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FDA New Drug Review Times, Prescription Drug User Fee Acts, and R&D Spending

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ABSTRACT

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, one which includes data from 1990 to 1999 on firm-level pharmaceutical R&D expenditures for 7 large, U.S.-based drug companies. We estimate the effect FDA approval times have on firm R&D spending. Controlling for other factors such as pharmaceutical profitability and cash flows, we estimate that a 10 percent decrease (increase) in FDA approval times leads to an increase (decrease) in R&D spending from between 0.9% to 1.7%. Combining this estimate with recent research on the link between PDUFA and FDA approval times, we calculate that for the firms in our sample, R&D spending in the 1990s increased by an additional 2.7% to 5.7% as a result of this legislation. This amounted to an additional $1.8 billion to $3.6 billion in pharmaceutical R&D expenditures (2005 $US), and possibly several new drugs. Because PDUFA continued to provide incentives for R&D after 1999, and because it is possible that firms not in our sample were and have been similarly affected by PDUFA, our estimates may be conservative. Recent economic research has shown that the social rate of return on pharmaceutical R&D is very high; therefore, 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 1990s 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. However, only about 6 months of this decline may be attributed to PDUDA (Berndt Gottschalk, Philipson, et al., 2004). Approval times were already trending downward prior to the first PDUFA (PDUFA-I). Carpenter (2004) finds statistical evidence that the dramatic rise, power, and wealth of patient advocacy groups (which often receive financing from the industry) along with expanded media coverage have exerted substantial political pressures on the FDA, and this has led to declines in approval times in recent decades. 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 Berndt, Gottschalk, et al., 2005).

To date, however, 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 (Hatch-Waxman). This Act allows a firm to recover any patent time lost due to FDA review (CBO Report, 1998). Nevertheless, more rapid access to the U.S. market could possibly 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 backward shift in a 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 every $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, at least for the firms in our sample, PDUFA has indeed been a stimulus for firm-level R&D spending. We do this by estimating several models of the determinants of pharmaceutical R&D expenditures and by including measures of 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 7 large, U.S.-based pharmaceutical 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 (PhRMA) surveys, where the composition of firms included in the surveys have changed 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 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 estimated that shorter FDA approval times significantly increase a drug manufacturer’s producer 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 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 firm’s demand for R&D, where one can imagine R&D projects being arranged in a decreasing order with respect 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. Mathematically, as previous authors have shown (Grabowski, 1968, 1994; Grabowski and Vernon, 1981, 2000; Giaccotto, Santerre, and Vernon, 2005; and Vernon, 2005), this intuitive equilibrium condition may be expressed as follows:

\[ \text{MRR}(\mathbf{X}, \text{RD}) = \text{MCC}(\mathbf{Z}, \text{RD}) \] (1)

In equation (1), the vector \( \mathbf{X} \) represents a set of exogenous variables affecting a firm’s expected returns to pharmaceutical R&D, and vector \( \mathbf{Z} \) 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,

1 Of course, more formal models that treat R&D projects as real options are readily available; see for example, Schwartz (2003) and Golec, Hegde, and Vernon (2006). The simple model we describe, however, adequately serves our purposes in the current paper.
1992), especially in the market for pharmaceutical R&D finance (Grabowski and Vernon, 1981, 2000; Giaccotto, Santerre, and Vernon, 2005; and 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:

\[
RD^* = f(X, Z) 
\]  

(2)

Our model for pharmaceutical R&D expenditures has been discussed in greater detail elsewhere (Grabowski, 1968, Grabowski and Vernon, 1981, 2000; Giaccotto, Santerre, and Vernon, 2005; Vernon, 2005). To illustrate how the current paper deviates from previous 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
The main points we wish to convey through Figure 1 are that more rapid FDA approval times (1) will move a product’s life-cycle cash-flow profile backward in time; and (2) could possibly 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. It is also possible, as other researchers have suggested (Philipson, Berndt, Gottschalk et al., 2005), that faster FDA approval times will translate into longer effective patent lives for some products, but under most circumstances provisions under Hatch-Waxman allow firms to recoup time lost during the FDA approval phase. For these reasons, the flattening of the dashed curve in Figure 1 is intended to show only that there may be an extended period of peak net sales prior to technological displacement and or generic erosion.

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 present value of the product’s net cash flows prior to the one year shift. For example, if the present value net

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2 This argument hinges on the extent to which pharmaceutical technological advances have an exogenous component to them that cannot be accelerated through higher levels of pharmaceutical R&D spending; possibly derived from advances in basic science or advances in other industries that are not influenced by advances in pharmaceutical science. If pharmaceutical technology were solely a function of the level of R&D investment (which seems 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 all firms’ R&D spending levels, and products would become displaced more rapidly. Hence, the gains associated with getting to the market sooner would be offset by earlier product displacement and technological obsolescence. Clearly, then, for shorter FDA approval times to have any effect like the one described in point 2, there has to be an exogenous research element to the rate of pharmaceutical R&D innovation; that is, pharmaceutical R&D innovation cannot be driven solely by firm R&D spending levels. While it is true that non-pharmaceutical technologies seldom replace pharmaceutical technologies (usually it is the other way around), advances in the non-pharmaceutical sciences may be a necessary prerequisite for some pharmaceutical discoveries or treatment options, and once these pharmaceutical discoveries are made they might rapidly replace existing pharmaceutical treatments and products. This effect, while plausible, is probably quite small.
cash flow associated with a particular product equals $10 billion, and the firm’s cost of capital is 11 percent, then the benefit of moving the cash-flow profile backward by 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 manufacturers. This highlights how expected returns to R&D will change as FDA review times change.

