THE PRESCRIPTION DRUG USER FEE ACTS:

TOWARDS AN ECONOMIC EVALUATION - I

by

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ABSTRACT

Congress enacted the first of several Prescription Drug User Fee Acts ("PDUFA") in 1992, mandating FDA performance goals in reviewing and acting on New Drug Applications within specified time periods, and in turn levying user fees on drug sponsors submitting applications to the FDA. PDUFA has been renewed twice since 1992. We model and quantify the impact of PDUFA-I and II on drug approval times, and then quantify impacts of the more rapid drug approvals by calculating induced changes in the present values of benefits and costs. Exploiting the plausible and reasonable assumption that marginal costs of a discovered and developed drug are likely less than a third of their patent-protected price, we demonstrate that with a linear demand curve and constant marginal costs, industry sales provide a lower bound to social (consumers' plus producers') surplus. In turn, social surplus can be divided one third into consumers' surplus, and two-thirds producers' surplus. This bounding condition extends to nonlinear demand curves, provided they are convex to the origin.

Using sales data from IMS Health, we find that with a real discount rate of 5%, PDUFA-induced changes in the present value ("PV") of sales over all therapeutic classes are $18 billion in 1992 dollars, many times the $664 million PV of PDUFA user fees, implying a net social surplus of about $17.3 billion. Assuming fixed profit margins, this represents about a 2.1% increase in producers' surplus. Allocating the net social surplus one-third to consumers' surplus ($5.8 billion) and two-thirds to producers' surplus ($11.5 billion) suggests that both for consumers and for producers, benefits from the enactment and implementation of PDUFA were many times larger than the $664 million in PDUFA fees. Our analysis suggests that other policies that affect the speed of the drug development and approval process could have very substantial net social surplus impacts.

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I. INTRODUCTION

In virtually all developed countries, regulatory authorities provide public oversight of the safety and efficacy of prescription drugs, prior to their being approved for marketing. In the U.S., such oversight is conducted by the Food and Drug Administration ("FDA"). The FDA's mission statement declares that:

> "The FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices…The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and food to protect their health".[1]

A central tradeoff facing the FDA involves balancing its two goals – protecting public health by assuring the safety and efficacy of drugs, and advancing the public health by helping to speed innovations. Some observers have argued that the FDA is not taking enough time evaluating new drugs and biologics, while others have argued that the agency is taking too long in doing so.[2]

Surprisingly, very little empirical evidence has been put forward to make the case that the FDA is too slow or too fast in its drug approval process. In this paper, we report on results of first steps in evaluating quantitatively the economic costs and benefits associated with passage of the Prescription Drug User Fee Act ("PDUFA") of 1992, later continued as PDUFA-II in 1997

and PUDFA-III in 2002. These legislative acts specified performance goals for the FDA in terms of reduced review times, while levying user fees on the industry in terms of payments required for consideration of new drug applications ("NDAs"), new biologic license applications ("BLAs"), and supplemental applications, as well as annual fees for existing manufacturing establishments and products. Between fiscal years 1993 and 2002, net annual collections from PDUFA to the FDA grew more than five-fold, from $28.5 million to $149.1 million. These user fee revenues represent a substantial portion of the FDA's total revenues obligated to processing human drug applications. For example, in 2002, of the $347.6 million total process costs, $161.8 million (47%) were covered by user fee revenues, while the remaining $185.8 million (53%) came from Congressional appropriations.[3]

In this paper we report on preliminary analyses of the costs and benefits associated with PDUFA, viewed from several perspectives. More specifically, based on data on 662 drug approvals prior to and following enactment of PDUFA (from years 1979 through 2004), using multivariate regression methods we attempt to isolate empirically the impact of PDUFA-I and PDUFA-II on affecting NDA/BLA approval times. For each of the 662 drug approvals, we then simulate a counterfactual world and predict what approval times would have been in the absence of PDUFA. Using a life cycle revenue framework, we then calculate the difference in present values of U.S. sales revenues associated with the more rapid approval of NDAs/BLAs by the FDA during the PDUFA years. We argue that under simple but plausible conditions these differences in present value of sales revenues constitute a lower bound to the estimated change in social (consumers' plus producers') surplus associated with PDUFA-I and II. We compare these changes in present values of revenues with the present values of PDUFA user fees paid by the NDA/BLA sponsors, all viewed prospectively in 1992. Using a real discount rate of 5%, our

principal finding here is that expressed in 1992 dollars, enactment and implementation of PDUFA-I and II resulted in an increase in present value of revenues (social surplus) of $18 billion (about a 2.1% increase in PV of gross revenues), and an increase in present value of PDUFA fees of $664 million, implying a net present value social surplus difference of $17.3 billion. Averaged over all therapeutic classes, the additional user fees are about 3.7% of the difference in PV of gross revenues.

Although our calculations are preliminary, they suggest that the incremental benefits from PDUFA were many times larger than the incremental costs associated with PDUFA. By having access to new drugs more quickly, patients (and their providers) benefited significantly from the enactment and implementation of PDUFA. Producers also gained in the form of increases in the present value of variable profits. We note that when demand curves are linear and marginal cost is constant, as long as price is more than three times marginal cost, consumers' surplus is one third of the social surplus, while producers' surplus is two-thirds of the social surplus. Given that lower bound estimates of the social surplus are about $18 billion with the split being about $6 billion for consumers' surplus and $12 billion for producers' surplus, for both consumers and producers the economic value of the incremental benefits from PDUFA are many times larger than the $660 million in incremental PDUFA user fees.

Our research to date is preliminary, and is based on a number of assumptions. Although it is possible that PDUFA also increased the number of drugs eventually withdrawn from the market for safety reasons, the evidence to date suggests the proportion of withdrawn drugs approved pre- and post-PDUFA is similar, and is small. While our principal qualitative findings appear to be robust over a relatively wide range of discount rates, the impacts of assumptions concerning sales over the product life cycle, the length of the product life cycle, and the

allocation of user fees need more thorough examination. We leave implementation and a more detailed disaggregated examination of the social and private costs and benefits of PDUFA-I and PDUFA-II to a subsequent paper.

The remainder of this paper proceeds as follows. In Section II we provide a brief overview of PDUFA-I and PDUFA-II. In Section III we discuss specification of a multivariate regression model relating FDA approval times to a number of factors, including PDUFA and other covariates. In Section IV we discuss data sources, provide a descriptive summary of our data, and then discuss empirical findings from the regression analysis. In Section V we outline a framework for assessing the impacts of PDUFA on social surplus via the present values of revenues and costs, and then in Section VI we summarize our NPV findings for revenues, PDUFA user fees, and social (consumers' plus producers') surplus. Finally, in Section VII we summarize our findings, note limitations of our research, and suggest directions for further research.

II. THE PRESCRIPTION DRUG USER FEE ACTS (PDUFA)

The concept of payment of user fees by individuals or firms being provided services by a government regulatory body has ample precedent, e.g., application submission fees to the U.S. Patent and Trademark Office. The development of the Prescription Drug User Fee Act permitted the FDA to collect fees from sponsors submitting an NDA or BLA for review. The passage of PDUFA-I in 1992 was, however, somewhat controversial in that the amount of fees collected for each sponsor application was very substantial, unlike that for patent applications. In the initial fiscal year 1993 user fee schedule, applications with clinical data were assessed a one-time fee of $100,000; each supplemental application with clinical data, and applications with no clinical data, $50,000; annual manufacturing establishment fees were $36,080, and annual product fees

were $6,000. With effective renewals of PDUFA-I in 1997 under the Food and Drug Modernization Act of 1997 ("PDUFA-II") and the Bioterrorism Preparedness and Response Act of 2002 ("PDUFA-III"), fees have escalated sharply. In fiscal year 2004, for example, applications with clinical data are assessed a one-time fee of $573,500; each supplemental application with clinical data, and applications with no clinical data, are assessed a user fee of $286,750; annual manufacturing establishment fees are $226,800, and annual product fees are $6,000. Waivers and exemptions are granted to small firms, and to sponsors submitting an application under the Orphan Drug Act of 1983.[4]

In exchange for the collected user fees, the FDA is legally obliged to "review and act on" NBA/BLA submissions. However, reviewing and acting on is not the same as reaching a final approve/do not approve decision. According to the PDUFA-III legislation, for example:

> "'review and act on' is understood to mean the issuance of a complete action letter after the complete review of a filed complete application. The action letter, if it is not an approval, will set forth in detail the specific deficiencies and, where appropriate, the actions necessary to place the application in condition for approval."[5]

In essence, therefore, PDUFA mandates responses and action letters from the FDA, but not necessarily approvals or final denials.

NDA/BLA submissions are assigned either a "standard" or "priority" status, depending in part on the novelty of the therapeutic and the existence of unmet needs. In the case of PDUFA-I, II and III, the FDA is required to deliver a "complete review" on 90% of priority applications within six months. For standard applications, the FDA was expected to review 90% of

applications in twelve months under PDUFA-I; currently, the FDA is expected to review 90% of standard applications in ten months.

On the action date mandated by PDUFA, the FDA issues one of three actions. The first action is a non-approvable letter indicating that the NDA/BLA has not satisfied the FDA's standards for safety and/or efficacy. The second type of action is an "approvable" letter that indicates the NDA/BLA can be approved if certain deficiencies and questions are appropriately acted upon by the sponsor. The third type of action is the ultimate approval letter that gives the sponsor company the right to market the drug to the public.

Researchers such as Peltzman [1974], Olson [1997,1998,2004] and Carpenter [2002] have long argued that personnel at the FDA are considerably more worried about committing Type 1 errors (approving a drug that is unsafe and/or lacks efficacy) than Type 2 errors (not approving a safe and effective drug).[6] Given the costs and punishment that can be meted out by Congress for Type 1 errors, it is not surprising that Type 1 errors receive disproportionate attention. While the costs of delaying lifesaving and quality of life improving medications are real and impose pain and suffering on patients seeking new medicines, such costs from Type 2 errors are not as visible as the Type 1 errors. Rather than mandate specific remedies that would attempt to deal more directly with Type II errors, Congress has attempted to provide incentives for improved efficiencies at the FDA; PDUFA is such an example.

Although PDUFA action date mandates have generally been met by the FDA, these action dates are not the same as approval dates. Is it feasible to argue that PDUFA, by mandating better response times via action dates, has in fact lowered approval times substantially?

Drug approval data provided us by the FDA indicate that approval times have been falling for quite some time, at least since 1979, and appear to have accelerated, particularly during PDUFA-I. As seen in Figure 1, mean approval time during 1979-86 was 33.57 months, 28.19 months in 1987-92, 18.61 months during PDUFA-I, and 16.09 months in PDUFA-II. Since the approval time data is skewed to the right, the corresponding median approval times are all smaller, but they too fall over time: 27.07 (1979-86), 23.83 (1987-92), 16.18 (PDUFA-I), and 12.27 (PDUFA-II).

An alternative way of depicting drug approval time trends is to construct "survival" curves that plot the proportion of approvals not yet completed within a fixed time period. More precisely, the "survival" curve in Figure 2 plots the percent approvals remaining over time in months, during different time frames. As the time scale increases along the horizontal axis in Figure 2, more NDAs/BLAs are approved, and thus the proportion of approvals remaining declines. In Figure 2, separate survival curves are plotted for the 1979-86, 1987-92, PDUFA-I and PDUFA-II time periods. Survival curves from more recent time periods are clearly separate from and ever closer to the origin than are those from earlier eras. The more rapid decline in survival curves during PDUFA-I and II relative to the pre-PDUFA time period indicates faster approvals. During PDUFA-II and PDUFA-I 50% of NDAs/BLAs were approved by twelve months and fifteen months, respectively, in contrast to 27 and 30 months for 1987-92 and 1979-86, respectively.

