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FDA New Drug Approval Times, Prescription Drug User Fees, and R & D Spending

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Executive Summary

FDA-approval times have declined significantly since the enactment of the Prescription Drug User Fee Act (PDUFA) in 1992. As a result, present value expected returns to pharmaceutical R&D have likely increased. In the current paper we employ a unique survey dataset, which includes for the first time data on firm-level pharmaceutical R&D. We estimate the effects that FDA-approval times have on R&D investments. Controlling for other factors such as pharmaceutical profitability and cash flows, we find that a 10 percent decrease (increase) in FDA-approval times results in a 1.7 percent increase (decrease) in R&D spending. Combining this estimate with previous research and publicly available data on industry-level pharmaceutical spending between 1992 and 2001, we conclude PDUFA, and its subsequent renewals, stimulated an additional $13.5 billion in pharmaceutical R&D (2005 $U.S.), and has presumably continued to do so since 2001. Recent economic research has shown the social rate of return on pharmaceutical R&D is remarkably high; thus, the social benefits of PDUFA (over and above the benefits of more rapid consumer access) are likely to be substantial.

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1. Introduction

Complaints over slow FDA-approval times in the early 1990's led Congress to pass the Prescription Drug User Fee Act (PDUFA) in 1992. It required pharmaceutical companies to pay user fees to the FDA so that the agency could hire more staff and review new drug applications (NDAs) more expeditiously. PDUFA mandated strict performance and review-time goals, and the user fees financed the resources (primarily staffing resources) needed to meet these goals. Just prior to PDUFA, which was subsequently renewed in both 1997 and 2002, FDA approval times exceeded two years on average; today, it takes closer to one year for the FDA to approve a new drug (Berndt et al., 2004). All of this decline may not be attributed to PDUFA, however. Recent research suggests that approximately 6 months of the decline is due to the Act. While many people have welcomed more rapid FDA approvals, PDUFA is not without its critics, who point out that drug safety may be compromised. One recent study considered both the economic costs and benefits of PDUFA and concluded that the benefits of this regulation were several times its costs (Philipson et al., 2005).

To date, no empirical study has examined the impact PDUFA, and FDA-approval times more generally, have had on firm incentives to invest in pharmaceutical research and development (R&D). For most drugs, more rapid FDA-approval times will not extend a drug's effective patent life (the period of time between FDA approval and patent expiration) due to provisions in the Drug Price Competition and Patent Term Restoration Act (Watchman-Hatch). That act allows a firm to recover any patent time lost due to FDA review. Nevertheless, more rapid access to the U.S. market may significantly affect the length of time a product has on the market prior to displacement by newer technologies—pharmaceutical or non-pharmaceutical; which, in turn, may significantly affect profitability and expected future profitability.

More fundamentally, however, the present value benefit of a shift backward in pharmaceutical product's net cash flows, ceteris paribus, is clearly valuable—especially for top-selling products. Theoretically, FDA-approval times should exert a significant influence on firms' incentives to invest in R&D. Given the highly productive nature of pharmaceutical R&D, which according to one researcher has produced on average one additional U.S. life year for ever $1,345 invested between 1960-1997 (Lichtenberg, 2002), PDUFA may be responsible for substantial social benefits. In this paper we examine this possibility, and we conclude that PDUFA has indeed been a stimulus for firm-level R&D. We do this by estimating several models of the determinants of pharmaceutical R&D expenditures and by including FDA-approval time as an additional explanatory variable.

This paper contributes to the literature in two principle ways: first, it employs a unique data set of firm-level pharmaceutical R&D expenditures; these data were obtained directly from seven of the industry's leading companies. Data were collected in this manner because firms do not publicly report pharmaceutical R&D expenditures separate from their total R&D expenditures. The latter typically include R&D on consumer products, medical devices, industrial chemicals, and other types of non-pharmaceutical R&D. Because of this, previous studies relied upon industry-level time series data (also based on surveys, but publicly reported in the aggregate only) or firm-level total R&D expenditure data, which do not exclude non-pharmaceutical R&D. Industry-level data are based on National Science Foundation (NSF) or Pharmaceutical Researchers and Manufacturers of America (P*h*RMA) surveys, where the firm sample compositions change over time.