More formally, we may represent the increase in expected returns 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:

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

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 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-review times. Shorter (longer) FDA-review 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 previous studies have faced in studying the determinants of pharmaceutical R&D expenditures has been the limited availability of data on pharmaceutical R&D expenditures and 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 medical 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 (Grabowski and Vernon 1981, 2000; Golec, Hegde, and Vernon, 2006; Vernon, 2005)\(^3\).

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\(^3\) 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 (PhRMA) annual surveys and their membership has changed significantly over the years. Moreover, PhRMA does not collect or publish industry pharmaceutical profitability data.
This has been a reasonable approach given the fact that pharmaceuticals are the most research-intensive divisions these companies have (Vernon, 2005).

In the current analysis, however, we have obtained segment-level data from seven of the top 15 global pharmaceutical firms (ranked based on 1999 pharmaceutical sales—the last year of data in our sample). These data include both pharmaceutical R&D expenditures and pre-tax pharmaceutical profits by year going back to at least 1990. These data were collected via surveys sent out in 2001 as attachments to the annual PhRMA survey. The PhRMA survey requests data on each firm’s previous year’s pharmaceutical R&D expenditures; these data are then reported in the aggregate for all PhRMA members in the annual PhRMA publication, *Pharmaceutical Industry Profile*.

The data we sought to collect were pharmaceutical R&D expenditures and pre-tax gross pharmaceutical profits for all years going back to 1980. Accompanying our survey was a signed confidentiality agreement that stated we would not release or report these data except in the aggregate. We further disclosed in the survey that we were interested in using the data for academic research on the determinants of firm-level pharmaceutical R&D spending. It is our understanding that our survey was mailed as an attachment to the PhRMA annual survey to the twenty largest PhRMA-member firms (based on pharmaceutical sales), with instructions that it was not an official PhRMA survey, that it was optional, and that if it was completed, either in part or in full, it was to be returned directly to us and not PhRMA. Our interest was in collecting data from large, established

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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.
pharmaceutical companies with many years of operating history (the types of firms that have made up earlier firm-level studies of the determinants of R&D expenditures, but which relied on total-firm R&D expenditures and not pharmaceutical R&D expenditures).

While we received twelve returned survey forms from the sampled firms, no surveys were completed in full for both gross pharmaceutical profits and R&D expenditures. Only one firm provided data on pharmaceutical R&D spending going back to 1980, but it did not report pharmaceutical profitability data. Some firms, because of mergers, provided data going back only as far as the date of merger (i.e., data for the merged firm only), while others reported historical figures that reflected the larger of the two firms pre-merger. In the end, we were able to construct a sample of 7 firms with complete data for the years 1990 to 1999. Given the low response rate and incomplete surveys we received, it is imperative to emphasize that sample selection bias could be a serious issue if we want to make generalizations beyond our sample of firms.

There are potentially many reasons why a firm’s decision to return our survey (or to provide more than a few years of data) might be systematically related to some of the key variables of interest in our study. This is particularly true given that the survey was received directly from the industry trade group, PhRMA, whose mission it is to represent the political and financial interests if its members, and because the nature of the research questions we were studying was revealed in the survey. Recall bias is another concern because we were requesting historical data. In sum, there are a plethora of reasons why it is necessary to temper the empirical findings from our data sample with caution and context.
These things kept in mind, the 7 firms in our sample were all large, U.S.-based companies that had been in existence for several decades. These firms included 5 of the top-10 and 7 of the top-15 firms in the industry based on rankings by 1999 global pharmaceutical sales. Accordingly, the 7 firms in our sample represented a significant share of industry sales and R&D expenditures. For example, the firms in our sample represented more than 50% of total PhRMA-member pharmaceutical R&D spending. Previous researchers have used these PhRMA-member data as a proxy for total industry pharmaceutical R&D (Scherer, 1996; 2001; Giaccotto, Santerre, and Vernon, 2005). Furthermore, all of the firms in our sample had between one-half and three-fourths of their pharmaceutical sales coming from the U.S. market (based on IMS data). As such, they are a group of firms that stood to be significantly 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 Poor’s Compustat files on total firm R&D expenditures, depreciation and depletion expenses, and net income. These data were used to construct a measure of firm 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 flow, which is the 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 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, Gottschalk, Philipson, et al., 2004). Interestingly, other researchers have found that industry R&D growth rates began 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. We rely heavily on previously published empirical specifications and variable formulations to test our hypothesis. In particular, previous studies have found that current and lagged measures of pharmaceutical profitability and firm-level cash flows are the principal determinants of pharmaceutical R&D expenditures (Grabowski, 1968; Grabowski and Vernon, 1981, 1990, 2000; Vernon 2004, 2005; and Giaccotto, Santerre, and Vernon, 2005; Golec, Hegde, and Vernon, 2006). Expected profitability obviously drives R&D expenditures; firm-level cash flows will influence R&D expenditures if internal funds have a lower cost of capital relative to external debt and equity, which both the theoretical and empirical literature suggests is indeed the case\(^5\). Our study is differentiated from earlier work because we employ a new dataset and seek to capture the effect FDA approval times have on R&D expenditures. With respect to the latter, we experimented with several specifications and variable formulations. Our general model specification is presented below, with variables transformed using logarithms and first differenced.

