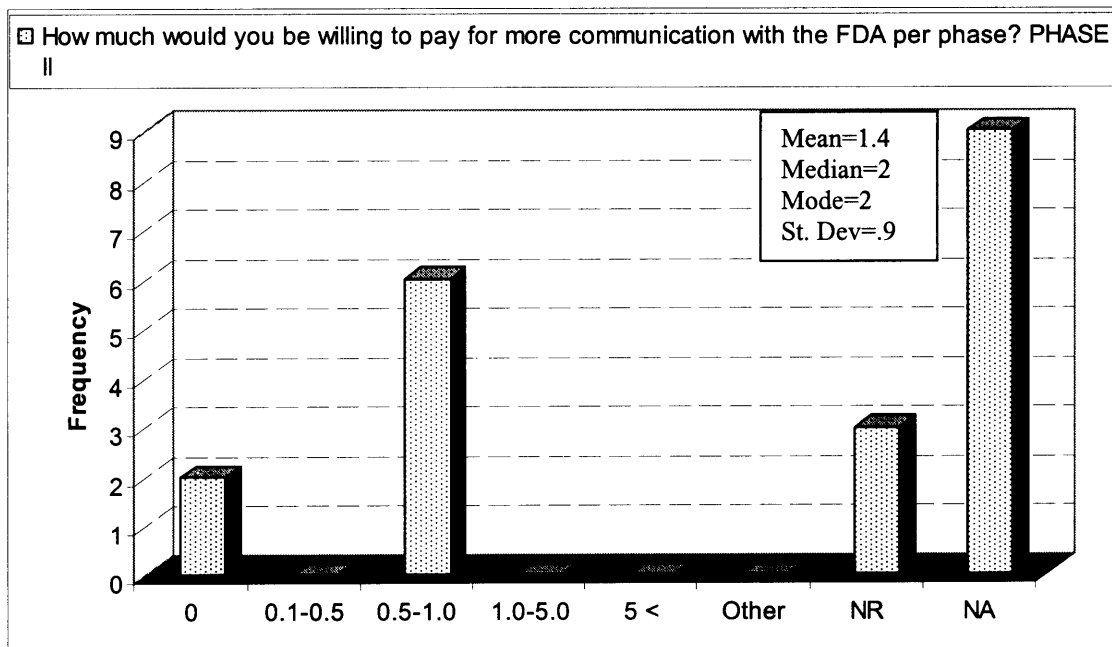


Figure 35. Pharmaceutical Companies: Projected Phase II User Fees

average believed that it was important to have more communication with the FDA and were willing to pay for it.

Next, I investigated how much companies would be willing to pay for more communication during Phase II trials. Of the pharmaceutical companies that responded to this question, half were willing to pay user fees between \$100K-500K for more communication with the FDA (Figure 35). Interestingly, the response from biotechnology companies was similar to pharmaceutical companies since greater than half of the personnel interviewed would be willing to pay between \$100-500K for more interaction (Figure 36).

From this analysis, I determined that pharmaceutical and biotechnology companies were somewhat likely to pay for more communication with the FDA during both Phase I and II trials. In addition, half the personnel interviewed from both types of companies would be willing to