Second, we include the length of FDA-approval time as an explanatory variable in our models of the determinants of pharmaceutical R&D expenditures. Contemporaneous profits, prices, and or cash flows, which have been used in previous studies (Scherer, 1996; Grabowski and Vernon, 1981,1990, 2000; Giaccotto, Santerre, and Vernon, 2005; Vernon, 2005), may not fully capture the present value expected returns to pharmaceutical R&D. Theoretically, shorter (longer) FDA approval times will increase (decrease) expected returns through a parallel shift in a product's net-cash-flow life-cycle profile, and possibly through a change in the shape of the profile itself. Empirically, it

has been shown that shorter FDA approval times significantly increase a drug manufacturer's producer's surplus (Philipson, 2005). FDA-approval times, therefore, when considered simultaneously with measures of pharmaceutical profitability and cash flows, should better capture the incentives to undertake pharmaceutical R&D.

This paper proceeds as follows. Section 2 presents the theoretical model. Section 3 describes the data and discusses how they are an improvement over data employed in previous studies. Section 4 presents the empirical model specifications and reports our results. Section 5 concludes.

2. Theoretical Model

Economic theory predicts pharmaceutical firms will invest in R&D up to the point where the expected marginal rate of return on the last dollar of R&D just equals the firm's marginal cost of capital. This equilibrium may be thought of in the classic way: as the intersection of a demand and supply curve. In the present case, the demand curve is the demand for R&D investment, where one can imagine R&D projects being arranged in a decreasing order with respected to each project's expected rate of return. The supply curve depicts the firm's opportunity cost of capital on the margin. Thus, if an individual R&D project has an expected rate of return that exceeds the project's cost of capital, the firm will undertake the project[1]. Mathematically, as previous authors have shown (Grabowski and Vernon, 1981; Giaccotto et al., 2005; Vernon, 2005), this intuitive equilibrium condition may be expressed as follows:

$$MRR(\mathbf{X}, RD) = MCC(\mathbf{Z}, RD) \quad (1)$$

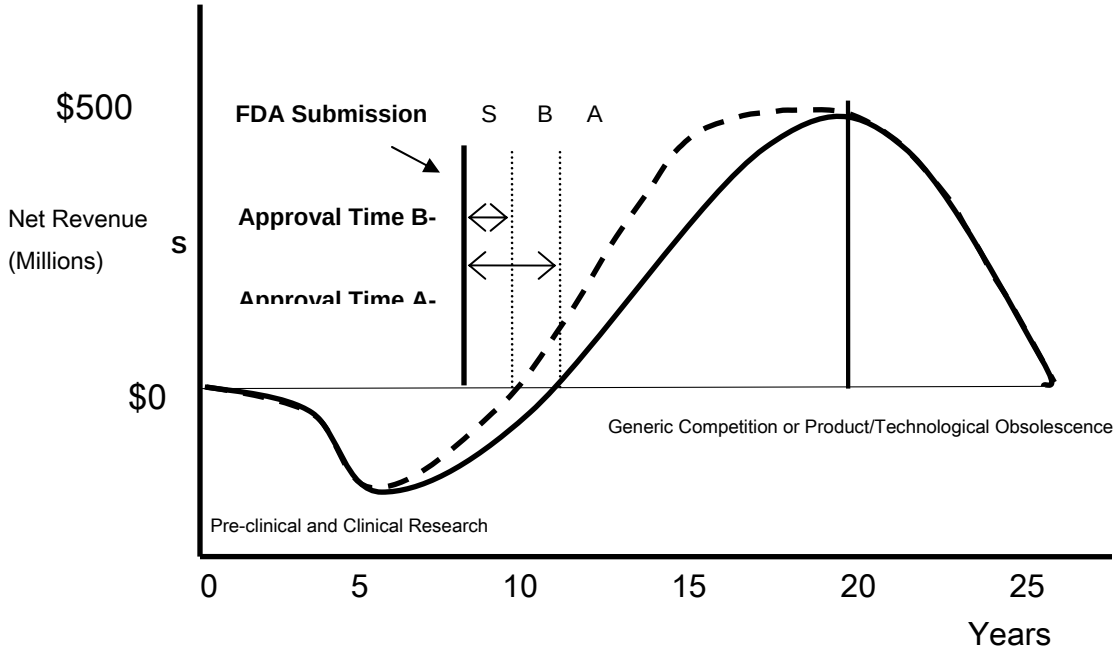
In equation (1), the vector **X** represents a set of exogenous variables affecting the expected returns to pharmaceutical R&D, and vector **Z** depicts a set of variables affecting the firm's cost of capital. The marginal cost of capital is a function of the level of R&D expenditures because both theoretical and empirical research have shown capital markets often function imperfectly (Hubbard, 1988; Fazzarri, Hubbard, 1998; Hall, 1992),

especially in the market for pharmaceutical R&D finance (Grabowski and Vernon, 1981, 2000; Giaccotto et al., 2005; Vernon, 2005). As a result, internal capital, or cash flows, may have a lower opportunity cost of capital relative to external debt and equity, and the level of firm cash flows may impact equilibrium R&D expenditures. The reduced-form solution to equation (1) is represented as follows:

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

Our model for pharmaceutical R&D investment has been discussed in greater detail elsewhere (Grabowski and Vernon, 1981; Giaccotto, Santerre, and Vernon, 2005; Vernon, 2005). To illustrate how the current paper deviates from prior work with respect to measuring expected returns, it is useful to begin by diagramming a hypothetical pharmaceutical product's life-cycle-cash-flow profile. This is done below in Figure 1.