\(^5\) Theoretical reasons for internal funds to have a lower cost of capital relative to external debt and equity, and thus exert a positive influence on R&D investment levels, are based upon: information asymmetries, agency problems, transaction costs, and financial gearing. Hubbard (1998) provides an excellent overview of these reasons. Hall (1992), Grabowski and Vernon (1981, 2000), and Vernon (2005) have found empirical support for this hypothesis.
The variables appearing in equation (4) are defined as follows:

\[ \Delta \ln( RD_{it} ) = \beta_0 + \beta_1 \Delta \ln( E\pi_{it} ) + \beta_2 \Delta \ln( CFI_{it} ) + \beta_3 \Delta \ln( FDA_t ) + u_{it} \]  

RD\(_{it}\) = Pharmaceutical R&D expenditures by the \(i^{th}\) firm in year \(t\);
\(E\pi_{it}\) = Index of expected pharmaceutical profitability for firm \(i\) in year \(t\),
\(CFI_{it}\) = Index of current and lagged cash flows for firm \(i\) in year \(t\),
\(FDA_t\) = Average industry FDA approval time in year \(t\);

We began with a simple model where R&D was as a function of current period, after-tax pharmaceutical profits and cash flows lagged one year (Vernon, 2005). FDA approval times were also lagged one year. This model performed well statistically in both firm-fixed effects and common intercept models. These results are reported in an earlier version of this paper published by the AEI-Brookings Joint Center for Regulatory Studies in their Working Paper Series (Vernon, Golec, Lutter, and Nardinelli, 2006). Feedback during several seminar presentations and other helpful comments we received during the course of this research resulted in the re-formulation of our independent variables using an indexing approach (an approach also used in some of the earlier studies of the determinants of pharmaceutical R&D spending). The indexing formulation that performed the best from a statistical perspective was the following, for the hypothetical independent variable \(x\) (with the right-hand side terms re-arranged):

\[ \sum_{j=1}^{4} \frac{x_{t-(4-j)}}{10} = 0.4x_t + 0.3x_{t-1} + 0.2x_{t-2} + 0.1x_{t-3} \]  

This lag structure, however, performed only marginally better than the others we experimented with for our independent variables, and all formulations were highly consistent in terms of the magnitudes of the estimated model coefficients. These indexing
formulations reduced the estimated affect of FDA approval times on R&D spending and attributed more influence to the other explanatory variables.

Descriptive statistics for these variables, and for the variable \( \text{PCTUS}_{it} \), which is defined to be the percentage of firm \( i \)’s pharmaceutical sales coming from the U.S. market in year \( t \), are presented in Table 1.

### Table 1: Descriptive Statistics for Model Variables (in millions of 2005 $US)

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>( \text{RD}_{it} )</th>
<th>( \pi_{it} )</th>
<th>( \text{CF}_{it} )</th>
<th>( \text{FDA}_{it} )</th>
<th>( \text{PCTUS}_{it} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>$1,106</td>
<td>$2,520</td>
<td>$2,711</td>
<td>1.9 years</td>
<td>63.3%</td>
</tr>
<tr>
<td>Median</td>
<td>$1,008</td>
<td>$2,418</td>
<td>$2,595</td>
<td>1.9 years</td>
<td>63.7%</td>
</tr>
<tr>
<td>Maximum</td>
<td>$4,045</td>
<td>$8,343</td>
<td>$7,061</td>
<td>2.6 years</td>
<td>74.2%</td>
</tr>
<tr>
<td>Minimum</td>
<td>$380</td>
<td>$472</td>
<td>$35</td>
<td>1.0 years</td>
<td>49.9%</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>$585</td>
<td>$1,368</td>
<td>$1,424</td>
<td>0.6 years</td>
<td>5.3%</td>
</tr>
</tbody>
</table>

Before proceeding to the statistical analyses and hypothesis tests, it is necessary to emphasize that our sample of firms, because it includes only large, traditional, U.S-based drug companies, should not be used to draw inferences about the entire industry’s experience over the decade of the 1990s, particularly with respect to PDUFA. While our sample of firms does account for about half of total industry pharmaceutical R&D during our sample time period, it represents only one type of firm. The experiences and economic behavior of small and medium-sized biotechnology companies, for example,
may have been quite different during this time period given their different firm characteristics.