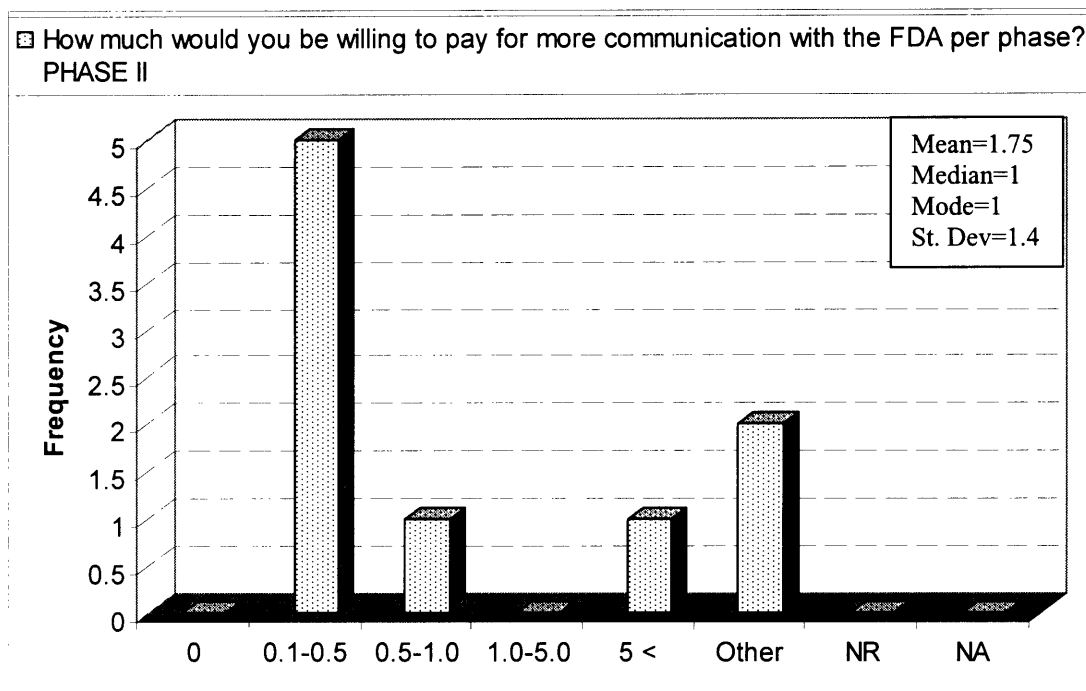


Figure 36. Biotechnology Companies: Projected Phase II User Fees

pay (\$100-500K) for more interaction in both Phase I and Phase II trials. These findings underscore the perceived importance of communication with the FDA during these early clinical Phases. These results also suggest that companies believe enhanced communication with the FDA would be useful in facilitating drug development.

In summary, this study revealed that both biotechnology and pharmaceutical companies currently believe interactions with the FDA in the early phases of clinical development is inadequate. These companies suggested in the interviews that more interaction would help expedite the development of their novel therapeutics and possibly increase the probability of clinical success. This is supported by the finding that companies would be willing to pay for more interaction during pre-clinical, Phase I and Phase II. Both biotechnology and pharmaceutical companies were willing to pay for more communication. The personnel from both types of companies were willing to pay similar ranges of fees. This result was surprising since the combined market capitalization for the biotechnology companies interviewed was \$137B versus the \$857B combined market cap for the pharmaceutical companies (determined in April 2004). In addition, the personnel interviewed believed that the precedent established by PDUFA would give them more confidence in paying additional user fees to the FDA for more communication.

# Chapter IV

## Discussion

The drug development process is long, costly and in some cases antiquated. Since there are many people in the world that need new medicines, it is important to try and reduce the time a drug spends in development without compromising safety.

The enactment of PDUFA in 1992 and its re-enactment in 1997 have had a substantial impact reducing drug approval times. In fact, the average time a drug spends in review has dropped by almost 50% since 1991. This reduction in approval time not only helps patients get novel drugs quicker, it also sparks innovation due to the incentives created by getting a drug to market earlier. Specifically, PDUFA has enhanced the returns to biotechnology and pharmaceutical companies as evidenced by the \$2B realized in net present value of sales for just the anti-infective and anti-neoplastic drugs. The net present value of sales gained for cardiovascular and CNS drugs approved six months earlier due to PDUFA is about \$5.6B. Thus, for anti-infective, anti-neoplastic, cardiovascular and CNS drugs, the total benefit of PDUFA is approximately \$7.5B (see Adrian Gottschalk's thesis, *HST '04, Improving the Efficiency of the Later stages of the Drug Development Process: Survey Results from the Industry, Academia and the FDA*). These findings indicate that companies are greatly benefiting from PDUFA. In addition, these findings suggest that companies now have more funds to invest in the research and development of new drugs. Studies performed by the FDA reveal that faster drug approval times have not resulted in a higher rate of drug withdrawals. In the future, it will be important for this Act to continue to improve drug approval times while maintaining its strong safety record. In summary, PDUFA I and II have had a significant impact on reducing drug approval times while increasing financial

returns to industry. The success of PDUFA I and II has set the standard for future acts that may be targeted to shorten drug development.