Figure 1: Hypothetical Pharmaceutical Product Cash Flow Profile: Two FDA Approval Time Periods



[1] Of course, more formal models that treat R&D projects as real options are readily available; see for example, Swartz (2003) and Golec, Hegde, and Vernon (2006). The simple model we describe, however, adequately serves our purposes in the current paper.

The main points of Figure 1 are that more rapid FDA-approval times will 1) move a product's life-cycle-cash-flow profile backward in time; and 2) likely change the shape of the cash-flow profile as a result of greater time on the market prior to technological displacement by improved future advances or breakthroughs—pharmaceutical or non-pharmaceutical.[2] Per this second point, the flattening of the dashed curve in Figure 1 is intended to show that there may be an extended period of peak net sales prior to this displacement effect.

Ignoring this shape change momentarily, the present value benefit of shifting the solid line in Figure 1 to the left by one year, for example, can easily be calculated at the time of FDA approval, by multiplying the firm's cost of capital by the net present value of the product's cash flow prior to the one year shift. For example, if the present value cash flow associated with a particular product equals $10 billion, and the firms cost of capital is 11 percent, the benefit of moving the life-cycle cash flows backward one year is $1.1 billion. It has been estimated by other researchers that for top-selling (top decile) drugs, net present value sales equal approximately $16 billion (Berndt, Glennerster, and Kremer, 2006). As such, a backward shift in a product's life-cycle-cash-flow profile, even ignoring other factors, will impart a significant present value benefit to manufactures. This highlights how expected returns to R&D will change as FDA-approval times change.

More formally, we may represent the increase in expected returns (change in present value net cash flows) from more rapid FDA-approval as the area between the dashed and solid curves in Figure 1, discounted back to time 0, or some other point in time, τ, when decisions are being made to continue or terminate a particular R&D project:

$$\delta EPV = \int_{\tau}^{\infty} [ECF_B(t) - ECF_A(t)]e^{-rt}dt \qquad (3)$$

[2] This argument hinges on the extent to which pharmaceutical technological advancement has an exogenous component to it; possibly derived from advances in basic science or advances in other industries. If pharmaceutical technology was solely a function of the level of R&D investment (which seems very unreasonable), then more rapid FDA-approval times, via the present value benefit of a parallel shift in a product's cash flow profile alone, would increase R&D and products would become displaced more rapidly Hence, the gains associated with more time on the market would be mitigated by earlier displacement (to

In equation (3), $ECF_A(t)$ and $ECF_B(t)$ represent the expected net cash flow at time *t* under FDA-approval times A and B, respectively. The firm's cost of capital is assumed to be constant and equal to *r*. Finally, it should be noted that we are focusing our analyses on the impact FDA-approval times have on the present value of net revenues. Changes in FDA-approval arising from shortened review times should not impact development costs in a significant manner, and production costs for most drugs are relatively small compared to revenues.

Within the context of the preceding discussion and theoretical model, we formulate the following principle hypothesis:

Principal Hypothesis: Expected returns to pharmaceutical R&D are significantly influenced by FDA-approval times. Shorter (longer) FDA-approval times will raise (lower) the expected returns to R&D and consequently lead to more (less) firm-level R&D investment.

In our empirical section, we test other hypotheses, but these have been tested previously in the literature. Our unique data set, however, should provide an additional opportunity to either affirm or refute these earlier findings, and control for any confounding effects. We turn to a discussion of our data next.

3. Data Sample

A major challenge researchers have faced when studying the determinants of pharmaceutical R&D expenditures is the limited availability of data on pharmaceutical R&D expenditures and pharmaceutical profitability at the firm level. Because most of the major firms in the pharmaceutical industry are diversified across multiple industries (e.g., Johnson & Johnson has large consumer products and device divisions), and because SEC regulations do not require firms to report business segment-level data (i.e., for their pharmaceutical divisions), previous firm-level studies of the determinants of pharmaceutical R&D have used total firm R&D as a proxy for pharmaceutical R&D

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some degree) by a better technology. An example of this, within the context of traditional chemical

(Grabowski and Vernon 1981, 1990, 2000; Golec et al., 2006; Vernon 2003, 2005)[3]. This has been a very reasonable approach given the fact that pharmaceuticals are the most research intensive divisions these companies have (Vernon, 2005)[4].