Equation (4) was estimated using pooled least squares with both a common intercept and firm fixed effects. Our log-first-differenced model specification implies we are explaining pharmaceutical R&D growth rates. Because previous researchers have documented the robust empirical links between pharmaceutical R&D spending, cash flows, and pharmaceutical profit expectations, our focus is on studying the relationship between R&D spending and FDA approval times. To do this, we experimented with several formulations of the FDA variable appearing in equation (4). We report results from several different regressions based upon the formulation of our FDA approval time variable. Specifically, we tested a single-period measure of this variable, two weighted-index measures, and a geometrically-distributed lag specification (Koyck lag). Moreover, because our FDA approval time variable is measured at the industry level, and not the firm level (as are the other variables in our model), we also estimated R&D equations in which this variable was interacted with the percentage of firm pharmaceutical sales coming from the U.S. market in year $t$, the $\text{PCTUS}_{it}$ variable previously defined$^6$.

Because FDA approval times are, as argued in Section 2, an economic cost to the firm (they delay new product launches), an industry-level measure of this variable imposes the restriction that this expected cost is uniform across firms in the sample, which is less likely to be the case the more heterogeneous the sample firms. For example,

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$^6$ Firm-level data on average approval times are likely to be very noisy because of the small number of new drugs approval in a given year for a single firm (in many cases, zero or one). FDA review processes and approval times at the industry level may provide a better gauge of trends and changes over time resulting from such policy changes as PDUFA.
an EU-based firm that sells most of its products in Europe (and very little in the U.S.) will face a smaller FDA-approval-time cost than a U.S.-based firm that sells its products exclusively on the U.S. market, where FDA approval is required.

As was discussed in Section 3, however, the 7 firms in our sample were all large, established, U.S.-based pharmaceutical companies. This fact should mitigate somewhat the problems imposed by constraining firm expectation to a common, industry-wide measure\(^7\). Indeed, previous research on firm R&D expenditure behavior (for a similarly homogeneous sample of firms) also employed industry-wide variables to proxy expectations at the firm level (Grabowski and Vernon, 2000). This being said, however, the identification of some firm-level variation in the expected cost of FDA approval times would provide us with a stronger-form test of our central hypothesis.

Theoretically, the interaction variable \((\text{FDA}_t) \times (\text{PCTUS}_{it})\) is appealing because firms selling a large fraction of their products in the U.S. will face higher FDA approval time costs than firms selling a small fraction on the U.S. market, all things considered. Moreover, if a firm does not sell any pharmaceuticals in the U.S., it should be indifferent to FDA-approval times, and the cost they impose via delayed access to the U.S. market. In these cases, the interaction variable equals zero, the theoretically appropriate value\(^8\).

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\(^7\) One important point is that average FDA approval times could vary by therapeutic class. This seems quite reasonable, and indeed probable. In terms of the way we model firm expectations around FDA approval times in this paper, this would be a particularly important variable if our sample of firms included small- to medium-sized firms with only a small number of products (or R&D projects) in a single therapeutic class (or in only a few therapeutic classes). This issue in our current analysis is somewhat (although not entirely) mitigated because our sample of firms includes exclusively large, highly-diversified (across therapeutic classes) companies.

\(^8\) This does not occur in our sample; all the firms in our sample had a large share of their pharmaceutical sales coming from the U.S. market. Thus, this limiting property of the interaction term is not critical. It does, however, have theoretical appeal nonetheless.
Thus, this interaction variable is likely to be a more precise measure of the expected economic cost of FDA approval times to the firms in our sample.

Formulations of the Expected Cost of FDA Approval Times

In our most simple formulation of expected FDA approval times, we use a single-period lagged value of average industry approval times. We employ a one-year lag because this variable is an industry average and, unlike a firm’s own profits or cash flow, industry trends in approval times may be less immediately apparent or observable to firms. We use an industry average because some firms bring few or no new drugs to market in a given year, and regulatory changes and approval times may not be immediately perceptible based on own experience contemporaneously. Firm-level data, because of limited observations, will be more sensitive to idiosyncrasies that are unrelated to regulatory reforms such as PDUFA. As such, a lagged industry average may serve as the best gauge of expected approval times.