The time a drug spends in clinical development has not changed over the last fifteen years. The reason why this stage of drug development has not been altered is due to the regulations that require a thorough evaluation of a drug. Due to the importance of getting investigational drugs through the clinic faster, I investigated how the FDA and industry can work together to reduce the clinical testing of a drug. The results of this analysis revealed that industry strongly seeks more communication with the FDA through all phases of clinical development. Both pharmaceutical and biotechnology companies generally believed that more interaction with the FDA would reduce uncertainty around clinical trials and help to provide a clear path to approval. The personnel interviewed at both biotechnology and pharmaceutical companies believe that if the FDA was more open to communication over the design and analysis of a trial their probability of success would likely improve.

From the various interviews, I learned that communication during the early stages of clinical development is key to the successful development of a drug. I observed that companies often design and implement pre-clinical and clinical studies without any feedback from the FDA. As result, good products fail in clinical tests or are slowed in development due to regulatory concerns that could have been addressed before the initiation of the trial. During pre-clinical testing, poor communication has often resulted in: i) using wrong animal models for toxicology studies, ii) not perform Qt prolongation tests, which the FDA uses as a surrogate for cardio-toxicity, and iii) design improper dosing regimens. Many companies also expressed that a pre-IND meeting focused on toxicology would be very useful.



Both biotechnology and pharmaceutical companies that we interviewed wanted to have the opportunity to get approval from the FDA over clinical study designs. The FDA created the special protocols assessment (SPA) provision so that companies could get a binding agreement over their Phase III trial study design. Several of the companies interviewed have used SPA; however, many wanted a similar provision for earlier clinical phases. Companies felt that if they were able to work more closely with the FDA over the development of their product they would have a higher likelihood of success in the clinic.

FDA reviewer turnover was another concern expressed by industry. Specifically, when the medical reviewer who had been working on a drug left, the quality and timeliness of the review was often adversely impacted. However, some companies thought that this problem could be mitigated if communication between the company and FDA personnel were enhanced. Specifically, it was expressed that more communication and transparency would have given the companies the ability to educate the reviewer on the science behind the drug and current regulatory strategies.

Currently, industry has multiple points of interaction during pre-clinical, Phase I, Phase II and Phase III with the FDA (Figure 42). However, the companies interviewed for this project generally believe they needed more interaction during each of the early clinical phases. The importance of more communication was underscored by the observation that both biotechnology and pharmaceutical companies were willing to pay the FDA a user fee for additional interaction. These results suggest that biotechnology and pharmaceutical companies perceive that existing points of interaction are not sufficient. However, it should also be noted that all of the companies highly valued their existing communication with the agency and wanted more of it.

Another suggestion raised by disparate interviewees was to allow the FDA to share their knowledge of clinical trial failures. Many companies felt that the FDA should have the authority to use their experience with previous clinical failures in order to help prevent new medicines from suffering the same demise. Currently, the FDA cannot share information about the clinical tests performed by other companies. As a result, valuable information about past studies cannot be used to help evaluate the testing of new drugs. This idea supports the general notion that the FDA should have more of a collaborative relationship with industry but still preserve confidentiality.

Recently, an initiative by the FDA called “the critical path” was created to help determine ways in which drug development could be expedited (34). This initiative is focused on identifying and exploiting new technologies that can be used to facilitate the successful pre-clinical and clinical development of a therapy. Some of these technologies evaluated in the critical path initiative include the use of imaging, molecular markers, animal models and computer simulation (34). This effort by the FDA is important since it will help define the role of new technology in drug development, which could result in quicker clinical trials. This thesis complements the critical path initiative since it is focused on trying to identify ways in which the FDA and industry can work together to expedite drug development.

The FDA has made significant progress in reducing drug approval times. To help meet the growing demand for new drugs, the FDA and industry will need to work together on all aspects of drug development. If the clinical phase of drug development could be reduced over the next ten years, analogous to the drop in approval times, the impact on patients, doctors and industry would be very significant. Thus, the findings outlined in this thesis could ultimately help the FDA and industry work together to improve the development of novel therapies.