In the current analysis, however, we have obtained segment-level data from seven of the top 15 global pharmaceutical firms (rankings based on 1999 pharmaceutical sales—the last year of data in our sample). While our panel dataset was not balanced, we did have 10 observations for 6 of the firms and 8 observations for the other firm, bringing our sample size to 68 firm-years. These data include both pharmaceutical R&D expenditures and pre-tax pharmaceutical profits, by year, going back to 1990[5]. While our survey response rate was relatively low, our sample of firms does represent approximately one quarter of 1999 world pharmaceutical sales (the last year in our sample due to mergers). Thus, while one cannot rule out sample selection bias, we nevertheless have a sample that represents a substantial portion of the global pharmaceutical market. Furthermore, the seven firms in our sample sold between two-thirds and three-fourths of their pharmaceuticals in the U.S. As such, they are a group of firms that stand to be greatly affected by FDA decisions and approval times.

In addition to the aforementioned pharmaceutical R&D and profit data, we also collected data from Standard and Poors Compustat files on total firm R&D expenditures, depreciation and depletion expenses, and net income. These data were used to construct a measure of cash flows. After-tax R&D spending is added to net income and depreciation to obtain a measure of the firm's pre-R&D level of cash flows, which is the

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pharmaceuticals might be gene therapy.

[3] Previous industry-level studies (e.g., Scherer, 1996; Giaccotto, Santerre, and Vernon, 2005) were based on pharmaceutical R&D data exclusively, but these data were obtained from the Pharmaceutical Researchers and Manufacturers of America (P*h*RMA) annual surveys and their membership has changed significantly over the years. Moreover, P*h*RMA does not collect or publish industry pharmaceutical profitability data.

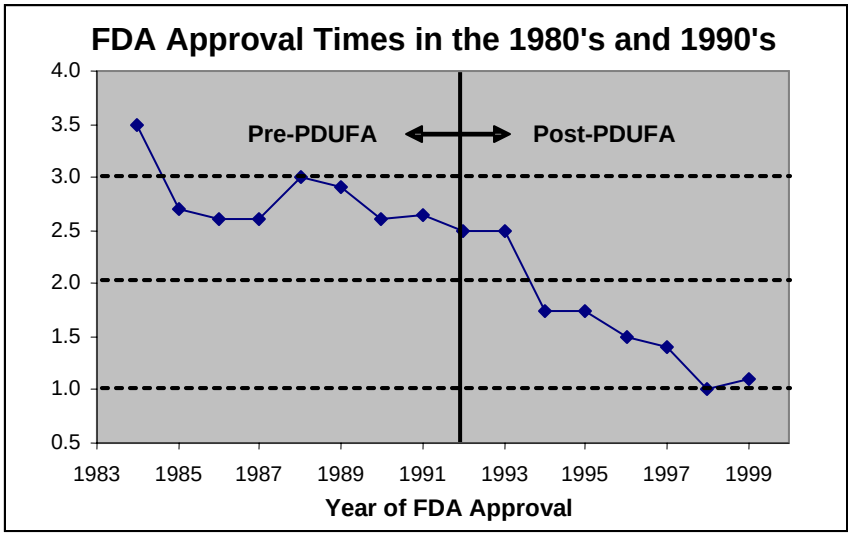
[4] In several of the studies, the authors attempted to control for this data challenge by including a control variable defined as the ratio of firm pharmaceutical sales to total firm sales, which by design accounts for the extent of a firm's non-pharmaceutical business diversification. Because the pharmaceutical business is very research intensive, total firm R&D should theoretically be higher, all else held constant, for firms more concentrated in pharmaceuticals. This variable was consistently found to be statistically significant.

[5] These data were collected via surveys sent out several years ago to leading P*h*RMA-member firms. Of the seven firms which agreed (under strict confidentiality assurances) to share their data with us, five were top-10 firms and two were top 15-firms, based on 1999 pharmaceutical sales figures (the last year of data used in our sample). Because some of the firms in our sample went through mergers around the turn of the century, we opted to limit our sample to data prior to this merger activity.

relevant measure for R&D-expenditure decisions. This formulation is designed to measure a firm's internally-generated funds before the payment of dividends and investment in R&D and other capital assets. Because R&D, unlike other capital assets, is expensed for tax purposes, after-tax R&D is required to obtain an estimate of a firm's pre-investment cash flows. Hall (1992) and Grabowski and Vernon (2000) describe this construction of a firm's pre-R&D level of internal funds in detail. Finally, FDA-approval time data may be found in DiMasi (2001).