III. ASSESSING THE IMPACT OF PDUFA ON APPROVAL TIMES

Although there is general agreement that PDUFA has lowered approval review times, given the presence of confounding factors, the quantitative magnitude by which it has done so has not been established.[7] In estimating the magnitude attributable to PDUFA, as was noted

above, it is important to note that approval times were already trending downwards prior to PDUFA-I, so that simply calculating pre- and post-PDUFA approval times would overstate the magnitude of the impact of PDUFA. Moreover, in response to patient advocacy groups highlighting the need for more rapid approval of drugs that treat certain life-threatening illnesses such as AIDS, the FDA has assigned NDAs in some therapeutic areas disproportionately high priority status. To isolate the impact of PDUFA on FDA approval times, it is imperative that changes over time in the composition among therapeutic classes of the NDAs be taken into account, as well as other changes that could have affected approval times.

We specify a multivariate linear regression model with the logarithm of the time between NDA/BLA filing and NDA/BLA approval in months (LNAPP) as the dependent variable. We hypothesize that LNAPP is related to a number of explanatory variables, including the following. We construct a TIME TREND variable as a time counter equal to 1 during fiscal year 1980 (10/01/1979 to 9/30/1980), equal to 2 during fiscal year 1981 (10/01/1980 to 9/30/1981), and so forth, up to 23 in fiscal year 2002 (10/01/2001 to 9/30/2002); each observation is assigned a TIME TREND value given the date the NDA/BLA was filed with the FDA (not the date it was approved). We expect the coefficient on TIME TREND to be negative, reflecting shorter review/approval times in more recent years.

In order to assess whether the decline in approval times has been accelerating or decelerating in the last decade, we also construct two interaction variables. First, in addition to the TIME TREND variable, we construct a variable TIME that counts years during the PDUFA eras: TIME equals 1 if the NDA/BLA was filed in the first year (actually, 13 months) during PDUFA-I (9/1/92 through 9/30/93), 2 if it was filed between 10/1/93 and 9/30/94, and so on, up to 10 if the NDA/BLA was filed between 10/1/2001 and 9/30/2002 (the last year of PDUFA-II).

PDUFA-I*TIME is then constructed as the product of TIME and a 0-1 indicator variable PDUFA-I that takes on the value one if the NDA/BLA was filed during PDUFA-I (9/1/1992 through 9/30/1997), else PDUFA-I is zero. The interaction variable PDUFA-II*TIME is constructed analogously.

With these variables of primary interest, and denoting other covariates by X_i, we specify a regression equation for the i^{th} observation as follows:

$$LNAPP_i = \beta_0 + \beta_1*TIMETREND_i + \beta_2*PDUFA\text{-}I*TIME_i + \beta_3*PDUFA\text{-}II*TIME_i + X_i\beta + \varepsilon_i \quad , \quad i = 1,\ldots,I, \qquad \text{(Eqn. 1)}$$

where ε_i is an independently and identically normally distributed random disturbance term, and the β's are parameters to be estimated. Note that in this specification, parameter estimates on the interaction variables represent any *differential* annual impact of the passage of time on LNAPP during the PDUFA eras, relative to that existing over the entire 1979-2002 time period. Negative (positive) parameter estimates on these interaction variables are interpreted as an acceleration (deceleration) of the decline in approval times during the PDUFA years. If approval times were not significantly different during the PDUFA eras relative to pre-PDUFA, then $\beta_2 = \beta_3 = 0$. If the annual differential impact of the passage of time on LNAPP were the same during PDUFA-I and PDUFA-II, then $\beta_2 = \beta_3$. These are of course testable hypotheses that we will assess empirically.

A number of potentially confounding covariates are also included among the regressors in X. Three 0-1 indicator variables include: ORPHAN (1 if the application was filed citing eligibility under the 1983 Orphan Drug Act, else 0); PRIORITY (1 if the application was assigned priority status by the FDA after 1991, or an A or B rating prior to 1991, else 0); and DOMESTIC (if the application sponsor was headquartered inside the US, else 0). We expect the

coefficient on PRIORITY to be negative. Although it is reasonable to expect the coefficient on ORPHAN to be negative as well, since almost all of the ORPHAN drug applications were assigned PRIORITY status, multicollinearity between these two variables may confound the expected association. Finally, to the extent DOMESTIC applicants have greater familiarity and cumulative experience with the FDA, we might expect the sign of the coefficient on DOMESTIC to be negative.

It is plausible that review times vary across therapeutic classes, due to inherent differences across diseases and therapies. To accommodate this possibility, we construct 0-1 indicator variables assigning each observed NDA/BLA approval to one and only one of the following 13 therapeutic classes: AIDS, ANTI-INFEC (anti-infective), ANTI-INFLAM (anti-inflammatory), BIOLOGIC (involving a Biologic License Application, rather than an NDA), CARDIO (cardiovascular or renal), CNS (central nervous system), DERM-OPTHAL (dermatologic or ophthalmologic), GI (gastrointestinal), METABOL-ENDO (metabolic or endocrine), NEOPLASTIC (oncologic), RADIO-DIAG (radiopharmaceutical or diagnostic), RESPIRATORY, and a miscellaneous OTHER category. Roughly speaking, this classification corresponds with the various division review structures at the Center for Drug Evaluation Research and the Center for Biologic Evaluation Research at the FDA existing up through 2002. In the regression results reported below, the BIOLOGICS class variable is omitted, and thus this serves as the reference class.

It is possible that in addition to variations across therapeutic classes, the complexity of certain sponsor development efforts affected review times at the FDA. For 621 of the 662 NDA/BLA approvals in the data base, we have also obtained information on the date at which the initial IND for that therapeutic was filed with the FDA. We construct the variable

LNINDNDA as the logarithm of the time in months between the filing of the IND and the filing of the NDA/BLA. A priori, the sign of the coefficient on LNINDNDA is ambiguous. If a more thorough drug development process prior to the filing of the NDA/BLA provides the FDA with additional useful information, facilitating a more expeditious subsequent FDA review, then the coefficient LNINDNDA would be negative. On the other hand, if the longer development time in between the IND and the NDA/BLA filing reflects inherent difficulties and complexities of the clinical development process for that drug, it may also take longer for the FDA to diligently review the application; in such a case, the coefficient on LNINDNDA would be positive.

There are instances in which a sponsor has never filed an IND with the FDA (this phase may have been carried out overseas), and in other cases the IND date data are simply missing; altogether, 41 of the 662 observations have missing IND date data. To allow for the possibility that these 41 observations missing IND dates are non-random or non-representative, we construct and include as a regressor a 0-1 indicator variable IND MISS that equals 1 if the observation has a missing IND value, else it is zero.

A rather different factor potentially affecting NDA/BLS approval times involves the presence or absence of top leadership at the FDA.[8] To address the issue of whether the presence or absence of a Congressionally-confirmed FDA Commissioner has impacted the speed of NDA/BLA approval times, we consider several alternative specifications that in different ways attempt to quantify the absence of a confirmed Commissioner.

Historically, between 1979 and 2002, six Commissioner vacancy periods occurred: June 30, 1979 to October 21, 1979 (113 days); January 20, 1981 to April 13, 1981 (83 days); September 11, 1983 to July 15, 1984 (308 days); December 17, 1989 to November 7, 1990 (325 days); February 28, 1997 to November 30, 1998 (640 days); and January 19, 2001 to November

14, 2002 (664 days). Note that the first two vacancy periods lasted less than four months, the second two between 10 and 11 months, and the last two more than 20 months. Thus, the longest Commissioner vacancies occurred during PDUFA-II, even as the FDA was implementing measures to reduce approval times.[9] This suggests that it may be difficult to disentangle the effects of PDUFA from those possibly due to the absence of a confirmed Commissioner.

In terms of quantification of vacancy prevalence, for each NDA/BLA, we first calculate the overlap in time period of the vacancy of a Commissioner with the time period during which the application was being reviewed at the FDA. The variable NOCOM% is then computed as the ratio of Commissioner absent days to days the NDA/BLA was under review before approval. We consider several alternative specifications to the "base case" in Eqn. (1) above. In Model I NOCOM% appears as an additional regressor relative to the base case specification. In Model II, the logarithm of NOCOM%, denoted LNNOCOM, is added instead as a regressor. In those instances in which NOCOM% is zero, we arbitrarily overrule it and instead assigned LNNOCOM a value of LOG(0.001). In Model III, a simple and coarse 0-1 indicator variable EVERNOCOM is added instead, taking on the value 1 if NOCOM% > 0, else EVERNOCOM = 0. In this specification, the mere occurrence anytime during the approval process of a non-confirmed Commissioner is hypothesized to affect approval time. Finally, in Model IV a 0-1 indicator variable NOABSENCE is first defined as being equal to 1 if NOCOM% = 0, else NOABSENCE equals zero. Then another variable, called LNNOCOMX, is constructed as being equal to LNNOCOM whenever NOCOM% >0, else LNNOCOMX = 0. In Model IV both NOABSENCE and LNNOCOMX are included as regressors.

If the absence of a confirmed Commissioner increased regulatory delays and approval times at the FDA, other things equal, then one would expect the coefficient estimates on

NOCOM%, LNNOCOM and EVERNOCOM to be positive in Models I, II and III, respectively. In the case of Model IV, while the parameter on NOABSENCE would be expected to be negative, that on LNNOCOMX would be positive. Of course, expected coefficient signs would be reversed if it were hypothesized that the absence of a confirmed Commissioner reduced FDA approval times, other things equal.

Finally, for purposes of comparison with time at the FDA prior to NDA/BLA approval, we also consider a specification in which we examine factors affecting the clinical development time between the sponsor's filing of the IND and the submission of the NDA/BLA. As has been noted by a number of observers, this time interval is typically two to four times larger than FDA review time prior to approval.[10] For this pre-NDA/BLA clinical development time analysis, we specify the same set of regressors as in the LNAPP regression, except now of course LNINDNDA becomes the dependent variable, and those 41 observations for which IND MISS = 1 must be deleted. We hypothesize that in this pre-NDA/BLA clinical development time regression, the TIME TREND coefficient is non-negative (either zero or positive), as is that on the PDUFA-I*TIME and PDUFA-II*TIME interaction variables. In terms of therapeutic class impacts, because of the rush to bring life-saving products to market, we expect clinical development times for AIDS drugs to be relatively short; due to the alleged nimbleness of biotech firms pursuing BIOLOGICS products, we expect that BIOLOGICS products will be associated with relatively short clinical development times. We do not have any *a priori* expectations concerning signs of the estimated coefficients on the remaining regressors.

IV. EMPIRICAL RESULTS: FACTORS AFFECTING APPROVAL TIMES

We now report on data sources, their descriptive statistics, as well as on results obtained from the multivariate regression analyses. We begin with data sources and descriptive statistics.

A. DATA SOURCES AND DESCRIPTIVE STATISTICS

Data on new molecular entities filed at the FDA between 1965 and 2003 were provided us by Ed Hass, Office of Policy and Planning, US Food and Drug Administration. Data fields included NME name (along with any withdrawal information), descriptive characteristics of the drug (whether NDA or BLA, vaccine, diagnostic, radiopharmaceutical, orphan drug, and nuclear related therapeutic); the developing company; developing country; FDA approval date; therapeutic significance rating (A,B,C prior to 1991; priority or standard thereafter); year of first world marketing; country of first world marketing; US trade name at time of approval; IND submission date; NDA/BLA clock date; IND number; elapsed approval time in months; years in the IND phase; total development years; NDA/BLA number; name of the sponsoring company; US/foreign developer code; orphan drug code; and US first marketing date. Additional data include 7-digit and 3-digit therapeutic class codes for each NME. FDA officials believe that these data series are error free and complete from the period of 1975 forward in regards to NDA/BLA approval length.