# Chapter V

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# Chapter VI

## Appendix

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	

**Figure 37. PDUFA I, II, III Goals**

**Qualitative Questionnaire**

**Company:**

\_\_\_\_\_

Location: \_\_\_\_\_

Date: \_\_\_\_\_

Start Time: \_\_\_\_\_

End Time: \_\_\_\_\_

Total Length of Interview (hrs, minutes): \_\_\_\_\_

Interviewees (First Name, Last Name, Title, Other Info):

\_\_\_\_\_ Business Card

\_\_\_\_\_ Business Card

\_\_\_\_\_ Business Card

\_\_\_\_\_ Business Card

\_\_\_\_\_ Business Card

Interviewers:       Berndt               Gottschalk               Strobeck

Other Contact Information:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

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

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Other Comments on Interview Setting, Interviewee Demeanor & Attitude

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

***Introduce Investigators:***

***Informed Consent and Confidentiality Statement:***

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

***Purpose and Procedure Statement:***

- Conducting semi-structured interviews with major biotechnology, pharmaceutical companies, and contract research organizations to:
  - Investigate best practices and challenges from Pre-Clinical to NDA submission
  - Commissioner McClellan has asked us to provide him feedback from the companies as to what can be done to improve the process without compromising patient safety and welfare
  - Interview will start with some preliminary background questions for you
  - We will ask a series of questions that ask you to rank your answer. This should take about five to ten minutes.
  - We will then ask some quantitative questions regarding drug development.
  - Finally, we will ask a combination of open ended and specific questions on the various Phases of development.
  - We will attempt to get specific examples and information on your company's interactions with the FDA. When possible, please use explicit examples to help us understand the issues.
- Your candid responses are very important to us.
- Please keep in mind that all of this information is strictly confidential and that any data presented to the FDA or journals will be scrubbed of your company name, individuals, product names, and any other labels that could identify you or your company

***General Definitions Given:***

- ***Drugs:*** small molecules and biologics
- ***Phases:*** Pre-Clinical, IND, Phase I, Phase II, Phase III, NDA/BLA, Phase IV



## **Individual Background and Experience**

1. Please describe your role and responsibilities with [insert company name].
2. How long have you been involved with the regulatory process?
3. In what portions of the clinical development process are you most involved?
4. On which therapeutic areas do you focus?
5. What is your perception of Commissioner McClellan's impact at the FDA?
6. What recent changes at the FDA could or have had the most significant impact on your company?

### **General Background on Company and Clinical Trial Process:**

7. How is your company organized to interact with the FDA? (Excellent, Good, Fair, Poor, Bad)
8. How many regulatory department FTE's are employed by your company?
9. What is your company's core competency in dealing with the FDA?
10. What is your company's most significant weakness in dealing with the FDA?
11. How does your company delineate between pre-clinical, IND, Phase I, Phase II, and Phase III?
12. Do your company's Phase I/II/III trials for a drug proceed sequentially or do the trials overlap? If they overlap, please describe how this works for your company.
13. How many NDA/BLA's has your company filed in the last five years? Could you please name them.
14. For each of the NDA/BLA's filed, did your company use Contract Research Organizations and other consultants to help design clinical trials for the drug?
15. For each of the NDA/BLA's filed, did your company use Contract Research Organizations and other consultants to run clinical trials?
16. Does your company collaborate with other drug development companies? What have these experiences been like? Does your company generally lead the interactions with the FDA?
17. In what major therapeutic areas does the company have significant experience?
18. Are you familiar with the Prescription Drug User Fee Acts (PDUFA)? *If NO then explain PDUFA, else* What is your impression of the appropriateness of the user fees associated with the NDA process?
19. Do you feel that the PDUFA acts have had a positive impact for your company? (Excellent, Good, Fair, Poor, Bad)
20. Would your company be willing to pay additional user fees to hire FDA staff to help with clinical development reviews, discussion, and issues? For which Phases in particular would you be willing to pay?