Furthermore, given that the total number of FDA approvals in any given year is not large (approximately thirty per year), the above rationale also supports using a weighted-average measure of lagged industry approval times as a proxy for expected future approval times. We do this using (1) a uniformly-weighted industry average of

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9 Indeed, Berndt, Gottschalk, Philipson, et al. (2004) note that while FDA review times under PDUFA were subjected to strict performance goals and actions (e.g., for drug applications under standard review it was stipulated that the 90th percentile of review time was to be twelve months), approval times were not, and they lagged considerably behind the PDUFA goals on review times (the authors report the 90th percentile of approval times under PDUFA-I and PDUFA-II were 42 and 36 months, respectively). FDA review time is the time it takes the FDA to render one of 3 actions: 1) non-approvable, 2) “approvable,” which means the drug or biologic can be approved if certain deficiencies and actions are appropriately acted on, and 3) ultimate approval which allows the sponsor to market the drug. Thus, approval times may lag considerably behind review times. Berndt, Gottschalk, Philipson, et al. describe this process with an analogy to publishing in academic journals. The time from submission to the first editorial decision (reject, accept, or revise and re-submit) is the review time, which is typically shorter than the time to final acceptance.
lagged FDA approval times in years \( t-1, t-2, t-3, \) and \( t-4; \) and (2) a weighted-average measure constructed using the same declining-weight structure employed for our profit and cash flow variables (see equation 5), where we weight FDA-approval times in years \( t-1, t-2, t-3, \) and \( t-4 \) by 0.4, 0.3, 0.2, and 0.1. The main idea behind this declining-weight structure is that more recent observations are likely to reflect better information about probable future values than observations lagged several periods\(^{10}\). We refer to these two indexing structures as a uniform index weighting (UIW) and a declining index weighting (DIW), respectively.

Finally, we modeled firm expectations of future FDA approval times as a geometrically-distributed lag of past industry approval times. To illustrate this specification, consider the following simplified model of firm-level R&D spending (cross-section subscripts, firm fixed effects, some explanatory variables, and variable transformations are suppressed for convenience):

\[
RD_t = \beta_0 + \beta_1 E\pi_t + \beta_2 \sum_{j=1}^{\infty} \lambda^j FDA_{t-j} + u_t \quad (0< \lambda <1)
\]  

(6)

Lagging equation (6) one period and multiplying through by \( \lambda \) yields a new equation that, when subtracted from the original equation (6) and after rearranging terms, yields the following Koyck transformation, which may be estimated empirically:

\[
RD_t = \beta_0 (1-\lambda) + \beta_1 (E\pi_t - \lambda E\pi_{t-1}) + \beta_2 FDA_{t-1} + \lambda RD_{t-1} + v_t
\]

(7)

\(^{10}\) We experimented with various weighting structures, both for the FDA variable and for our profit and cash flow variables; results were highly consistent across the different formulations and the number lags employed.
The procedure for obtaining estimates of the parameters in equation (6) is based on an iterative estimation of equation (7). For an example of a Koyck model used to estimate firm-level R&D spending (in 7 U.S. industries), see Branch (1974).

Tables 2 and 3 summarize our empirical results from the different versions of equation (4) we estimated, as well as from the Koyck models. Firm fixed effects were included in the models presented in Table 3, but are not reported.

Table 2: Log-First-Differenced Common Intercept Regression Results Based on a Panel of 7 Large U.S. Firms from 1990-1999 (t-statistics are reported in parentheses)

<table>
<thead>
<tr>
<th>Formulation of Expected FDA Approval Time Variable</th>
<th>$E\pi_{it}$</th>
<th>$CF_{it}$</th>
<th>Approval Time Variable</th>
<th>Adj. $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$FDA_{it-1}$</td>
<td>0.254***</td>
<td>0.134**</td>
<td>-0.146**</td>
<td>0.242</td>
</tr>
<tr>
<td></td>
<td>(2.41)</td>
<td>(1.56)</td>
<td>(-1.68)</td>
<td></td>
</tr>
<tr>
<td>$(FDA_{it-1}) \times (PCTUS_{it})$</td>
<td>0.259***</td>
<td>0.142*</td>
<td>-0.105*</td>
<td>0.288</td>
</tr>
<tr>
<td></td>
<td>(2.37)</td>
<td>(1.53)</td>
<td>(-1.44)</td>
<td></td>
</tr>
<tr>
<td>$UIW$</td>
<td>0.218***</td>
<td>0.173**</td>
<td>-0.212**</td>
<td>0.336</td>
</tr>
<tr>
<td></td>
<td>(2.22)</td>
<td>(1.74)</td>
<td>(-1.69)</td>
<td></td>
</tr>
<tr>
<td>$UIW \times (PCTUS_{it})$</td>
<td>0.243***</td>
<td>0.180**</td>
<td>-0.136*</td>
<td>0.417</td>
</tr>
<tr>
<td></td>
<td>(2.36)</td>
<td>(1.70)</td>
<td>(-1.29)</td>
<td></td>
</tr>
<tr>
<td>$DIW$</td>
<td>0.207***</td>
<td>0.161*</td>
<td>-0.205**</td>
<td>0.327</td>
</tr>
<tr>
<td></td>
<td>(2.04)</td>
<td>(1.53)</td>
<td>(-1.74)</td>
<td></td>
</tr>
<tr>
<td>$DIW \times (PCTUS_{it})$</td>
<td>0.239***</td>
<td>0.164*</td>
<td>-0.181*</td>
<td>0.422</td>
</tr>
<tr>
<td></td>
<td>(2.30)</td>
<td>(1.55)</td>
<td>(-1.56)</td>
<td></td>
</tr>
<tr>
<td>$Koyck$</td>
<td>0.274***</td>
<td>0.125**</td>
<td>-0.139**</td>
<td>0.260</td>
</tr>
<tr>
<td></td>
<td>(4.04)</td>
<td>(1.70)</td>
<td>(-1.67)</td>
<td></td>
</tr>
<tr>
<td>$Koyck \times (PCTUS_{it})$</td>
<td>0.273***</td>
<td>0.130**</td>
<td>-0.096*</td>
<td>0.283</td>
</tr>
<tr>
<td></td>
<td>(3.65)</td>
<td>(1.68)</td>
<td>(-1.31)</td>
<td></td>
</tr>
</tbody>
</table>