For purposes of our analysis, we considered all NDA/BLA filed at the FDA beginning with fiscal year 1980 (October 1, 1979 through September 30, 1980) up through fiscal year 2002 (October 1, 2001 through September 30, 2002). This yielded 649 observations, 321 of them being from the pre-PDUFA era up through August 31, 1992, and 328 of them in PDUFA-I or PDUFA-II. Of these, 123 were missing data on therapeutic class codes. A research assistant entered class code data for these products, using information from the 2003 Physicians' Desk Reference. To mitigate problems of right-censoring for submissions filed but not yet approved by April 2003 (when the FDA data set was last updated), in May 2004 we augmented the FDA

data by adding 13 additional FDA approvals from April 2003 up through May 1, 2004. This yielded a total of 662 observations, 321 pre-PDUFA, and 341 post- PDUFA.

In the top panel of Table 1 we list approval time descriptive statistics for each of the 13 therapeutic classes, and over all NDAs/BLAs, along with sample sizes. Samples sizes are largest in the CARDIO (n =95), ANTI-INFEC (94) and BIOLOGICS (90) classes, and are smallest in the OTHER (20) and AIDS (15) categories.[11] While the mean approval time over all classes is 24.04 months, the range is enormous, from a minimum of 0.60 months to more than 11 years (134.63 months). The smallest mean approval times are in the AIDS (7.96), NEOPLASTIC (14.55) and DERM-OPHTHAL (18.88) therapeutic classes, while the longest mean approval times are for NDAs in the ANTI-INFLAM (37.78 months) and RESPIRATORY (38.06) classes. In terms of regressors, the mean of LNINDNDA is 3.845 (when exponentiated, 46.75 months). About 6% of observations are missing data on the IND date, 43% of NDAs/BLAs are filed by DOMESTIC applicants, 18% are filed under provisions of the Orphan Drug Act of 1983, and about 30% are assigned PRIORITY status.

B. REGRESSION ANALYSIS FINDINGS

The principal regression findings from our analysis are presented in columns two through four of Table 2. Coefficient estimates with p-values less than 0.05 are highlighted in bold.

Before discussing PDUFA-related findings, we first comment on the impacts of various covariates. The coefficient estimate on LNINDNDA is virtually zero and statistically insignificant, implying that apparently there is no spillover between the time spent in clinical development by the sponsor and the approval time at the FDA. The coefficient estimate on IND MISS is also insignificant, suggesting that the observations missing the IND date are unlikely to be non-representative of the larger sample. NDAs/BLAs assigned PRIORITY status, other

things equal, have a review time only 61% (exponentiation of -0.4902) as long as those applications assigned STANDARD review status. This difference is statistically significant. By contrast, drugs having an ORPHAN status and those sponsored by a DOMESTIC applicant have no significant impact on approval time. Recall that the vast majority of ORPHAN drugs also were assigned PRIORITY status. Having an ORPHAN drug designation in addition to PRIORITY status does not appear to affect approval times significantly.

In terms of therapeutic class, recall that in the multivariate regression specification the BIOLOGICS class is the reference group. Relative to the expected approval times of BIOLOGICS, NDAs from the AIDS therapeutic class have the shortest approval times (44% as long), followed by OTHER (70%), ANTI-INFEC (74%), and NEOPLASTIC (74%) applications, each of which is statistically different from that for the BIOLOGICS. By contrast, NDAs involving RESPIRATORY drugs have a significantly longer approval time than those for the reference case BIOLOGICS – 33% greater. Coefficient estimates for the remaining therapeutic class indicator variables are not statistically significant.

We now turn to a discussion of PDUFA-related impacts on approval times. As seen near the top of Table 2, the coefficient estimate on TIME TREND is -0.017, indicating that approval times were declining about 1.7% annually, *ceteris paribus*, even in the absence of PDUFA; this estimate is statistically significant (p-value 0.038). Declines in approval time accelerated significantly, however, during the PDUFA-I years, with a differential decline from the overall trend of about -7.6% annually. Hence, during the PDUFA-I era, approval times declined more than 9% annually (1.7% + 7.6% = 9.3%), significantly greater than the -1.7% during the pre-PDUFA era.

While declines in approval time continued during PDUFA-II, the declines were smaller than during PDUFA-I. As seen in Table 2, relative to the pre-PDUFA time period, approval times for NDAs/BLAs submitted during PDUFA-II declined about 3.6% more rapidly, not as dramatic a differential as during PDUFA-I, but still significant and meaningful, especially when cumulated over time. This pattern of greater acceleration in shortened approval times during PDUFA-I than during PDUFA-II is consistent with the notion that during PDUFA-I "low hanging fruit" procedures were implemented initially, which had a very significant impact on reducing approval times. While subsequent efforts by the FDA continued to result in reductions in approval times during PDUFA-II, these efforts yielded smaller annual improvements, in part reflecting the fact that significant improvements had already been achieved.

One way of envisioning the implications of these PDUFA-related findings is to create a counterfactual situation in which there is no PDUFA, i.e., one in which the PDUFA-I*TIME and PDUFA-II*TIME variables are set to zero, only the TIME TREND variable changes over time, and all other regressors are evaluated at their overall sample means.[12] The time trend of predicted approval times from this base case regression equation, with and without the PDUFA variables, is plotted in Figure 3. As is seen there, had PDUFA-I and PDUFA-II not been implemented, between 1991 and 2002 average approval times would have fallen about 16% from 24.2 to 20.4 months. Instead, because of PDUFA-I and PDUFA-II, between 1991 and 2002 approval times declined about 42% to 14.2 months. Of the total 10.1 month decline, therefore, approximately 62% is due to PDUFA-I and II. Most of this reduction occurred during PDUFA-I. Without PDUFA-I, mean reductions in approval time would have declined from 24.2 in 1991 to 22.3 months in 1997 (a 1.9 month or 8% reduction), but with PDUFA-I the reduction was much larger to 14.9 months (a 9.3 month or 38% reduction). Hence, declines in mean approval times

between 1991 and 1997 were 80% due to PDUFA-I, and 20% to pre-existing trends. However, during PDUFA-II, initially the mean approval time increased from 14.8 in 1997 to 17.6 months in 1998, but after that approval times steadily declined, and by 2002 they had fallen a total of 0.7 months to 14.2 months. Proportionally, the PDUFA-II reduction was smaller at 5%.

As a further assessment of estimated coefficients on the PDUFA-related variables, we tested two hypotheses. The first is that the annual differential reductions in approval times during PDUFA-I were the same as those in PDUFA-II; this corresponds to the null hypothesis that $\beta_2 = \beta_3$. Using an F-test analysis of variance procedure, we reject this hypothesis decisively ($F_{1,641} = 8.325$, p-value 0.004). Not surprisingly, then, we also reject the null hypothesis that both these parameters simultaneously equal zero, i.e., that there is no differential impact of the passage of time on average approval times during PDUFA-I and PDUFA-II ($F_{2,641} = 5.678$, p-value 0.004).

The estimated regression equation in Table 2 is based on a number of assumptions. Although the null hypothesis of homoskedasticity of the disturbance terms is rejected (White test procedure, p-value 0.005), heteroskedasticity-consistent standard errors for the coefficients on the TIME TREND, PDUFA-I*TIME and PDUFA-II*TIME variables are virtually identical to those in Table 2 – 0.008, 0.023 and 0.015, respectively.[13] Another assumption is that the coefficients on the variables other than the 0-1 therapeutic class indicator variables are equal across the various therapeutic classes. Using a modified Chow test procedure, we are unable to reject the null hypothesis that these coefficients are equal across classes ($F_{96,545} = 1.2157$, p-value 0.0948).

Inspection of parameters in the 13 separately estimated therapeutic class regressions and comparisons with those from the partially pooled specification in Table 2 reveal that though not

always statistically significant, coefficient estimates on the PRIORITY and PDUFA-I*TIME and PDUFA-II*TIME variables are generally negative (and never positive and statistically significant), while that on TIME TREND is more often negative than positive, and occasionally negative and significant. The negative point estimates of coefficients on the PDUFA related variables are substantially larger (in absolute value) in the ANTI-INFEC, CARDIO and NEOPLASTIC classes, while those in the BIOLOGICS, CNS, GI, and RADIO-DIAG therapeutic classes are considerably less negative (in some cases, even positive).

As noted earlier, for purposes of comparison we have also estimated an auxiliary regression specification in which LNINDNDA – the logarithm of the time in months between the IND and NDA/BLA filings – is the dependent variable. Results from this pre-NDA/BLA clinical development time regression appear in the final three columns of Table 2. Estimates on the PRIORITY, ORPHAN and DOMESTIC indicator variables are not statistically significant (p-values of around 0.25 and larger). Relative to the time in clinical development for BIOLOGICS, drugs in the ANTI-INFLAM class have the longest clinical development time (exp 0.6738 = 96% longer), followed by CNS (71% longer), NEOPLASTICS (62%), CARDIO (58%), RESPIRATORY (47%), DERM-OPTHALM (45%), and METAB-ENDO (41%), each of which is statistically significantly longer than that for BIOLOGICS. The only therapeutic class with a negative parameter estimate is that for AIDS, which is -0.0764 but not significant. One way of interpreting these findings is that the time in clinical development is relatively short for BIOLOGICS and AIDS drugs, much shorter than that in most other therapeutic classes.

In terms of the impact of PDUFA-related variables on clinical development time, as seen in Table 2, the coefficient on the overall TIME TREND is positive and significant, increasing about 2.6% per year (p-value 0.015). While the estimated coefficients on PDUFA-I*TIME and

PDUFA-II*TIME are negative and of similar magnitude (-0.0445 and -0.0423, respectively), only the latter is statistically significant (p-value 0.039). Since the impact of the passage of time during the PDUFA years is the sum of the estimated coefficients on TIME TREND and PDUFA-II*TIME (0.0271 – 0.0443 = -0.0172), the total impact is quite small, and likely insignificant.

Our final line of empirical analysis involves a preliminary exploration of the impact of the absence of a Congressionally-confirmed FDA Commissioner on approval times, controlling for other confounding variables. Our results are provocative but fragile, and clearly call for more detailed examination. Parameter estimates on the various Commissioner-absence measures in Models I through IV, as well as those on the TIME TREND and PDUFA interaction variables, along with parameters from the "base case" specification in Table 2, are given in Table 3.

In a specification with NOCOM% (Model I) as an additional regressor, the coefficient estimates is 0.0321, but with a p-value of 0.710, it is clearly not significant. Parameter estimates on the TIME TREND and PDUFA interaction variables are not much affected, relative to the base case. It is worth noting that because approval time is in the denominator of NOCOM% and also appears in log-transformed form as the dependent variable in this specification, one would expect the coefficient estimate on NOCOM% to reflect a spurious negative correlation, and thus be downward biased.

In Model II, where LNNOCOM is instead the additional regressor (and observations for which NOCOM% = 0 are arbitrarily assigned a value of log[0.001]), the coefficient estimate is 0.0591, with a p-value of <0.001. In this specification, the elasticity of approval time with respect to NOCOM% is positive, but small. Because the log of approval time appears on both the left and right-hand side of the regression specification, again one might expend the coefficient estimate on LNNOCOM to be downward biased. Notice also that in this

specification, the TIME TREND coefficient estimate becomes positive and significant, and both PDUFA-related coefficient estimates become much more negative. Recall that the extent of Commissioner absence was much greater during PDUFA-I and especially PDUFA-II than it was earlier -- 61% of all Commissioner absence days occurred during PDUFA-I and II, while only 39% prior to PDUFA. Because in Model II the increased prevalence of Commissioner absences lengthens approval times, the impact of PDUFA on reducing approval times is estimated as being even greater than in the base case.