21. Where does your company spend most of its funds and time during the drug development process?
22. Roughly what proportion is spent in pre-clinical, Phase I, Phase II, Phase III, and NDA/BLA?
23. Have you been able to give adequate feedback to the FDA regarding clinical trials, processes, and reviewers in any manner in the past?
24. If you were at the FDA, what changes would you advocate to improve communications between drug development sponsors and FDA reviewers/personnel?

**Pre-Clinical:**

25. Is there much interaction with the FDA during pre-clinical development?
26. Would you want more/less interaction with the FDA at this point?
27. To what extent are you using imaging in pre-clinical work?
28. How current are the requirements that the FDA accepts in regards to data from animal models and other pre-clinical indicators?
29. How might protocols be improved during the pre-clinical Phase?
30. How might communication with the FDA be improved during the pre-clinical Phase?
31. Do you file any pre-clinical information electronically?
32. What else would you like to add in regards to the pre-clinical Phase interactions with the FDA?

**Phase I/II Clinical Trials:**

33. Please describe your interactions with the FDA during Phase I/II trials
34. What are the greatest challenges in Phase I/II development in regards to the FDA?
35. Has your company used imaging in Phase I/II trials? In what manner?
36. What, if any, changes at the FDA have helped your company during Phase I/II development?
37. What changes within your company have affected your company during Phase I/II development?
38. What changes at the FDA have affected your company during Phase I/II development?
39. What is the role of information technology in Phase I/II trials at your company and at the FDA? Are the IT systems beneficial or are they burdensome?
40. Does the FDA have any specific IT solutions in place to help during Phase I/II?
41. What procedures would you change internally to ensure better success with Phase I/II trials?
42. In retrospect, how well did the Phase II dosing studies compare to the pre-clinical work? Overall, how predictive and useful were the Pre-clinical studies in decision making in Phase I and Phase II?

43. What would be the top 5 areas/issues that cause delays in Phase I/II? Please describe per area the difficulties you have encountered in dealing with the FDA and/or internally.
44. What has been your experience with surrogate markers in clinical trials? What is your perspective on their use in Phase I/II? What guidelines would you like to see from the FDA?
45. What, if any, new technologies and tools would you like to use for conducting Phase I and Phase II trials?
46. What procedures and protocols could be improved during the Phase I/II Phases?
47. How might communication with the FDA be improved during the Phase I/II Phase?
48. How valuable is the consultation with the FDA at the end of Phase II – beginning of Phase III? (Very Valuable, Valuable, Ambivalent, Not Valuable, Useless) How would you improve this process?

### **Phase III Clinical Trials:**

49. Please describe your interactions with the FDA during Phase III trials
50. In how many Phase III's has your company participated in the last 3 to 5 years?
51. What do you estimate the total development cost for Phase III alone is?
52. How have FDA policies and procedures influenced these costs?
53. Do you believe that sample sizes in Phase III have been over inflated as a result of FDA requirements or are they a function of the competitor drugs in the therapeutic area?
54. Have you considered biostatistical methods to reduce sample size?
55. Why are there so many Phase III failures given the positive results in Phase II trials? Which of the following issues, if any, are implicated in this result: Patient selection issues in Phase II; Enrollment of patients; Dosing study issues; Physician experience; Inexperienced CRO team?
56. What are the greatest challenges in Phase III development in regards to the FDA?
57. How do you decide which studies to perform in the US versus abroad?
58. Do you believe that there are adequate guidelines for conducting trials overseas?
59. In which countries would you prefer to conduct clinical trials?
60. Is the FDA mandating more post-approval studies for your company? Are any of these required for initial approval? Do you have a sense for the relative costs of these studies to Phase III trials? Would you potentially have run these studies without the FDA request?
61. What is the role of IT in post-approval studies? Have you seen any use of retrospective insurance claims data to track adverse events and issues?
62. Do you believe it is possible and beneficial to shift costs from Phase III to Phase IV post approval studies?
63. Has your company used imaging in Phase III trials? In what manner?