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

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Table 3: Log-First-Differenced Fixed Effects Regression Results Based on a Panel of Seven Large U.S. Firms from 1990-1999 (t-statistics are reported in parentheses)

<table>
<thead>
<tr>
<th>Formulation of Expected FDA Approval Time Variable</th>
<th>$E_{\pi t}$</th>
<th>$CF_{it}$</th>
<th>Approval Time Variable</th>
<th>Adj. $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA$_{t-1}$</td>
<td>0.268***</td>
<td>0.171**</td>
<td>-0.149*</td>
<td>0.245</td>
</tr>
<tr>
<td></td>
<td>(2.76)</td>
<td>(2.04)</td>
<td>(-1.83)</td>
<td></td>
</tr>
<tr>
<td>(FDA$_{t-1}$)×(PCTUS$_n$)</td>
<td>0.274***</td>
<td>0.179**</td>
<td>-0.109*</td>
<td>0.285</td>
</tr>
<tr>
<td></td>
<td>(2.66)</td>
<td>(2.09)</td>
<td>(-1.57)</td>
<td></td>
</tr>
<tr>
<td>UIW</td>
<td>0.225***</td>
<td>0.205**</td>
<td>-0.202**</td>
<td>0.333</td>
</tr>
<tr>
<td></td>
<td>(2.40)</td>
<td>(2.27)</td>
<td>(-1.70)</td>
<td></td>
</tr>
<tr>
<td>UIW×(PCTUS$_n$)</td>
<td>0.258***</td>
<td>0.213**</td>
<td>-0.139*</td>
<td>0.417</td>
</tr>
<tr>
<td></td>
<td>(2.62)</td>
<td>(2.36)</td>
<td>(-1.38)</td>
<td></td>
</tr>
<tr>
<td>DIW</td>
<td>0.212**</td>
<td>0.194**</td>
<td>-0.179*</td>
<td>0.319</td>
</tr>
<tr>
<td></td>
<td>(2.20)</td>
<td>(2.00)</td>
<td>(-1.49)</td>
<td></td>
</tr>
<tr>
<td>DIW×(PCTUS$_n$)</td>
<td>0.251***</td>
<td>0.198**</td>
<td>-0.168*</td>
<td>0.415</td>
</tr>
<tr>
<td></td>
<td>(2.55)</td>
<td>(2.13)</td>
<td>(-1.45)</td>
<td></td>
</tr>
<tr>
<td>Koyck</td>
<td>0.278***</td>
<td>0.191**</td>
<td>-0.135**</td>
<td>0.268</td>
</tr>
<tr>
<td></td>
<td>(4.66)</td>
<td>(2.62)</td>
<td>(-1.80)</td>
<td></td>
</tr>
<tr>
<td>Koyck×(PCTUS$_n$)</td>
<td>0.280***</td>
<td>0.198**</td>
<td>-0.089*</td>
<td>0.296</td>
</tr>
<tr>
<td></td>
<td>(4.20)</td>
<td>(2.68)</td>
<td>(-1.37)</td>
<td></td>
</tr>
</tbody>
</table>

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

The results in Tables 2 and 3 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 R&D expenditures in the pharmaceutical industry, expected profitability is a statistically significant explanatory variable. Our elasticity estimate range suggests that a 10 percent increase (decrease) in our indexed measure of pharmaceutical profitability measure will be accompanied by between a 2 and 3 percent increase (decrease) in pharmaceutical R&D spending, approximately. 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 0.20 (Vernon, 2005)\textsuperscript{11}.

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, Santerre, and Vernon (2005) employed a measure of real pharmaceutical prices in the U.S. lagged one period to capture both an expected-profitability and a cash-flow effect. The notion behind this variable was 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 proximate future; it also should capture expected future-period real pharmaceutical prices, at least in the near term and on average. Furthermore, real pharmaceutical prices also impact industry cash flows\textsuperscript{12}. Their 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 expected profit and cash flow variable coefficients is a more direct comparison to these aforementioned industry-level studies, and it does, of course, yield higher elasticity estimates. This sum ranged from 0.37 to 0.48 in our models, with the Koyck specification in the fixed effect models generating the

\textsuperscript{11} 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, respectively. Thus, the elasticity of R&D intensity to pharmaceutical profit margins ranges roughly between 0.17 and 0.21.