In Model III, however, where the 0-1 EVERNOCOM indicator variable takes on the value of 1 whenever NOCOM% > 0, the positive coefficient estimate becomes much larger at 0.3928, with a p-value of <0.001. In this specification, the mere existence of any absence of the Commissioner while the NDA/BLA is being reviewed increases approval times by about 48%, other things equal. We view this result as rather implausible. Note also that again the estimated coefficients on the TIME TREND and PDUFA interaction variables change considerably from the base case specification, with the PDUFA-related coefficient estimates becoming much larger in absolute value.

Finally, in Model IV, the most complex specification , both NOABSENCE and LNNOCOMX appear as regressors. Here the estimated coefficient on NOABSENCE is negative at -0.2445 (p-value <0.001), while that on LNNOCOMX is -0.1183 (p-value <0.001). Although the negative estimate on NOABSENCE is consistent with the hypothesis that Commissioner absence increases approval times, other things equal, the negative estimate on LNNOCOMX is inconsistent with that hypothesis. As in Models II and III, the estimated annual differential impacts of passage of time during the PDUFA-I and PDUFA-II eras are much larger (in absolute value) than in the base case.

Although these various specifications point to the possibility that the extent of Commissioner absence increases drug approval times, other things equal, the magnitude of the estimated impacts are clearly fragile. Informal conversations we have had with officials at the FDA and with industry regulatory affairs personnel reflect considerable skepticism that the presence or absence of a confirmed Commissioner would have any substantial impact on day-to-day application review procedures and other daily review operations, and thus on average approval times. Rather, industry officials suggest that while the Commissioner may become involved in particularly controversial situations, these are likely to be relatively infrequent.[14] We conclude here that this issue deserves much more detailed examination, with a clear need to develop more defensible and independent measures of the impact of a confirmed Commissioner on day-to-day operations.

With these regression results in hand, we now move on to a discussion of the measurement of the net present value (NPV) benefits and costs from PDUFA-I and II.[15]

V. MEASUREMENT OF THE BENEFITS AND COSTS OF PDUFA

We first consider sales and costs in two scenarios: (i) the observed world in which actual FDA approval dates are employed; and (ii) a counterfactual world in which PDUFA-I and II did not occur. In this second case, for each approved NDA/BLA, the counterfactual approval date is the observed approval date plus the predicted change in approval date for that drug with and without the PDUFA interaction variables set to zero. This predicted change is based on the estimated base case regression equation given in Table 2. We assume here that whether the NDA/BLA was ultimately approved by the FDA is unaffected by passage and implementation of the PDUFA legislation.

Measures of the benefits and costs of PDUFA depend on the perspective taken. Let p(y) denote the inverse (downward sloping) demand curve from classic microeconomics textbook analyses, and let c(y) be the variable cost function, where y is the quantity sold, and where the variable cost function excludes any fixed or sunk costs of research and development. Note these R&D costs are sunk regardless of approval time changes brought about during PDUFA.

The producer surplus (also called variable profits, or in some cases free cash flow) $\Pi(y)$ and consumer surplus s(y) are specified as

$$\Pi(y) = p(y)*y - c(y) \text{ and} \qquad \text{Eqn. (2)}$$

$$s(y) = \mu(0,y)\,[p(s) - p(y)]ds. \qquad \text{Eqn. (3)}$$

From basic microeconomics, producers' surplus in Eqn. 2 represents revenues minus variable costs, whereas consumers' surplus is the area under the demand curve but above the price. Recall that when a firm has exclusivity rights to a product such as the "monopoly" power granted a patentee, the optimal price is set where marginal revenue equals marginal cost, yielding optimal output y* and optimal price p(y*). The area under the demand curve then consists of consumers' surplus, producers' surplus, variable costs and a deadweight loss component. Denote the sum of consumers' plus producers' surplus as the social surplus, or social value of a product. It is of course the case that generally both the consumers' and producers' surplus are unobservable. However, we argue below that under rather modest identifying restrictions, they can be estimated from readily available sales data.

Regardless of the mathematical form of the inverse demand and variable cost functions, by definition the total social surplus is bounded from below whenever social surplus is greater than sales, i.e. when

$$\Pi(y) + s(y) \geq p(y)*y. \qquad \text{Eqn. (4)}$$

Substituting in for $\Pi(y)$ from Eqn. (2) and rearranging yields

$$s(y) \geq c(y), \qquad \text{Eqn. (5)}$$

i.e., consumers' surplus is at least as large as variable costs. This condition in Eqn. (5) is quite plausibly satisfied for an industry such as pharmaceuticals, for marginal costs of production are widely perceived as being relatively small, especially relative to the fixed costs of R&D. Notice that when the condition in Eqn. (5) is satisfied, then from Eqn. (4), observed sales provide a lower bound to the estimated social (consumers' plus producers') surplus, i.e. industry sales understate social surplus.

Further identification can be achieved by imposing additional but familiar restrictions on the shape of the variable cost and inverse demand functions. If the inverse demand curve is assumed to be linear, as in $p(y) = a - by$, and if marginal costs are assumed to be constant, as in $c(y) = c$, then the variable profit-maximizing output is

$$y^* = \text{argmax } \Pi(y) = (a - c)/2b. \qquad \text{Eqn. (6)}$$

This situation is depicted in Figure 4. Since marginal cost is constant at c, if the market were competitive, the price would be equal to c. Given exclusivity due to patent protection, the optimal quantity produced by the "monopolist" is at y^*, yielding a price of $p(y^*)$. Total variable costs is area D in Figure 4. Note that y^* is one half the competitive output, which would be where the demand curve intersects the marginal cost curve, yielding $p(y) = c$. A useful implication of this is that the amount of consumer surplus (area A in Figure 4) is the same magnitude as the amount of deadweight loss (area C in Figure 4). In this case, consumer surplus A is half the producer surplus B, i.e.,

$$s(y^*) = \Pi(y^*)/2, \text{ or area A} = \tfrac{1}{2} \text{ area B.} \qquad \text{Eqn. (7)}$$

Note that this is true regardless of the magnitude of the demand and cost parameters a, b and c (provided a and b are positive, and c is non-negative). Hence of the total social surplus, consumers' surplus is one third, while producers' surplus is two thirds of the total surplus.

Together, one important implication of this is that the total social (consumers' plus producers') surplus is bounded from below whenever

$$[1 + ½]\Pi(y^*) \geq p(y)^*y. \qquad \text{Eqn. (8)}$$

Substituting in and rearranging yields

$$c/p(y) \leq 1/3. \qquad \text{Eqn. (9)}$$

What this means is that under linear demand and constant marginal costs, whenever marginal cost is less than a third of the price, data on product sales provide a lower bound on the amount of social (consumers' plus producers') surplus. This again appears to us to be reasonable and plausible for many pharmaceuticals in which marginal costs of producing tablets, capsules or injectables are relatively small.

For example, using generic prices several years after initial generic entry as an estimate of marginal costs, and based on data from the 1980s and early to mid-1990s, Grabowski and Vernon [1992] and Berndt, Cockburn and Griliches [1996] report that in most cases the brand price is more than three times the estimated marginal costs.[16] Similarly, using more recent 2001 data, the Center for Medicare and Medicaid Services [2003], Office of Research, Development and Information, estimates that on average for branded pharmaceutical companies, costs of goods sold are about 30% of revenues (implying gross margins of 70%, or price/cost ratios of 3.3), while for biotechnology companies costs of goods sold are an even smaller proportion of goods sold (16%, implying an 84% gross margin, or price/cost ratio of 6.25).[17]

While the above analysis is admittedly simple, and avoids issues such as the impacts of taxes and moral hazard, in the calculations we undertake below that provide an economic evaluation of PDUFA, we treat product sales as a lower bound estimate of total social (consumers' plus producers') surplus.[18] It is worth noting here that even when the demand curve is nonlinear, it is readily observed that at long as it is convex to the origin, area A will be greater than area D, implying that A + B (social surplus) is greater than B + D (sales revenues). Thus, our use of sales revenues as a lower bound to social surplus is appropriate even in more general contexts than assumed here.

An alternative perspective on the economic valuation of PDUFA is from the view of the innovating producer. PDUFA affects an innovator's returns by raising both the costs and the benefits of an innovation. The cost is raised by the amount of the user fee (a type of fixed cost, that does not vary annually with the level of output y), while the benefit is raised by the gains in the present value of the innovator's return induced by the more rapid FDA approval.

In terms of empirical implementation, we specify the following framework. Let α_i denote the time between the enactment of PDUFA-I (September 1, 1992) and the NDA/BLA submission filing date for drug i. Let τ_i be the time between the NDA/BLA filing date and the final FDA approval for drug i. Based on the multivariate regression model, let δ_i be the difference between the predicted counterfactual NDA/BLA approval time in the absence of PDUFA and the predicted NDA/BLA approval time under PDUFA. Then let μ_i be the time between the FDA approval date and the US market launch of drug I; in our analysis below we will assume this approval to launch delay is unaffected by PDUFA. Let ω be the number of years the approved drug will be marketed, i.e. the length of the product life cycle. Below we assume this is 15 years. Defining r as the real discount rate, CF_{ij} as sales cash flow in year j of the lifecycle of drug i,

viewed at the beginning of PDUFA-I, the present value of sales over all i drugs under PDUFA is then computed as

$$PV(Sales)_{PDUFA} = \Sigma_i [1/(1 + r)^{w(i)}][\Sigma_j^{\omega}{}_{=1}(CF_{ij}/(1 + r)^j)]$$

where

$$w(i) = \alpha_i + \tau_i + \mu_i . \qquad \text{Eqn. (10)}$$

For the counterfactual case in the absence of PDUFA, the present value of sales over all I drugs is computed as

$$PV(Sales)_{NOPDUFA} = \Sigma_i [1/(1 + r)^{w'(i)}][\Sigma_j^{\omega}{}_{=1}(CF_{ij}/(1 + r)^j)]$$

where

$$w'(i) = \alpha_i + \tau_i + \delta_i + \mu_i . \qquad \text{Eqn. (11)}$$

The difference between Eqn. (10) and Eqn. (11) is then the difference in present value of sales (the gross benefit) over all I drugs associated with enactment and implementation of PDUFA-I and II, i.e.,

$$\text{Gross Benefit} = PV(Sales)_{PDUFA} - PV(Sales)_{NOPDUFA} . \qquad \text{Eqn. (12)}$$

As discussed above, under simple but plausible conditions, this difference in Eqn. (12) can be interpreted as the change in social surplus associated with PDUFA.

A similar set of calculations can be undertaken to compute the present value of the additional user fee costs associated with PDUFA. Subtracting these present values of PDUFA user fees from the gross present value benefits calculated in Eqn. (12) yields an estimate of the net social surplus associated with enactment and implementation of PDUFA.

To implement these calculations empirically, data are needed on actual and predicted sales of drugs over their life cycle, as well as actual and predicted PDUFA user fees. Through a third party agreement with IMS Health Inc., the FDA provided us comprehensive retail plus

hospital sales data for all drugs on the U.S. market from February 1998 through December 2002. The sales data included the following channels: independent pharmacies, chain pharmacies, mass merchandisers with and without pharmacies, mail order pharmacies, food stores with pharmacies, non-federal hospitals, federal facilities, clinics, long-term care facilities, home health care, closed HMOs, and miscellaneous channels (starting in 1999, prisons, universities and other).[19]

Given that many drugs were approved prior to 1998 and given that data on future sales beyond 2002 were unavailable, estimates of sales outside years 1998 through 2002 were needed. Fortunately, IMS Health has reported results of an analysis of launch to peak sales for new chemical entities, based on 816 new chemical entities launched since 1983 (information on the terminal year is not available).[20] Results from this analysis relate over a 15 year life cycle the average yearly sales as a percent of peak sales. Although the IMS analysis found that a drug on average reaches its peak sales 13 years after launch, sales in years 10 through 13 are relatively flat, and then drop off precipitously.[21]

Based on the IMS data and analysis, for each drug, sales were first annualized if the available sales data did not begin in January of a given year.[22] Predicted peak sales for that drug were then computed using the IMS life cycle year to peak percentages, as were sales for all other years not observed in the IMS data. All sales were then deflated to 1992 dollars using the GDP deflator.