64. What, if any, changes at the FDA have affected your company during Phase III development?
65. What changes within your company have affected your company during Phase III development?
66. What is the role of information technology in Phase III trials?
67. Does the FDA have any specific IT solutions in place to help during Phase III?
68. What procedures would you change internally to ensure better success with Phase III trials?
69. What do you wish the FDA did differently during Phase III trials?
70. What would be the top 5 areas/issues that cause delays in Phase III? Please describe per area the difficulties you have encountered in dealing with the FDA and/or internally.
71. What has been your experience with surrogate markers in clinical trials? What is your perspective on their use in Phase III?
72. Have manufacturing issues impacted the duration and cost of Phase III trials for your company?

**Miscellaneous Other Questions:**

73. If you were designing the FDA de novo, what would be the most fundamental differences from what it is today?
74. Do you believe that the FDA is effective at keeping unsafe drugs off the market?
75. What is your perspective on the FDA's risk/benefit analysis?
76. How would you rate your company's interactions in regards to quality relative to your competitors?
77. How competent would you say the FDA reviewers are in understanding your drug applications? (Excellent, Good, Fair, Poor, Bad) Are they sufficiently trained and motivated?
78. What else would you like to add in regards to the clinical trials process?
79. Electronic filing?
80. Do you have any questions for us?
81. Please feel free to contact any of us with additional comments or observations. They will be treated confidentially.

**Figure 38. Qualitative Questionnaire**

## All Therapeutic Areas with AIDS Separated

10/01/1979 to 09/30/2002

### Regression Statistics

Multiple R	0.621453557
R Square	0.386204523
Adjusted R Square	0.373638632
Standard Error	0.575384282
Observations	649

	Coefficients	Standard Error	t Stat	P-value
Intercept	3.4047	0.1273	26.7429	0.0000000
LNINDNDAMONTHS	0.0247	0.0239	1.0338	0.3016293
TIMETREND	-0.0154	0.0087	-1.7605	0.0787972
PRIORITY	<b>-0.4955</b>	0.0562	-8.8097	<b>0.0000000</b>
TREND_PDUFA1	<b>-0.0180</b>	0.0056	-3.1830	<b>0.0015290</b>
TREND_PDUFA2	<b>-0.0198</b>	0.0061	-3.2262	<b>0.0013190</b>
ORPHAN	0.0945	0.0647	1.4609	0.1445419
NATION	-0.0495	0.0452	-1.0948	0.2740237
DRG_CARDIO	0.1131	0.0665	1.7004	0.0895473
DRG_ANTIINFECT	<b>-0.2833</b>	0.0707	-4.0067	<b>0.0000689</b>
DRG_NEOPLASTIC	<b>-0.2608</b>	0.1002	-2.6020	<b>0.0094847</b>
DRG_CNS	0.0655	0.0808	0.8108	0.4177958
DRG_BIO	0.0336	0.0764	0.4400	0.6601198
DRG_AIDS	<b>-0.8568</b>	0.1686	-5.0823	<b>0.0000005</b>