Before turning to our empirical models and hypothesis tests, we illustrate how FDA-approval times have changed over the sample time period, and specifically since the enactment of PDUFA in 1992. Because we will be addressing the issue of how PDUFA has influenced this trend in a subsequent section of the paper, we demarcate the time periods as pre- and post-PDUFA. These data are illustrated below in Figure 2.

Figure 2: Average Time from New Drug Application (NDA) Submission to FDA NDA Approval



As previous researchers have documented, there has been a steady decline in FDA-approval times, especially after 1992 when PDUFA was first enacted (DiMasi, 2001; Berndt et al., 2006). Interestingly, other researchers have found that industry R&D

growth rates begin to significantly decline around the early 1990s (Golec and Vernon, 2006). Thus, at naïve first glance, one might suspect that PDUFA had no effect (or even a negative effect) on R&D spending. This observation will be discussed in detail in the forthcoming section.

4. Empirical Models and Results

To test the hypothesis that FDA-approval times exert a negative influence on firm-level pharmaceutical R&D expenditures, we estimate several models of the determinants of pharmaceutical R&D expenditures. Specifically, we rely on previously published R&D models and empirical specifications to guide our own specifications. As previously stated, however, the principal differences in the current analysis are that we employ a new dataset and seek to capture the effect FDA-approval times have on R&D expenditures. As such, we specify the following log-log equation:

$$\ln(RD_{it}) = \beta_0 + \beta_1 \ln(\pi_{it}) + \beta_2 \ln(CF_{it}) + \beta_3 \ln(CF_{it-1}) + \beta_4 \ln(FDA_{t-1}) + u_{it} \qquad (5)$$

The variables appearing in equation (5) are defined as follows:

RD_{it} = Pharmaceutical R&D expenditures by the i^{th} firm in year t;
π_{it} = Pre-tax pharmaceutical profits for the i^{th} firm in year t;
CF_{it} = Cash flow for firm i in year t (net income plus depreciation and pre-tax R&D);
FDA_t = Average FDA-approval time in year t.

Equation (5) was estimated using pooled ordinary least squares (OLS) and generalized least squares (GLS). The later was necessary to correct for within-group and contemporaneous serial correlation. Furthermore, while all the firms in the sample were large, U.S.-based pharmaceutical companies of similar sizes, a White correction for heteroskedasticty was nonetheless needed. Because our models are specified in logarithms, the coefficient estimates can be interpreted as elasticities. Our empirical

results for the levels equations are shown in Table 1 (t-statistics based upon White heteroskedasticty-consistent standard errors are reported in parentheses below the elasticity estimates).

Table 1: Model (5) Levels Regression Results Based on a Panel of Seven Large U.S. Firms from 1990-1999 (Dependent Variable is Pharmaceutical R&D Expenditures)

MODEL SPECIFICATION	LN($_{IT}$)	LN(CF_{IT-1})	LN(FDA_{T-1})	AR(1)	ADJ. R^2
Levels OLS					
Common Intercept	0.30**** (3.89)	0.32**** (4.39)	-0.50**** (-3.96)	---	0.76
Firm Fixed Effects	0.19**** (3.29)	0.12 (0.99)	-0.76**** (-6.11)	---	0.90
Levels GLS					
Common Intercept	0.15**** (4.12)	0.14*** (2.73)	-0.10* (-1.56)	0.97**** (36.37)	0.99
Firm Fixed Effects	0.18**** (3.94)	0.09* (1.33)	-0.49**** (-3.56)	0.74**** (7.09)	0.97
Firm Random Effects	0.21** (2.78)	0.17* (1.47)	-0.70**** (-5.55)	---	0.90

One-tail significance levels: * p<0.10; ** p<0.05; ***p<0.01; **** p<0.001

We also estimated models using log first differences as specified in equation (6) below:

$$\Delta \ln(RD_{it}) = \beta_o + \beta_1 \Delta \ln(\pi_{it}) + \beta_2 \Delta \ln(CF_{it}) + \beta_3 \Delta \ln(CF_{it-1}) + \beta_4 \Delta \ln(FDA_{it}) + u_{it} \quad (6)$$

The predictive power of this specification was relatively low. Therefore, we also estimated log-first-difference models using additional measures of cash flow and

pharmaceutical profits. This approach is similar to an earlier industry-level analysis (Scherer, 1996). These results are presented in Table 2.