Incremental costs associated with PDUFA include calculations of the present value of PDUFA user fees. PDUFA fees consist of application fees, establishment fees, and product fees; as noted earlier, these have risen sharply since 1992. PDUFA fees for 2005 and forward were estimated based on the compound annual growth rates (CAGR) observed from 1993 to 2004.

Given that the US Congress has renewed PDUFA in 1997 and 2002, and given that the renewal year has generated a much larger percentage increase in the user fee schedule than the relatively minor subsequent increases within PDUFA-I. PDUFA-II and PDUFA-III, we forecasted significant increases for 2008 and 2013, the next times PDUFA will likely need to be reauthorized. Specifically, we constructed large percentage increases in reauthorization years and subsequent minor increases between reauthorizations so as to yield a CAGR in real user fees of 15%, approximately equal to that observed historically. Similar to the sales curves, the actual PDUFA fees were deflated to 1992 dollars using the GDP deflator.

Novel NDA/BLA application fees were charged during the year of an NDA/BLA submission to the FDA. Product fees and establishment fees were allocated during each year of sales. We allocated 100% of the establishment fee to each NME. This likely overstates such fees, since many establishments manufacture more than one drug or biologic; informal conversations with the FDA indicated that on average, approximately three drugs/biologics are manufactured per location. This allocation therefore biases upward the user fee cost calculations.

It was also necessary to forecast the number of future supplemental applications. Though detailed information is not yet readily available to us, from PDUFA performance reports of 1997, 1999 and 2003, we noted that between 1993 and 2003, a total of 1,266 original NDAs/BLAs were filed at the FDA (not all of which were of course approved). Over the same time period, 1,518 efficacy supplements were also filed (of which how many were approved we do not know). The ratio of filed supplements to filed original NDAs/BLAs over this time period is 1.199. Since it is plausible to expect that the proportion of supplemental submissions approved by the FDA is larger than the proportion of novel NDA/BLA submissions that is approved, we

expect the actual number of supplementals approved for each approved NDA/BLA to be larger than 1.199. We therefore make the assumption that for every approved NDA/BLA, two supplemental applications are submitted in the second year post market launch. This is a relatively "conservative" assumption in that 2.0 is a large number, and that the timing of both supplements being in the second year post launch likely overstates the rapidity with which such supplementals are filed. These assumptions on supplementals therefore bias upwards the present value of the PDUFA supplemental user fees. Since supplemental NDAs/BLAs do not increase the product fee or establishment fee already being paid by a sponsor, no further adjustments are made.

VI. RESULTS FROM THE PDUFA NPV ANALYSIS OF SOCIAL SURPLUS

We implement the NPV calculations using a range of real discount rates – 1%, 3%, 5%, 7%, 9% and 11%, using the same discount rates for costs as for benefits.[23] Although we undertake separate calculations for drugs in each of the 13 therapeutic classes, in each of these classes we employ the same shape of the sales product life cycle profile – the average profile based on IMS analysis of 813 new NDAs/BLAs since 1983. To the extent the shape of the product life cycle sales profile differs among therapeutic classes, class-specific findings should be viewed with considerable caution. In total over all therapeutic classes, however, we believe use of the average profile provides a reasonable approximation. Here we report only on aggregate calculations over all 13 therapeutic classes. In future research we will examine the sensitivity of our findings to use of other life cycle profiles.[24]

In Figure 5 we plot the difference in present value of industry sales with and without PDUFA, summed over all therapeutic classes, as a function of alternative real discount rates. Recall that this provides a lower bound to the social (producers' plus consumers') surplus. Also

plotted in Figure 5 is the net present value (PV of industry sales minus PV of total PDUFA fees); the PV of PDUFA fees are plotted separately in Figure 6. Total PV benefits of sales, indicated in solid black in Figure 5, range from $6.8 billion to $18.6 billion, with the largest estimate based on a 7% real discount rate and the smallest corresponding to a 1% real discount rate. The solid white bars in Figure 5 indicate the NPV after the PDUFA fees (displayed in Figure 6) are subtracted. Relative to the PV gross benefit, the PV of PDUFA user fees are small, and become increasingly small as the real discount rate increases. At discount rates of 5% and 7%, the PV of PDUFA user fees are only 3.7% and 2.7% of the PV gross benefit, respectively, yielding net social surplus estimates of $17.3 and 18.1 billion, respectively.

Viewed from the perspective of total social (producers' plus consumers') surplus, and assuming linear demand curves, constant marginal costs, and using a 5% discount rate, the increase in NPV of sales of about $17.3 billion can be broken down into approximately one third consumers' surplus (about $5.8 billion) and two thirds producers' surplus (about $11.5 billion). Hence, even if consumers rather than industry had directly paid the entire PDUFA user fees of $664 million, the investment would appear to have been a wise one, yielding a NPV of a bit more than $5.1 billion.

Viewed from the perspective of industry, the increase in PV of sales of about $18 billion (assuming a 5% discount rate) is a large multiple of the $664 million increase in PDUFA user fees. However, because of the reduced FDA approval times and more rapid product launch induced by PDUFA, industry also experienced present value increases in its construction, manufacturing, marketing and other costs. If one assumes that profitability margins (however measured, but not counting the PDUFA fees) as a percent of revenues would have been the same after 1992 had PDUFA not been enacted and implemented, then the $17.3 NPV increment

associated with PDUFA would represent about 2.1% of the $862.9 billion counterfactual PV of sales, implying that because of PDUFA, the present value of industry profits increased by about 2.1%. This represents a relatively modest increase in "profits" that could be plowed back into further R&D, thereby creating incentives for further innovation. However, this constant profitability margin assumption may be inappropriate. Marketing, construction and other launch-related costs are known to figure predominantly in the early years of the product life cycle, and the evidence presented above suggests quite clearly that PDUFA accelerated launch dates, thereby perhaps accelerating present values of costs even more than revenues on a proportional basis. Thus a considerably more detailed assessment of changes in the PDUFA-induced present value of costs is called for, perhaps involving the free cash flow life cycle framework utilized by Grabowski, Vernon and DiMasi [2002]. Such an analysis is left for future research.

VII. DISCUSSION, LIMITATIONS AND CONCLUDING REMARKS

In this paper we have modeled and quantified the impact of PDUFA-I and II on drug approval times at the FDA, in part by constructing a counterfactual hypothetical situation in which PDUFA did not exist. We find that PDUFA-I resulted in an acceleration of the decline in NDA/BLA approval times at the FDA. Of the 10 month decline from about 24 months in 1991 to 14 months in 2002, about 60% is attributable to the enactment and implementation of PDUFA. Declines in approval time decelerated significantly, however, between PDUFA-I and PDUFA-II, with annual differential declines about half as large during PDUFA-II.

As an auxiliary analysis, we have obtained provocative but fragile evidence concerning the impact of the extent of absence of a Congressionally-confirmed FDA Commissioner on drug approval times. That issue deserves much more detailed examination.

We evaluate the economic benefits and costs of PDUFA by considering impacts on changes in consumers' surplus, producers' surplus and their sum – social surplus, using the framework of microeconomic pricing with market power. When the demand curve is linear and marginal costs are constant, as long as the marginal cost of a patent-protected drug is less than one thirds its price, industry sales provide a lower bound estimate of social surplus, one third of which is consumers' surplus and two thirds of which is producers' surplus. Evidence from generic drug pricing, and from other industry observers, suggests that for pharmaceutical and biotech industry products, that marginal costs are less than one third the U.S. brand price is likely a reasonable and plausible condition. However, industry sales provide a lower bound estimate of social surplus even when the demand curve is nonlinear, provided it is convex to the origin. Using data from IMS Health, we estimate social surplus using a variety of discount rates. At a discount rate of 5%, the PV of gross PDUFA-induced sales is about $18 billion, while the PV of the associated PDUFA user fees is only 3.7% as large at about $664 million, implying a net social surplus of about $17.3 billion. Assuming fixed margins, producers' surplus grew about 2.1% as a result of PDUFA. Allocating the net social surplus one-third to consumers ($5.8 billion) and two-thirds to producers ($11.5 billion), we conclude that for both consumers (patients/providers) and producers, incremental benefits of PDUFA far outweighed the $664 million in PDUFA-related user fees.

Our analysis is based on a number of assumptions and limitations, some of which we plan to investigate in subsequent research. First, our benefit-cost and social surplus calculations are aggregated over all drug classes. Further research should focus on disaggregation into specific therapeutic areas and "blockbuster" products. In addition, we have employed a product life cycle sales profile pattern based on data and analysis from IMS Health. Other life cycle sales profiles,

such as that in the rate of return calculations by Grabowski, Vernon and DiMasi [2002] could be used instead; moreover, their framework allows for a more detailed free cash flow analysis that allows the intensity of marketing, manufacturing and other costs to vary over the product life cycle. Although we have interpreted the relationships among social surplus and industry sales within the context of a linear demand curve, explicit nonlinear formulations of the demand curve are worthy of further examination. The analysis reported here ends with NDAs/BLAs submitted to the FDA by the end of PDUFA-II (September 30, 2002), and approved by the FDA up through May 2004. It would be useful to update the approval data, to ensure that right censoring is not a significant issue.

Our study contains a number of additional limitations. One possible cost of PDUFA not included in our cost calculations is that while PDUFA may have accelerated the approval process, it may also have altered the set of drugs to be approved, lowering the quality of approved drugs. Indeed, many argue that the FDA serves as a principal source of evidence-based medicine and that compromising its ability to assess the safety of new medications would entail large social costs.

There is only limited evidence on whether PDUFA affected the quality of drugs approved by the FDA. A study published by the U.S. Government Accounting Office [2002] at the time PDUFA-III renewal was being considered reported that from 1985 to 1992, 3.10% (6 of 193) of drugs approved by the FDA were subsequently withdrawn for safety-related reasons, whereas during PDUFA between 1993 and 2000 a slightly higher percentage, 3.47% (9 of 259) FDA approved drugs were withdrawn for safety reasons. The GAO study did not report whether this difference was statistically significant. [25] In response, the FDA noted not only issues of possible lack of statistical significance given that withdrawals were relatively rare events, but also that the

GAO had excluded biologics from their analysis. Moreover, in some cases post-PDUFA FDA approvals were attributed to the PDUFA time frame but in fact NDAs for these NMEs had been submitted prior to PDUFA-I. According to FDA analysis, the withdrawal percentage from 1979 to 1992 was close to 2.5%, while for NDAs approved during PDUFA-I and II until 1999, the withdrawal rate was virtually identical at 2.6%.[26] While a detailed assessment of drug withdrawals pre- and post-PDUFA would be most useful, as would be quantification of the costs and benefits associated with use of these drugs prior to their being withdrawn, such an analysis is clearly beyond the scope of this study.

A related set of costs not incorporated into the current analysis involves consideration of whether the proportion of NDAs/BLAs that failed or were withdrawn changed during the PDUFA era. Due to confidentiality obligations to sponsor companies, the FDA was unable to provide detailed or aggregate information on NDAs/BLAs that were rejected or withdrawn. It is possible that failure rates of NDAs/BLAs did not change from the pre-PDUFA time period to the PDUFA era (or that trends in rates did not change). However, if failure rates increased during PDUFA, this added cost is unaccounted for in the current analysis. This could have a significant negative impact on the overall benefit of the findings reported here. Likewise, a reduction in failure or withdrawal rates would increase the benefits delivered by PDUFA. While lack of data availability precludes a robust analysis of this issue, this issue nonetheless does not negate the benefits realized from faster approvals that actually occurred under PDUFA.