Figure 39. Multivariate Linear Regression Data

#	Generic	NDA/BLA Trade	NDA Applicant	Approval	Introduction*	Withdrawal
1	fenfluramine	16618 Pondimin	Wyeth	6/14/1973	7/15/1973	9/15/1997
2	azaribine	16899 Triazure	Parke-Davis	2/28/1975	8/18/1975	8/12/1976
3	ticrynafen	18103 Selacryn	Smith Kline & French	5/2/1979	5/10/1979	1/16/1980
4	zompiriac	18236 Zomax	Johnson & Johnson	10/28/1980	10/15/1980	3/8/1983
5	benoxaprofen	18250 Oraflex	Lilly	4/19/1982	4/15/1982	8/4/1982
6	nomifensine	18224 Merital	Hoechst-Roussel	12/31/1984	6/15/1985	1/22/1986
7	terfenadine	18217 Seldane	Hoechst Marion Roussel	5/8/1985	5/15/1985	2/1/1998
8	suprofen (oral)	18949 Suprol	RW Johnson	12/24/1985	1/15/1986	5/15/1987
9	encainide	18981 Enkaid	Bristol-Myers Squibb	12/24/1986	4/15/1987	12/16/1991
10	astemizole	19402 Hismanal	Janssen	12/29/1988	1/15/1989	6/21/1999
11	temafloxacin	20043 Omniflox	Abbott	1/30/1992	2/15/1992	6/5/1992
12	flosequinan	19960 Manoplax	Knoll	12/30/1992	2/15/1993	7/19/1993
13	cisapride	20210 Propulsid	Janssen	7/29/1993	9/15/1993	7/14/2000
14	troglitazone	20720 Rezulin	Parke Davis	1/29/1997	3/15/1997	3/22/2000
15	mibefradil	20689 Posicor	Roche	6/20/1997	7/15/1997	6/8/1998
16	bromfenac	20535 Duract	Wyeth- Ayerst	7/15/1997	7/15/1997	6/22/1998
17	cerivastatin	20740 Baycol	Bayer	7/26/1997	1/15/1998	8/8/2001
18	grepafloxacin	20695 Raxar	Glaxo-Wellcome	11/6/1997	1/15/1998	10/27/1999
19	rotavirus vaccine	970111 or 970924 Rotashield	Wyeth-Ayerst	8/31/1998	9/15/1998	10/15/1999
20	rapacuronium	20984 Acceleron	Organon	8/18/1999	10/15/1999	3/27/2001
21	alsoetron	21107 Lotronex	Glaxo-Wellcome	2/9/2000	2/15/2000	11/28/2000