Table 2: First Differences Regression Results Based on A Panel of Seven Large U.S. Firms from 1990-1999 (Dependent Variable is Pharmaceutical R&D Expenditures)

MODEL SPECIFICATION	$\Delta LN(\pi_{IT})$	$\Delta LN(\ _{IT-1})$	$\Delta LN(CF_{IT})$	$\Delta LN(CF_{IT-1})$	$\Delta LN(FDA_{T-1})$	ADJ. R^2
First Differences Basic Model						
No Intercept	0.20^{****} (5.84)	---	---	0.16^{***} (2.84)	-0.40^{****} (-3.56)	0.02
Common Intercept	0.13^{***} (3.14)	---	---	0.09^{*} (1.53)	-0.15^{*} (-1.39)	0.21
Firm Fixed Effects	0.13^{****} (3.42)	---	---	0.09^{*} (1.57)	-0.14^{*} (-1.42)	0.19
First Differences Expanded Model						
No Intercept	0.21^{****} (6.12)	0.08^{**} (2.36)	0.02^{**} (1.93)	0.10^{**} (1.80)	-0.37^{****} (-3.40)	0.06
Common Intercept	0.15^{***} (3.19)	0.06^{*} (1.65)	0.01^{*} (1.52)	0.05 (0.91)	-0.15^{*} (-1.36)	0.20
Firm Fixed Effects	0.15^{***} (3.57)	0.07^{**} (1.84)	0.02^{***} (2.42)	0.05 (0.92)	-0.17^{*} (-1.56)	0.21

One-tail significance levels: * p<0.10; ** p<0.05; ***p<0.01; **** p<0.001

The results in Tables 1 and 2 strongly affirm our central hypothesis that FDA-approval times are a significant determinant of firm-level R&D expenditures. Longer (shorter) FDA-approval times are associated with less (more) firm-level R&D spending. Before discussing these results in detail, we first turn our attention to the other explanatory variables in the model.

As has been the case in all previous studies of the determinants of firm-level pharmaceutical R&D expenditures, contemporaneous pharmaceutical profitability is a statistically significant explanatory variable. Our elasticity estimates suggest that a 10

percent increase (decrease) in pharmaceutical profits will be accompanied by between a 1 and 3 percent increase (decrease) in pharmaceutical R&D spending. This is consistent with the most directly comparable firm-level study in which the elasticity of total firm R&D with respect to pre-tax pharmaceutical profit margins was approximately 0.2 (Vernon, 2005)[6].

Regarding industry-level studies of pharmaceutical R&D spending, our estimates are also similar, albeit somewhat smaller in magnitude. These studies, however, may not be directly comparable for several reasons. For example, Giaccotto et al. (2005) employed a measure of real pharmaceutical prices in the U.S., lagged one period, to capture both an expected-profitability and cash-flow effect. The notion behind this variable is that real pharmaceutical prices serve as a reasonable proxy for the general economic climate of the U.S. pharmaceutical marketplace, both contemporaneously and in the near term; it may also capture expected future-period real pharmaceutical prices, at least in the near term and on average. Real pharmaceutical prices also impact industry cash flows[7]. The elasticity of R&D to real drug prices was estimated to be 0.58, which is similar to an earlier industry-level analysis that modeled R&D as a function of lagged industry cash flows and profits (Scherer, 1996). In the current research, summing both the profit and cash flow coefficients is a more direct comparison to these aforementioned industry-level studies, and it does of course yield higher elasticity estimates. In the common intercept levels estimation, for example, these coefficients sum to 0.62, but in all other specifications these coefficients sum to a lower value.

The coefficient estimates on the cash flow variable are also broadly consistent with previous firm-level studies. However, the evidence is less compelling in the current study, and our elasticity estimates are considerably smaller when the data are first differenced. This finding is consistent with arguments put forth by Lichtenberg (2001), and may reflect the possibility that cash flows in earlier studies were picking up unobserved pharmaceutical profit expectations, which are likely to be positively

[6] In a study of 14 large firms from 1994-1997, Vernon (2005) obtained an estimated coefficient on pharmaceutical profit margins between 0.059 and 0.073. Mean profit margins and R&D intensities for the sample were 0.303 and 0.107, respectfully. Thus, the elasticity of R&D intensity to pharmaceutical profit margins ranges roughly between 0.17 and 0.21.

[7] There are numerous nuances to these arguments along with several caveats. The interested reader is referred to the original paper for more details.

correlated with firm cash flows, both contemporaneous and lagged. It seems possible that our additional profit expectations variable (FDA-approval time), because it more fully captures expected returns to pharmaceutical R&D, mitigates part of the empirical challenge associated with measuring the impact internal funds have on R&D spending.