Another limitation of our study is that the sales data used in the benefit calculations represent U.S. sales only. Ex-US sales for drugs are typically 75-100% of U.S. sales. The extent to which accelerated approval in the United States affected international approvals and launch dates was not incorporated into our calculations. If earlier U.S. approval encouraged more rapid

approval abroad, then the NPV social surplus benefit of PDUFA would be greater than we have calculated.

To the extent that accelerated FDA approval of NDAs/BLAs resulted in an increase in the duration of patent protection prior to patent expiration, it is possible that our calculations understate producers' benefits from PDUFA. Two considerations suggest that any such impact is likely to be rather small. First, patent expiration typically takes place 12 or so years following product launch ("effective patent life"), and thus viewed in present value terms at the beginning of PDUFA in 1992, such end of product life benefits are likely to be very small when discounted.[27] Second, under the Hatch-Waxman Act, the maximum amount of time a drug could enjoy market exclusivity was set at 14 years (with possible 6-month extensions for sponsors proving efficacy in the pediatric population); precisely how many of the drugs in our sample would have run into this exclusivity ceiling is unclear, but is likely to be non-trivial. To the extent this would occur, accelerated FDA approval would not translate into longer effective patent life.

A final limitation of our study is that we have not undertaken a separate analysis of "fast track" provisions that involve rolling submissions to the FDA. We believe the impact of this omission is likely to be relatively minor, for not only is the number of NDAs/BLAs granted fast track study in our sample up through 2002 likely to be small, but preliminary analyses by several researchers suggests that the differential impact of fast track from priority status on approval times is small, and in some cases fast track may even lengthen approval times.[28]

The framework we have employed in this study for evaluating the costs and benefits of regulatory actions at the FDA involves assessing shifts in the timing of submissions, approvals, costs, and revenues. This framework could be extended to numerous policies beyond PDUFA,

such as facilitating more rapid FDA approvals by allowing greater use of surrogate markers as endpoints, while simultaneously requiring post-approval surveillance studies. More generally, since the clinical development time between filing of the IND and submission of the NDA/BLA is two to four times larger than review time of the NDA/FDA at the FDA, the framework developed here might be useful in examining potential costs and benefits of numerous policies that could affect the critical pathway from pre-clinical discovery through submission of an NDA/BLA.

In summary, our evaluation of the incremental benefits and costs associated with passage and enactment of PDUFA-I and PDUFA-II implies that U.S. patients/providers ("consumers") as well as industry producers have received benefits many times the size of the PV of the PDUFA user fees. While our analysis is preliminary and more detailed research is called for, the sheer size of benefits relative to costs makes it unlikely that our qualitative findings will be overturned by future research.

Table 1					
Descriptive Statistics on Approval Times and Regressors					
Approval Time in Months by Class (n)	Mean	Minimum	Median	Maximum	Std. Dev.
AIDS (15)	7.96	2.37	5.93	30.23	6.91
ANTI-INFEC (94)	19.84	1.40	16.50	83.30	14.35
ANTI-INFLAM (20)	37.78	5.93	26.93	124.20	33.80
BIOLOGICS (90)	24.58	4.80	18.52	134.63	21.22
CARDIO (95)	28.81	6.00	24.77	101.77	17.44
CNS (66)	28.35	0.60	23.08	85.47	17.95
DERM-OPHTHAL (50)	18.88	2.90	18.33	45.83	10.91
GI (26)	23.54	7.47	20.45	52.00	11.83
METABOL-ENDO (82)	21.50	3.77	15.92	77.60	15.30
NEOPLASTIC (43)	14.55	1.53	10.00	51.00	11.15
OTHER (20)	19.03	8.70	17.70	38.60	7.43
RADIO-DIAG (38)	30.34	8.63	29.93	78.97	13.54
RESPIRATORY (23)	38.06	5.57	33.00	90.53	24.09
OVERALL (662)	24.04	0.60	20.00	134.63	17.83
Regressors					
LNINDNDA	3.845	0	4.075	6.119	1.236
IND MISS	0,062	0	0	1	0.241
DOMESTIC	0.427	0	0	1	0.516
ORPHAN	0.180	0	0	1	0.384
PRIORITY	0.301	0	0	1	0.459

Table 2						
ECONOMETRIC RESULTS FROM MULTIVARIATE REGRESSIONS						
	Dependent Variable: LNAPP			Dependent Variable: LNINDNDA		
REGRESSOR	Estimate	Std. Err.	P-value	Estimate	Std. Err.	P-value
Constant	**3.5153**	**0.156**	**<0.001**	**3.5559**	**0.149**	**<0.001**
LNINDNDA	-0.0014	0.031	0.965	NA	NA	NA
IND MISS	0.1032	0.160	0.521	NA	NA	NA
TIME TREND	**-0.0171**	**0.008**	**0.038**	**0.0271**	**0.011**	**0.012**
PDUFA-I*TIME	**-0.0807**	**0.024**	**0.001**	-0.0485	0.032	0.129
PDUFA-II*TIME	**-0.0367**	**0.015**	**0.018**	**-0.0443**	**0.020**	**0.030**
PRIORITY	**-0.4902**	**0.056**	**<0.001**	0.0848	0.075	0.259
ORPHAN	0.1088	0.065	0.094	0.0667	0.088	0.449
DOMESTIC	-0.0718	0.045	0.114	-0.0582	0.063	0.358
AIDS	**-0.8118**	**0.168**	**<0.001**	-0.0776	0.220	0.724
ANTI-INFEC	**-0.3061**	**0.095**	**0.001**	0.1402	0.131	0.285
ANTI-INFLAM	0.1015	0.152	0.505	**0.6937**	**0.200**	**0.001**
CARDIO	0.1199	0.094	0.203	**0.4616**	**0.129**	**<0.001**
CNS	0.1279	0.102	0.211	**0.5463**	**0.136**	**0.001**
DERM-OPHTHAL	-0.1884	0.110	0.087	**0.3699**	**0.147**	**0.012**
GI	-0.0877	0.135	0.516	0.3470	0.179	0.053
METABOL-ENDO	-0.0616	0.094	0.514	**0.3369**	**0.130**	**0.010**
NEOPLASTIC	**-0.3042**	**0.116**	**0.009**	**0.4496**	**0.156**	**0.004**
OTHER	**-0.3518**	**0.150**	**0.019**	0.1225	0.199	0.539
RADIO-DIAG	0.1827	0.118	0.122	0.0020	0.164	0.990
RESPIRATORY	**0.2885**	**0.140**	**0.040**	**0.4389**	**0.186**	**0.018**
N	662			621		
R-squared	0.3925			0.0866		
Eqn. F-statistic	20.708			3.170		

Notes: The reference case is for a BIOLOGICS BLA assigned a standard rating, not an ORPHAN drug, sponsored by a non-DOMESTIC applicant. NA is not applicable.

Table 3					
RESULTS FROM ALTERNATIVE COMMISSIONER ABSENCE SPECIFICATIONS					
(Standard Errors in Parentheses, P-values in Brackets)					
Variable	Base Case	Model I	Model II	Model III	Model IV
TIMETREND	-0.0171	-0.0166	0.0020	0.0074	0.0096
	(0.008)	(0.008)	(0.008)	(0.008)	(0.008)
	[0.038]	[0.049]	[0.811]	[0.382]	[0.254]
PDUFA-I*TIME	-0.0807	-0.0843	-0.1424	-0.1475	-0.1337
	(0.0241)	(0.026)	(0.025)	(0.024)	(0.025)
	[0.001]	[0.001]	[<0.001]	[<0.001]	[<0.001]
PDUFA-II*TIME	-0.0367	-0.0392	-0.0872	-0.0939	-0.0869
	(0.015)	(0.017)	(0.017)	(0.016)	(0.016)
	[0.0178]	[0.020]	[<0.001]	[<0.001]	[<0.001]
NOCOM%		0.0321			
		(0.086)			
		[0.710]			
LNNOCOM			0.0573		
			(0.009)		
			[<0.001]		
EVERNOCOM				0.3928	
				(0.050)	
				[<0.001]	
NOABSENCE					-0.2445
					(0.064)
					[<0.001]
LNNOCOMX					-0.1183
					(0.033)
					[<0.001]
R-Squared	0.3925	0.3926	0.4320	0.4468	0.4578