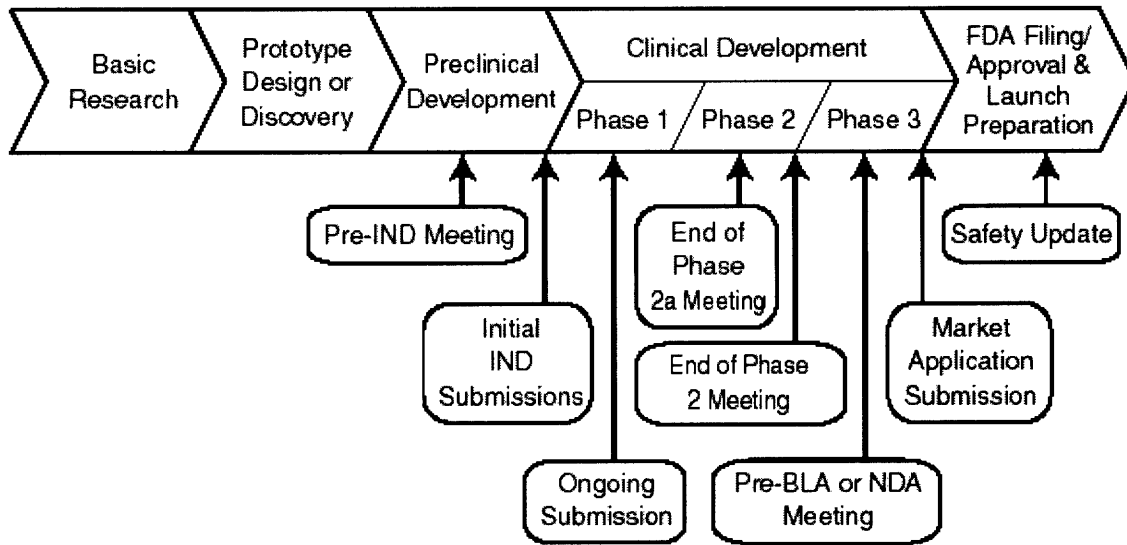
**Figure 40. NME Safety Withdrawals**

	n =	Mean	Median	Mode	Std. Dev	NR	NA	Biotech vs. Pharma (p-value for t-test)
<b>1 = BAD / 2 = POOR / 3 = FAIR / 4 = GOOD / 5 = EXCELLENT</b>								
What is your overall perception of the FDA in regards to regulating drug development and appropriately weighing the risk/benefits of new drugs?	32	3.53	4	4	0.68	0	0	0.248
How would you rate the FDA's effectiveness of keeping unsafe drugs from the market?	32	4.08	4	4	0.65	0	0	0.233
Please rate how well your company is organized to interact with the FDA?	31	3.98	4	4	0.86	1	0	<b>0.082</b>
Please rate the progress your company has made in reducing clinical development times on issues that your company can control.	29	3.61	3.5	3	0.79	3	0	0.272
How would you rate your company's experience with Contract Research Organizations?	27	3.31	3	3	0.79	5	0	0.313
Please rate the quality of communication your company has with the FDA during the following phases PRE-CLINICAL	29	3.13	3	3	0.77	3	0	<b>&gt; 0.000</b>
Please rate the quality of communication your company has with the FDA during the following phases PHASE I	30	3.24	3	3	0.74	2	0	<b>0.053</b>
Please rate the quality of communication your company has with the FDA during the following phases PHASE II	32	3.37	3	3	0.68	0	0	0.549
Please rate the quality of communication your company has with the FDA during the following phases PHASE III	32	3.82	4	4	0.67	0	0	0.136
Please rate the quality of communication your company has with the FDA during the following phases NDA	32	3.69	4	4	0.99	0	0	0.561
Please rate the following in regards to the FDA reviewers. The quality of FDA reviewers is:	27	3.27	3	3	0.71	4	0	0.481
Please rate the following in regards to the FDA reviewers. Accountability of FDA reviewers is:	29	3.07	3	3	0.78	3	0	0.411
Please rate the following in regards to the FDA reviewers. Training for FDA reviewers is:	19	2.94	3	3	0.86	13	0	0.515
Please rate the following in regards to the FDA reviewers. Direct Leadership of FDA reviewers is:	28	3.46	3.5	4	0.68	4	0	0.292
The clinical protocols my company submits to the FDA are on average:	21	4.30	4	4	0.57	2	9	0.626
When responding to FDA inquiries or questions, your company responds effectively and efficiently.	23	4.20	4	4	0.70	0	9	0.265

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)
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	29	3.73	4	5	1.31	3	0	0.600
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	29	3.91	4	5	1.32	3	0	0.529
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	28	4.02	5	5	1.42	4	0	0.807
How much would you be willing to pay for more communication with the FDA per phase? PHASE I	31							0.761
How much would you be willing to pay for more communication with the FDA per phase? PHASE II	31							0.622
How much would you be willing to pay for more communication with the FDA per phase? PHASE III	31							0.106
How likely is your company to use surrogate markers in clinical trials as the primary endpoint under the current FDA guidelines?	30	3.14	3	2	1.57	2	0	0.338
How likely is your company to use surrogate markers if patent opportunities and incentives were available on the surrogate marker?	28	3.94	5	5	1.50	4	0	0.690
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)
How valuable is the consultation with the FDA at the end of Phase II - beginning of Phase III?	30	4.66	5	5	0.55	2	0	0.895
Please rate how valuable additional informal communication would be with the FDA during the following phases. PRE-CLINICAL/IND	29	4.36	5	5	0.83	3	0	0.529
Please rate how valuable additional informal communication would be with the FDA during the following phases. PHASE I	31	4.17	4	5	0.87	1	0	0.331
Please rate how valuable additional informal communication would be with the FDA during the following phases. PHASE II	31	4.48	4.5	5	0.53	1	0	0.800
Please rate how valuable additional informal communication would be with the FDA during the following phases. PHASE III	30	4.66	5	5	0.55	2	0	0.195
Please rate how valuable additional informal communication would be with the FDA during the following phases. NDA	31	4.73	5	5	0.52	1	0	0.596
How valuable has information gathering technology been in helping reduce clinical development times in the following phases? PRE-CLINICAL/IND	29	3.18	3	3	0.94	3	0	0.516
How valuable has information gathering technology been in helping reduce clinical development times in the following phases? PHASE I	27	3.10	3	3	0.87	5	0	0.552
How valuable has information gathering technology been in helping reduce clinical development times in the following phases? PHASE II	27	3.19	3	3	0.93	5	0	0.790
How valuable has information gathering technology been in helping reduce clinical development times in the following phases? PHASE III	26	3.26	3	3	1.11	6	0	0.212

Figure 41. Quantitative Questionnaire and Results





**Figure 42. Points of Interaction with the FDA**