The principal hypothesis we test in the current paper is that FDA-approval times influence expected returns to pharmaceutical R&D, and this in turn affects firm-level R&D spending. Our results in Tables 1 and 2 suggest this is indeed the case. It is striking to observe that this variable is statistically significant at the 10-percent level or better in all of our model specifications[8]. Coefficient estimates suggest an elasticity range from -0.10 to -0.70. Because of the within-group serial correlation detected in our levels OLS and the random effects model specifications, we opt to rely on the other models for drawing policy inferences. In particular, we will focus on the firm-fixed-effects model estimated using the first-differenced data. Therefore, we conclude that for every 10 percent increase (decrease) in FDA-approval times, R&D expenditures decrease (increase) by 1.7 percent. Of course it may not be appropriate to generalize this result beyond our sample, or beyond large U.S. pharmaceutical manufacturers[9].

Before we discuss the direct link between PDUFA and R&D spending, it is worth noting that during the post-PDUFA period, when FDA-approval times were declining steadily, industry-level pharmaceutical R&D growth rates were actually slowing considerably from the previous decade (Golec and Vernon, 2006). The reason for this

[8] We employ a one-period lag measure because it performs marginally better from a statistical perspective than a contemporaneous value, especially in the first-differences specifications. Moreover, unlike a firm's own profits or cash flows, the average industry FDA-approval time for new drugs may be less immediately apparent to firms. Some firms may bring few or no new drugs to market in a given year, and regulatory changes and approval times may be less transparent contemporaneously relative to own firm profits and cash flows. A lagged cash flow variable is also included for different reasons; cash may be carried forward from year to year and an accumulation of internal funds is what is relevant. Previous studies have also used a one-period lag for firm cash flows.

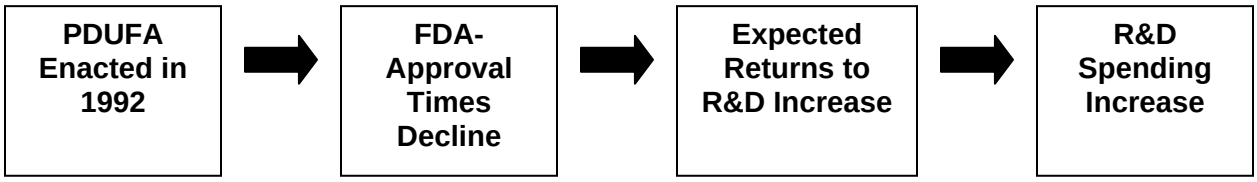
[9] It should be mentioned that we also experimented with variables measuring effective pharmaceutical patent lives (the time from FDA marketing approval to patent expiration) as a determinant of firm-level R&D spending. This variable was very robust in all of our levels specifications, with an average magnitude of approximately 1.0 (unit elastic), but this variable did not hold up well when we first differenced the data. There was also a lot of variability across reported estimates of effective patent life; published research reported estimates based upon different methodologies. We are still exploring this line of research. As a final note, however, FDA approval times seem more theoretically appealing because their impact occurs at the beginning of a new product's cash flow life cycle; changes in effective patent lives could be the result of an additional year at the end of a product's patent life. The present value impact of such a change during the R&D project phase would be greatly diminished because of discounting.

may be the declining growth rate in pharmaceutical prices and profits during the period. Real pharmaceutical prices began growing more slowly after 1993, when the Clinton administration's proposed Health Security Act was being debated and considered; this Act contained provisions for prescription drug price controls in the U.S. (Abbott, 1996; Golec et al., 2006; Golec and Vernon, 2006; Ellison and Mullin, 2001). As a result of this proposed legislation, pharmaceutical prices grew at a rate very close to inflation after 1993; many firms pledged to restrict their annual price increases to the rate of inflation during this period (Ellison and Wolfram, 2006; Golec et al., 2006). In contrast to this, during the 1980's, drug prices grew at a rate well in excess of inflation. Golec et al. (2006) and Golec and Vernon (2006) have argued the effects of the proposed 1993 Act changed the political environment with respect to pharmaceutical prices, and as a result moderated both contemporaneous and expected future pharmaceutical profits and cash flows, and thus R&D spending. The clear implication from our empirical findings is that PDUFA, to the extent it reduced FDA-approval times, partially mitigated this observed slow-down in R&D growth rates. That is, were it not for the enactment of PDUFA in 1992, R&D growth might have slowed down even more during the 1990's. We will address the potential economic consequences of this next.

The Causal Links between PDUFA, FDA-Approval Times, and R&D Expenditures

As Figure 2 illustrated, FDA-approval times declined significantly after the enactment of PDUFA in 1992. However, FDA-approval times were declining somewhat before PDUFA. In the last section, we documented a robust empirical relationship between FDA-approval times and firm expenditures on pharmaceutical R&D. What is most interesting to investigate, in our opinion, is the direct causal impact PDUFA may have had on firm-level R&D spending. We illustrate this chain of causal events below in Figure 3.