\textsuperscript{12} There are numerous nuances to these arguments along with several caveats. The interested reader is referred to the original paper for more details.
highest elasticity estimate. The cash flow variable coefficient estimates are also highly consistent with previous firm-level studies.

The principle hypothesis we test in the current paper is that FDA approval times influence the expected returns to pharmaceutical R&D because they delay product launches and impose a cost on the firm, and this affects firm-level R&D spending on the margin. Our results in Tables 2 and 3 suggest this is indeed the case for the firms in our sample from 1990-1999. It is striking to observe that this variable is statistically significant at the 10-percent level or better in all of our model specifications. Coefficient estimates suggest an elasticity range from -0.09 to -0.21.

We also estimated levels models that generated higher coefficient estimates, but within-group serial correlation was detected in these specifications, and thus we do not report those results here. Unlike first-difference models, levels models are also more susceptible to omitted variable bias if, for example, unobserved determinants of R&D expenditures have a similar time trend to FDA approval times, which followed a strong downward trend over our sample time period. Examples might be changes in the composition of R&D spending over time, possibly due to greater external requirements (external payer demands) for pharmacoeconomic studies, or changes in regulatory stringency and clinical data requirements set by the FDA.\(^{13}\) In terms of differentiating among the sixteen different models summarized in Tables 2 and 3, it seems most reasonable to rely on estimates from models that allowed for both firm-specific baseline R&D growth rates (fixed-effects models) and heterogeneous expectations of future FDA

\(^{13}\) It is also the case that user fees paid to the FDA are generally expensed as R&D, and thus are captured in our measure of R&D spending; however, user fees during this period, relative to firm R&D budgets, were extremely small and less than one-half of one percent during 1999, when user fees were at the highest level during our sample period.
approval time costs\textsuperscript{14}. The range of estimated coefficients generated by these models for our FDA variable was -0.09 to -0.17, implying a smaller effect on R&D spending\textsuperscript{15}.

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 relative to the previous decade (Golec and Vernon, 2006). The reason for this may be the declining growth rate in pharmaceutical prices and profits during the period. Real pharmaceutical prices began moderating after 1993, when the Clinton administration’s proposed Health Security Act (HSA) was being debated and considered; this Act contained provisions for prescription drug price controls in the U.S. (Abbott, 1996; Golec, Hegde, and Vernon, 2006; Golec and Vernon, 2006; Ellison and Mullin, 2001).

As a result of this proposed legislation, pharmaceutical prices grew at a rate 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, Hegde, and

\textsuperscript{14} We tested the relationship between FDA approval times and R&D spending using a larger sample of firms with several additional years, but instead of using pharmaceutical R&D expenditures as the dependent variable we used total firm R&D expenditures, and then controlled for non-pharmaceutical R&D using the ratio of firm pharmaceutical sales to total firms sales (because among firms in the pharmaceutical industry, pharmaceuticals are by far the most research intensive business segments within the firm). Our results, while hampered by limitations on the data used to measure firm pharmaceutical segment profitability, were highly consistent with the results observed using our survey data (there was, however, a lot of overlap between the samples). The coefficient on the FDA approval-time variable was slightly smaller in many cases. For example, in our models that employed a single period lagged measure of FDA approval times, we observed a coefficient range from -0.083 to -0.124; versus the range estimated using our survey data, which was from -0.105 to -0.149.

\textsuperscript{15} 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 life could be the result of an additional year at the end of a product’s patent. The present value impact of such a change during the R&D project phase would be significantly diminished because of discounting.
Vernon, 2006). In contrast to this, during the 1980s, drug prices grew at a rate well in excess of inflation. Golec, Hegde, and Vernon (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. An 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, at least for the firms in our sample. That is, was it not for the enactment of PDUFA in 1992, R&D growth rates for these firms might have slowed down even more during the 1990s. 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 in the last section of this paper illustrated, FDA approval times declined significantly after the enactment of PDUFA in 1992. However, approval times were already trending downwards prior to 1992. In fact, Berndt, Gottschalk, Philipson, et al. (2004) estimated this pre-PDUFA trend was 1.7% per year. Presumably, therefore, approval times would have continued to decline at this rate even if Congress had not approved the PDUFA legislation.

In the last section, we documented a robust empirical relationship between FDA approval times and firm-level expenditures on pharmaceutical R&D. What is interesting to investigate, therefore, is the direct causal impact PDUFA may have had on pharmaceutical R&D spending by the firms in our sample. We illustrate this causal chain of events below in Figure 3.
To establish a link between PDUFA and R&D expenditures, we begin by considering the effect PDUFA had on FDA approval times. Specifically, we rely on the aforementioned empirical research by Berndt, Gottschalk, Philipson, et al. (2004). These researchers estimated that the PDUFA-induced reduction in FDA approval times between 1992 and 2001 was 6.2 months. While approval times declined from 24.2 to 14.2 months during this period, their empirical analysis showed not all of this decline could be attributed to PDUFA. In particular, they concluded that in a counterfactual world without PDUFA, approval times would have declined to 20.4 months by 2001—a rate of 1.7% per year. PDUFA, however, accelerated this trend and reduced approval times to 14.2 months by 2001.