Figure 1
Mean and Median Approval Times for All NDAs/BLAs: 1979 to 2002

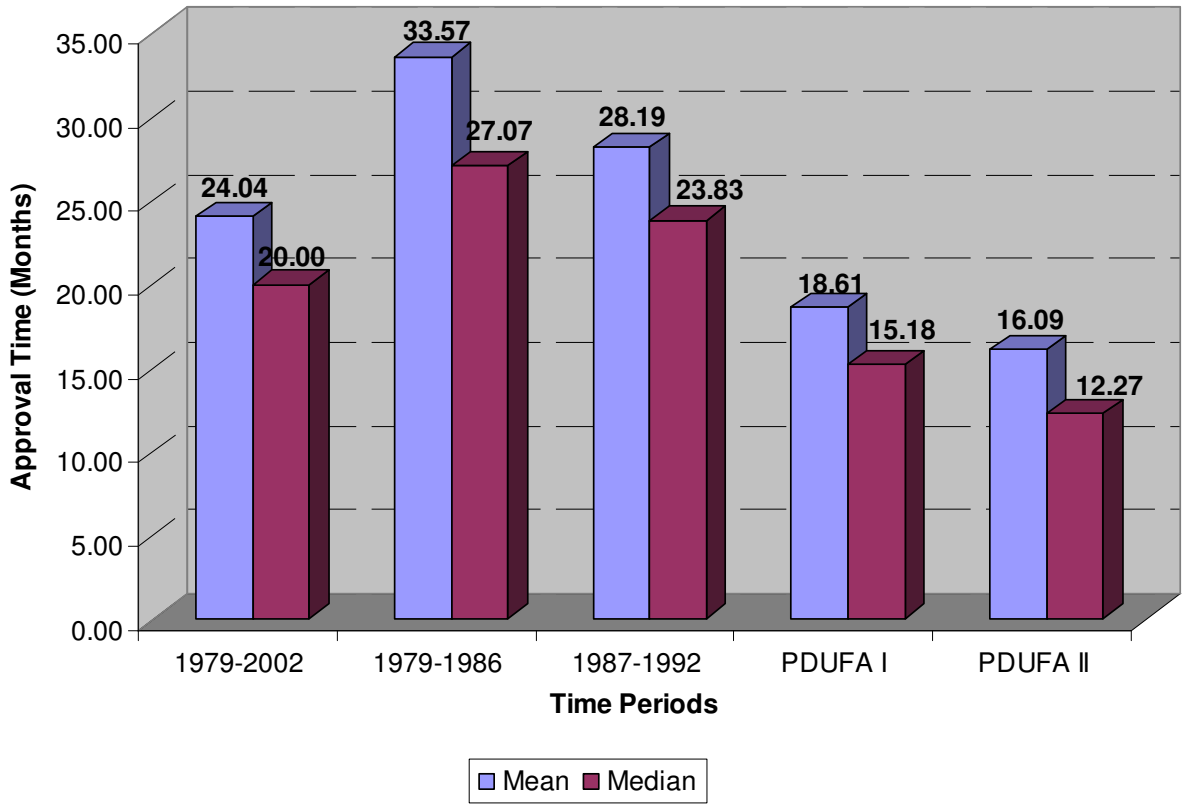


Figure 2
Survival Curves for All NDA/BLA Types

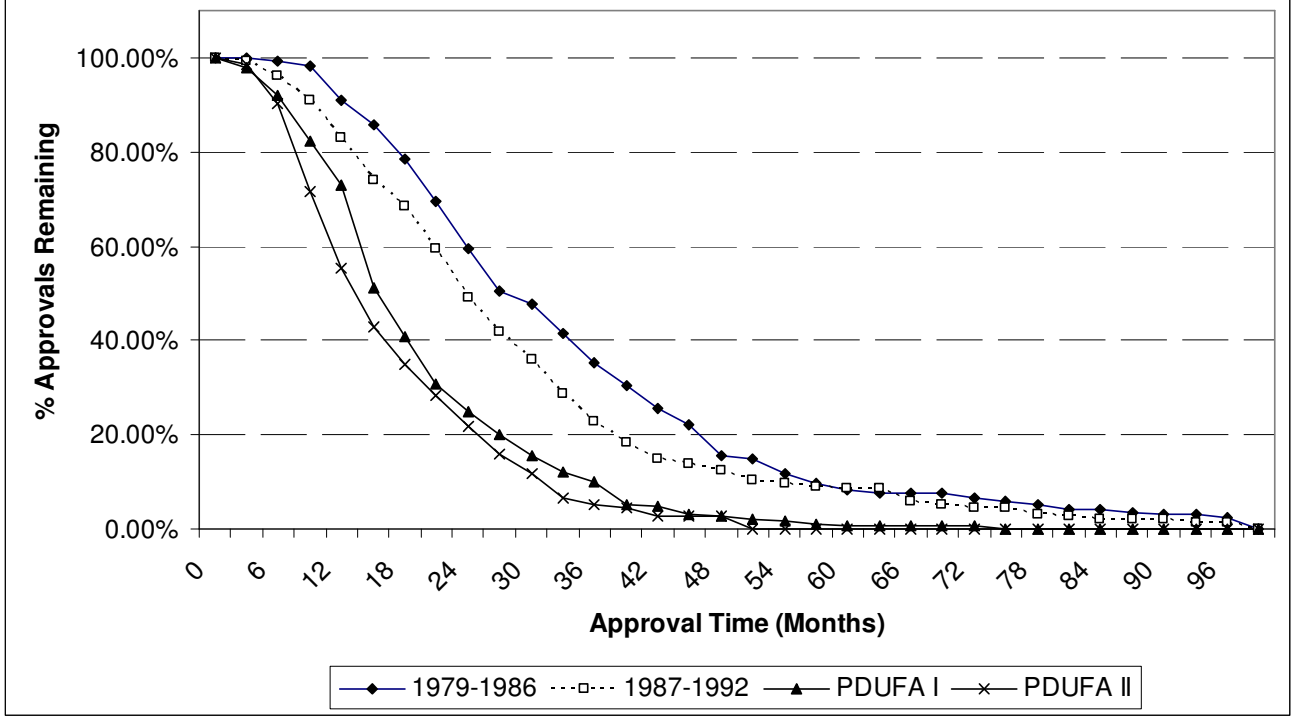


Figure 3
Predicted NBA/BLA Approval Times with and without PDUFA I/II
(Regressors Evaluated at Overall Sample Means)