Figure 3: The Causal Links from PDUFA to R&D Investment



To establish the link between PDUFA and FDA-approval times, we rely on the empirical research by Berndt et al. (2004), who estimated that the PDUFA-induced reduction in FDA-approval times between 1992 and 2001 was 6.2 months. While their data showed that approval times declined from 24.2 to 14.2 months over this period, it was determined that part of this decline could not be attributed to PDUFA. In a counterfactual world without PDUFA, Berndt et al. predicted approval times would have declined to 20.4 months over this period. PDUFA accelerated this trend and reduced approval times to 14.2 months in 2001. We will use this evidence to map out the links depicted in Figure 3.

This estimated decline in FDA-approval times from 20.4 months to 14.2 months represents a -35.8 percent change (6.2 divided by 17.3, or the average of 20.4 and 14.2). Multiplying this estimate by our log-first differenced model elasticity estimate of -0.17 predicts that PDUFA induced a 6.1 percent (-0.358*-0.17) increase in pharmaceutical R&D expenditures. Based on PhRMA-member survey data between 1992 and 2001, total real pharmaceutical R&D expenditures equaled $222 billion (in 2005 $US). Therefore, based on the analysis just described, PDUFA may reasonably be approximated to have induced an additional $13.5 billion in pharmaceutical R&D over this period, and has presumably continued to do so to the present day. If a new chemical entity (NCE) costs about $450 million (DiMasi et al., 2003) to develop and bring to market ($403 million in cash outlays inflated to 2005 $U.S.), this increase in R&D is therefore roughly responsible for 30 NMEs over this period, or about 3 NMEs per year[10]. We do not

[10] This simple calculation ignores the drug development lag. Many, if not all, of the additional PDUFA-induced drugs may not be brought to market until after the time period used for this calculation. However, we are indeed being very conservative in our estimates because we truncate the additional R&D spending in our calculation at the year 2001. The reduction in FDA-approval times, if maintained, will have a much

include the financing cost component of the R&D because the $222 billion figure is a non-capitalized sum. While the pooling of multiple empirical estimates in this manner must be considered with caution, it does appear likely that the social welfare implications of PDUFA, in terms of the Act's impact on pharmaceutical innovation, are likely to quite large.

5. Conclusions

In this paper we employ an original data set containing previously unavailable pharmaceutical R&D data to estimate the impact FDA-approval times have on firm-level R&D expenditures. Earlier studies relied primarily upon contemporaneous measures of pharmaceutical profitability and prices to capture the expected returns to pharmaceutical R&D. We argue that an additional element of expected returns, and specifically present value expected returns, may be captured using FDA-approval times as an additional explanatory variable. For top-decile selling drugs, it has been estimated that net present value sales for drugs brought to market in the early 1990s equal about $16 billion; clearly, the benefit to firms of moving these life-cycle-cash-flow profiles backward 6 months (ignoring other competitive benefits of an earlier FDA-approval) is substantial. During the R&D phase, this will have a more significant expected present value impact than an additional 6 months of market exclusivity at the end of a product's patent life. It also seems reasonable that this intertemporal-present-value effect may not be captured by current profits and profit margins, which previous studies have relied upon.

Using multiple empirical model specifications, we find that FDA-approval times exert a robust and economically meaningful impact on firm-level pharmaceutical R&D expenditures. Based upon our fixed-effects-first-differenced model specification, we estimate the elasticity of R&D expenditures with respect to FDA-approval times to be approximately -0.17. This suggests that a 10% reduction (increase) in FDA-approval times will lead to a 1.7 percent increase (decrease) in pharmaceutical R&D spending. Combining our analyses with the empirical findings of previous researchers (Berndt et

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larger effect in perpetuity. See Golec and Vernon (2004) for a related analysis using Gordon-growth models.

al., 2006) who studied the impact PDUFA had on FDA-approval times. We estimate that PDUFA increased pharmaceutical R&D spending by about 6.1 percent. According to PhRMA-member firm surveys, total pharmaceutical R&D spending between 1992 and 2001 totaled approximately $222 billion (in real 2005 $U.S.). As such, we estimate that PDUFA induced an additional $13.5 billion in R&D over this same time period, and presumably has continued to do so since 2001. Given previous researchers findings regarding the productivity of pharmaceutical R&D (e.g., Lichtenberg, 2003), the social benefits of this PDUFA-driven increase in R&D is likely to be very substantial.

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