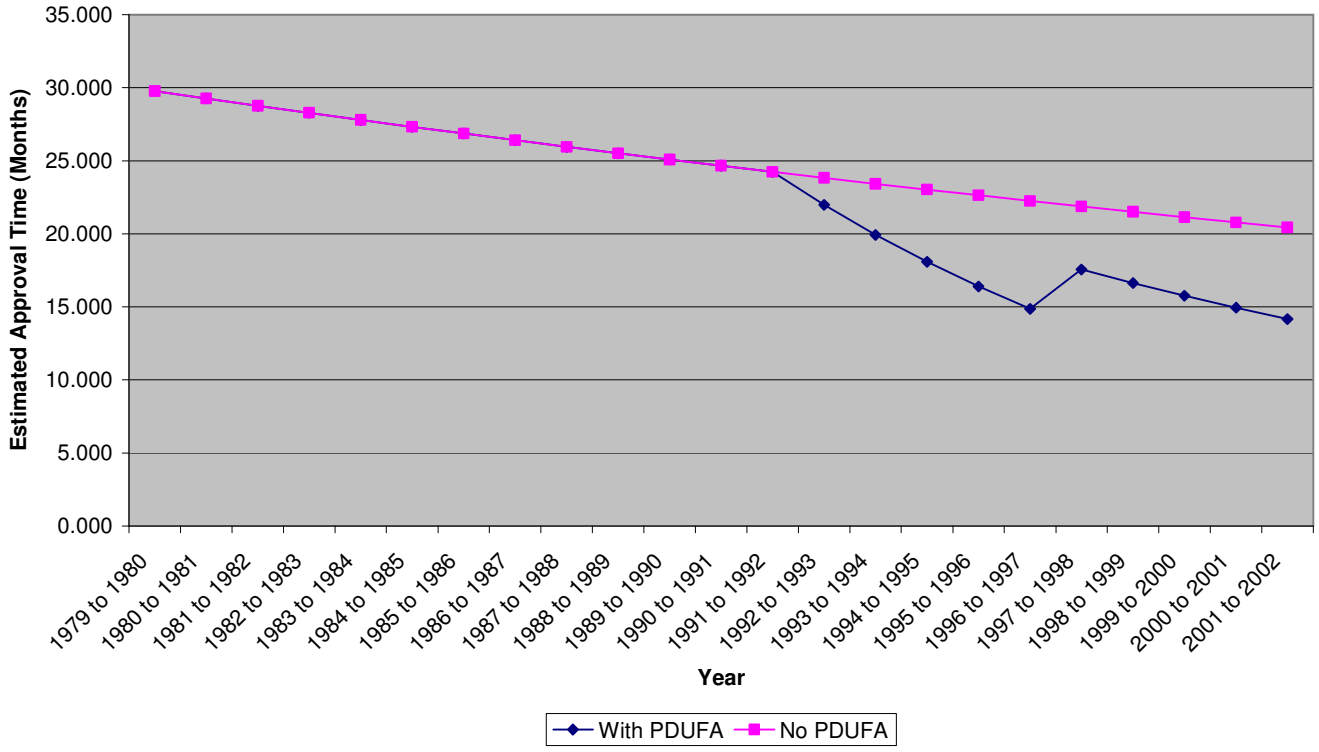


Figure 4
Social Surplus and Sales with Linear Demand and Constant Marginal Cost

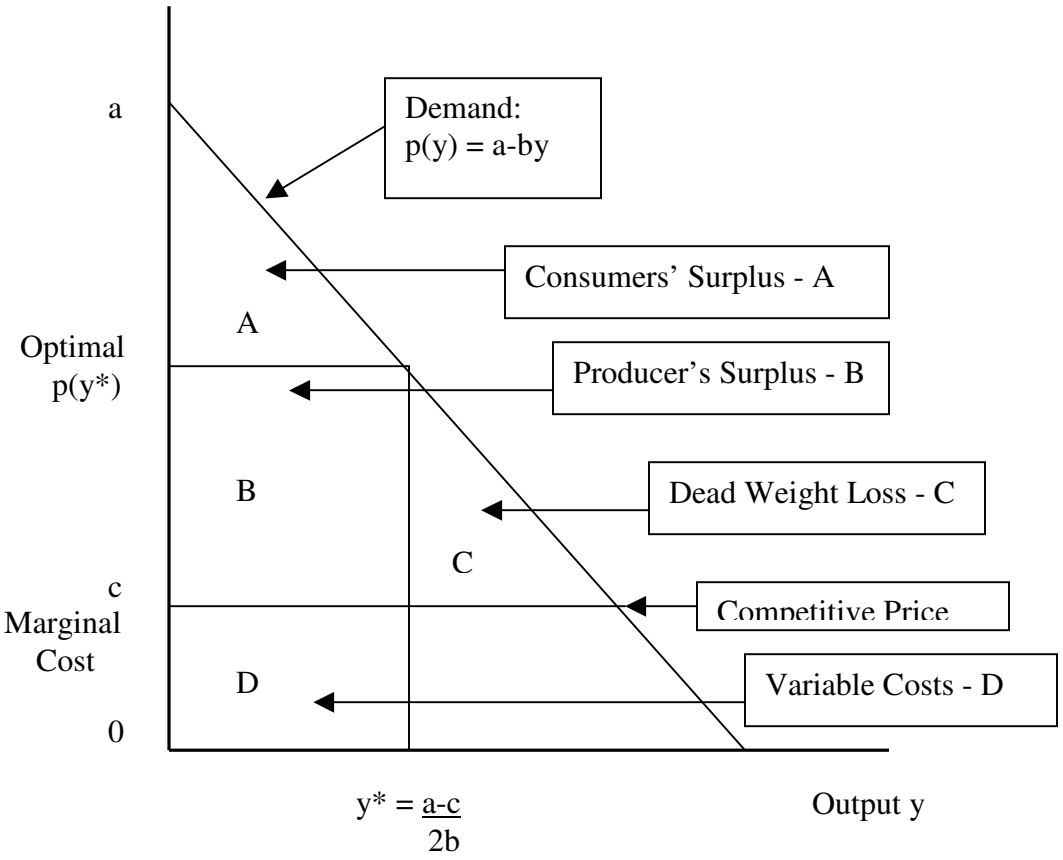


Figure 5
Present Value of Sales and NPV of PDUFA Net Social Surplus

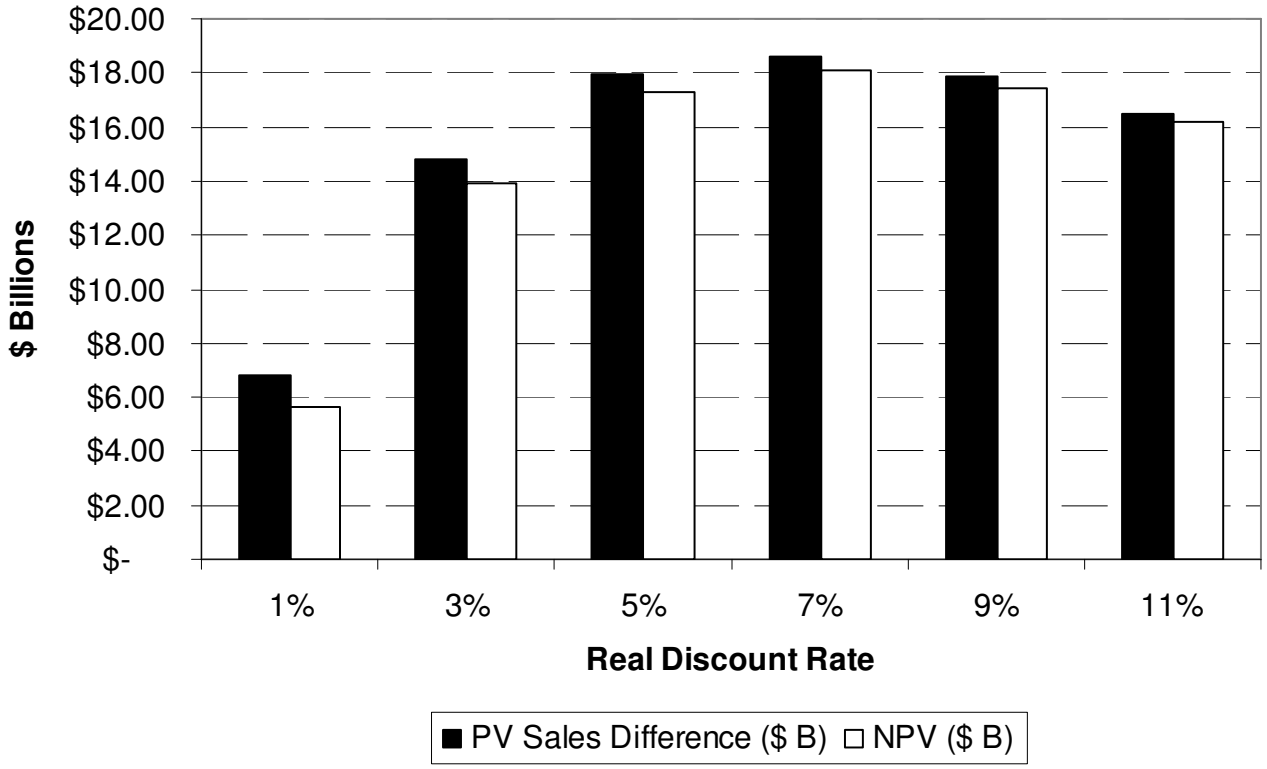
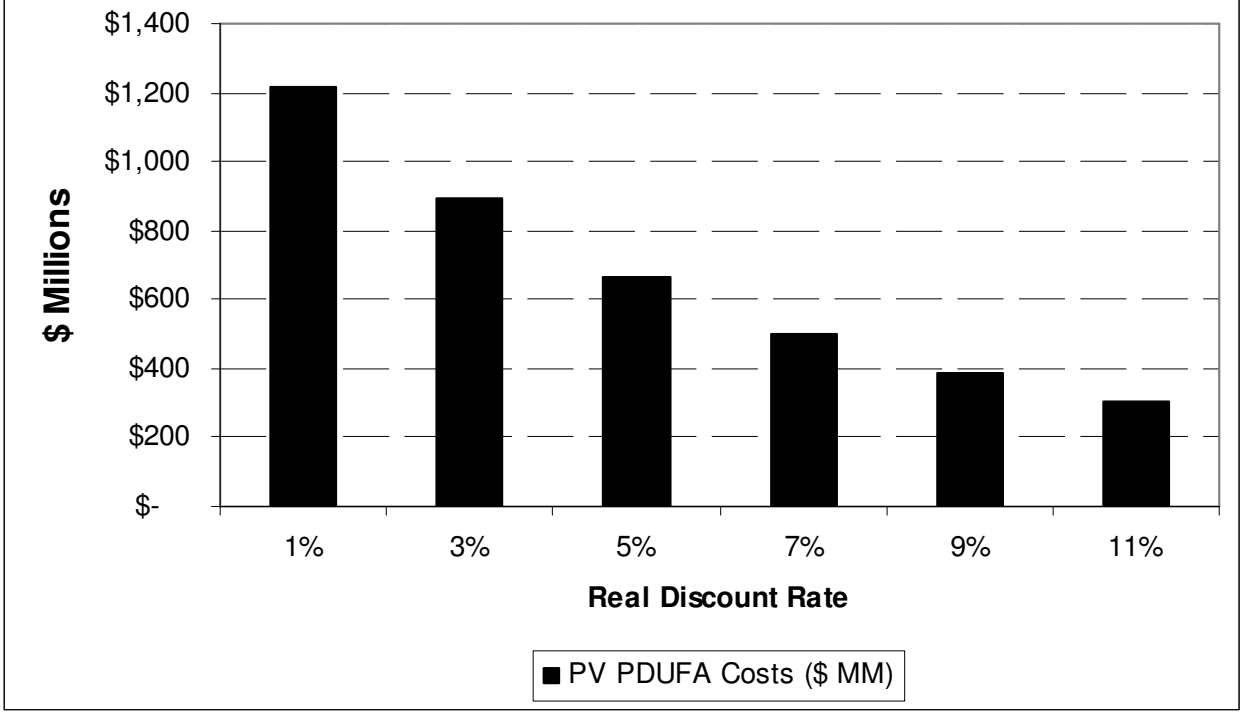


Figure 6
Present Value of PDUFA User Fee Costs ($ MM)



FOOTNOTES

[1] U.S. Food and Drug Administration, "FDA's Mission Statement", [online], accessed 4 June 2004, http://www.fda.gov/opacom/morechoices/mission.html.

[2] For discussion and references, see Michael Dickson and Jean Paul Gagnon [2004], "Key Factors in the Rising Cost of New Drug Discovery and Development", Nature Reviews: Drug Discovery, Vol. 3, May, 417-429. An early critique of the FDA is that by Samuel Peltzman [1974], Regulation of Pharmaceutical Innovation: The 1962 Amendments, Washington DC: American Enterprise Institute for Public Policy Research.

[3] U.S. Food and Drug Administration, FY 2002 PDUFA Financial Report [2003], p. 6, and p. 9.

[4] U.S. Food and Drug Administration [2004], "Prescription Drug User Fees—Overview", *U.S. Food and Drug Administration* [online] (cited 27 April 2004), http://www.fda.gov.oc/pdufa/overview.html.

[5] U.S. Food and Drug Administration [2004], "PDUFA Reauthorization Performance Goals and Procedures", U.S. Food and Drug Administration [online], (cited 27 April 2004), <http://www.fda.gov/oc/pdufa/PDUFAIIIGoals.html>.

[6] Peltzman [1974], supra. Mary K. Olson [1997], "Firm Characteristics and the Speed of FDA Approval", Journal of Economics and Management Strategy, Summer, 377-401; Olson [1998], "Pharmaceutical Regulation", in The New Palgrave Dictionary of Economics and the Law, Peter Newman, ed., New York: Stockton Press, 40-45; Olson [2004], "Managing Delegation with User Fees: Reducing Delay in New Drug Review", Journal of Health Politics, Policy and Law, forthcoming; Daniel P. Carpenter [2002], "Groups, the Media, Agency Waiting Costs, and FDA Drug Approval", American Journal of Political Science, July, 490-505; also see Wickson and Gagnon [2004], supra..

[7] See, for example, Janice M. Reichert [2003], "Trends in Development and Approval Times for New Therapeutics in the United States", Nature Reviews: Drug Discovery, Vol. 2, September, 695-702, and the references cited therein.

[8] For further discussion of political economy issues involving sponsors and the FDA, see Carpenter [2002], supra; and Carpenter, Michael Chernew, Dean G. Smith and A. Mark Fendrick [2003], "Approval Times for New Drugs: Does the Source of Funding for FDA Staff Matter?", Health Affairs – Web Exclusive, 17 December, W3-618 to W3-624.

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

[10] See, for example, Reichert [2003] supra, and Dickson and Gagnon [2004].

[11] Drugs in the AIDS class are separated out from the more general ANTI-INFEC therapeutic class.

[12] Since LNAPP is the dependent variable and since we have assumed a normally distributed random disturbance term, to create a predicted value in natural (non-logarithmically transformed) units, we exponentiate (predicted value of LNAPP plus $0.5s^2$), where s^2 is the mean squared error from the estimated regression equation.

[13] None of the standard errors in Table 2 increase by more than 15% when adjusted for heteroskedasticity; but that on the OTHER variable falls about 25% to 0.114.

[14] For a recent discussion, see Simon Frantz [2004], "Another Long Leaderless Period in Store for FDA" , Nature Reviews: Drug Discovery, Vol. 3, April 2004, p.289.

[15] More detailed disaggregation by therapeutic class and further discussions are presented in the MIT Master's. theses by Gottschalk and Strobeck. See Adrian H. G. Gottschalk [2004], "Improving the Efficiency of the Later Stages of the Drug Development Process: Survey Results from the Industry, Academia, and the FDA", M.S. thesis submitted to the Harvard-MIT Division of Health Sciences and Technology, May; and Matthew W. Strobeck [2004], "The Drug Development Process: Evaluation of PDUFA I/II and an Investigation into Reducing Drug Development Times", M.S. thesis submitted to the Harvard-MIT Division of Health Sciences and Technology, May.

[16] Henry G. Grabowski and John M. Vernon [1992], "Brand Loyalty, Entry, and Price Competition in Pharmaceuticals After the 1984Drug Act", Journal of Law and Economics, Vol. 35, October, 331-350; Ernst R. Berndt, Iain M. Cockburn and Zvi Griliches [1996], "Pharmaceutical Innovations and Market Dynamics: Tracking Effects on Price Indexes for Antidepressant Drugs", Brookings Papers: Microeconomics 1996, 133-188.

[17] Center for Medicare and Medicaid Services [2003], Health Care Industry Market Update: Pharmaceuticals, dated January 20. Available from <http:www//cms.hhs.gov>, Figure 11, p. 22.

[18] With respect to moral hazard, to the extend the demand curves reflect the demands of insurers, the premiums set by insurers already take into account the expected moral hazard behavior by the insurees.

[19] The U.S. Food and Drug Administration provided IMS sales data via a signed contract involving Professor Berndt of the MIT Sloan School of Management,, the FDA and IMS Health.

[20] The information on life cycle sales is taken from "An Analysis of Launch-to-Peak Sales for NCEs", in M. P. Mathiew, ed., PAREXEL's Pharmaceutical Statistical Sourcebook 2003/2004, p. 46.

[21] Average sales as a percent of peak sales were, for years 1 through 15, 6%, 21%, 32%, 41%, 46%, 53%, 64%, 75%, 83%, 96%, 96%, 95%, 100%, 76% and 71%, respectively.

[22] For 56 of the 341 NDAs/BLAs submissions filed during PDUFA-I and II and approved up to May 2004, there is no sales data in the IMS Health data set. These could include drugs whose sales did not meet a minimum threshold, or drugs approved but never marketed. We also excluded one drug from the anti-infective class since it was withdrawn from the US market.

[23] A 0% discount rate assumes there is no time value for moneys, and is therefore implausible. We employ a very low 1% rate simply for purposes of illustration and bounding. The NIH Cost-Effectiveness panel suggested using 3% as a preferred real discount rate, but also recommended assessing sensitivity at 0%, 5% (used most commonly) and 7%. See Martha R. Gold, Joanna E. Siegel, Louise B. Russell, and Milton C. Weinstein, eds., Cost-Effectiveness in Health and Medicine, New York: Oxford University Press, 1996. The Office of Management and Budget has recently recommended use of 3% and 7% real discount rates, the former to capture intergenerational discounting, and the latter representing an estimate of the average before-tax rate of return to private capital in the U.S. See Office of Management and Budget [2003], Regulatory Analysis: Circular A-4, September 17, pp. 31-34. Finally, in their recent cost of drug development analyses, DiMasi and coauthors use 11% as the real cost of capital. See Joseph A. DiMasi, Ronald W. Hansen and Henry G. Grabowski [2003], "The Price of Innovation: New Estimates of Drug Development Costs", Journal of Health Economics, 22:2, March, 151-185; and Grabowski, John Vernon and DiMasi [2002], "Returns on Research and Development for 1990s New Drug Introductions", PharmacoEconomics, 20 (Supplement 3), 11-29.

[24] One alternative is that depicted in Grabowski, Vernon and DiMasi [2002], supra.

[25] U.S. Government Accounting Office, Effect of User Fees on Drug Approval Times, Withdrawal, and other Agency Activities, Washington DC: GAO Report 02-958, September [online], http://www.gao.gov/new.items/d02958.pdf.

[26] FDA internal analyses and presentation material provided by Ed Hass.

[27] See, for example, Henry G. Grabowski and John Vernon [2000], "Effective Patent Life in Pharmaceuticals", International Journal of Technology Management, 19, 98-100.

[28] See, for example, Christopher Milne and E. M. Bergman [2001], "Fast Track Designation Under the Food and Drug Administration Modernization Act: The Industry Experience," Drug Information Journal, 35:1, 71-83; also see Lisa Piercey [2003], "Life in the Fast Lane", Signals [online], http://signalsmag.com/signalsmag.nsf/CA, May 23, 1-14.