These researchers further determined that PDUFA-I and PDUFA-II had a differential impact on approval times, with PDUFA-I having a more substantial impact. Specifically, PDUFA-I was estimated to have accelerated approval times during this period by 7.6% per year (resulting in an annual decline of 1.7% + 7.6% = 9.3% during the PDUFA-I era). In contrast to this, the re-authorization of PDUFA in 1997, or PDUFA-II, was determined to have accelerated approval times by an additional 3.6% per year (resulting in an annual decline of 1.7% + 3.6% = 5.3% during the PDUFA-II era). A
plausible explanation for this difference, according to the authors, was the fact that prior to PDUFA-I there was a backlog of applications under review and the enactment of PDUFA-I resulted in a significant one-time savings from this “low-hanging fruit.”

It is possible to use the findings by Berndt and colleagues to approximate the effect PDUFA had on pharmaceutical R&D spending for the firms in our sample. We do this by performing a simple policy simulation. First, we construct a counterfactual time series of FDA approval times based on the work by Berndt, Gottschalk, Philipson, et al. (2004). We do this by using the estimated trend in FDA approval times prior to the enactment of PDUFA and extrapolating. More precisely, we use the model by Berndt, Gottschalk, Philipson, et al. and set their PDUFA-I and PDUFA-II indicator variables, which interact with the aforementioned time-trend variable, equal to 0, and then generate a counterfactual time series of FDA approval times in the absence of PDUFA. This is the same policy experiment these authors conducted when they predicted FDA approval times would have declined to 20.4 months by 2001 if PDUFA-I and PDUFA-II were never implemented.

Using this counterfactual time series of predicted approval times along with the observed values of the other independent variables in our model, we generated predicted R&D spending levels using the estimated models presented in Tables 2 and 3. We then

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16 We also tested a model similar to the Berndt, Gottschalk, Philipson, et al. (2004) analysis. We replaced our approval time variable with a time trend variable that entered into the model separately and interactively with both a PDUFA-I and a PDUFA-II indicator variable; thus, we estimated three separate time trends in firm-level R&D spending from 1990 to 1999. Our results suggested that PDUFA-I exerted a more significant impact on R&D spending than PDUFA-II. The coefficient estimates on these three variables were 0.039, 0.011, and 0.004, respectively, and all were significant at the 0.05-level or better. The interpretation is that, after controlling for other explanatory variables, R&D spending was growing at a real rate 3.9% prior to PDUFA-I, it then increased to a 5.0% rate (0.039 + 0.011) until PDUFA-II was passed, when it grew at a 4.3% rate (0.039+ 0.004), ceteris paribus. The elasticity estimates for the expected profitability variable and the cash flow variable were 0.299 and 0.131, respectively. However, only the profit expectation variable was statistically significant at traditional levels (p< 0.01). The cash flow variable was statistically insignificant (p = 0.16).
compared these predicted R&D levels (i.e., what R&D spending would have been in the absence of PDUFA) with observed R&D spending through the year 1999, which is the last year in our sample. The difference between the observed and the predicted R&D is therefore an approximation of the marginal R&D induced by PDUFA.\(^ {17}\)

In 2005 U.S. dollars, total pharmaceutical R&D spending for the 7 firms in our sample during the PDUFA-eras, up to and including the year 1999, was approximately $65.5 billion. R&D spending in the counterfactual world without PDUFA was estimated to be between 2.7% and 5.7% less than this amount, or between $1.77 and $3.64 billion. Thus, it seems reasonable to conclude that for the 7 firms in our sample, PDUFA stimulated between $1.8 and $3.6 billion in additional pharmaceutical R&D, and has presumably continued to induce additional R&D spending since 1999. According to research by DiMasi, Hansen, and Grabowski (2003) on the cost of drug development during a similar time period, total R&D outlays for new molecular entities (NMEs), inclusive of product line extension costs, were approximately $590 million (2005 $US). Therefore, PDUFA may have been responsible for the development of between 3 and 6 NMEs.\(^ {18}\)

While extrapolating these estimates beyond our sample of large, U.S.-based firms would be inappropriate, it is worth pointing out some of the relative scales involved. For example, in 1999, the last year in our sample, total pharmaceutical expenditures by the 7 firms in our study represented 51.2% of total PhRMA-member pharmaceutical R&D

\(^ {17}\) This retrospective policy simulation is similar to one employed recently by Giaccotto, Santerre, and Vernon (2005), which approximated the effect of a hypothetical pharmaceutical price control policy on aggregate industry R&D expenditures.

\(^ {18}\) This simple calculation ignores the drug development lag. For example, if PDUFA induced an additional $590 million in R&D (out of pocket R&D cost per NME) the first year after the legislation was passed, this additional R&D would obviously not produce a NME during the same year. Nevertheless, this calculation can be informative on average and in the long run.
($12.9 billion and $25.1 billion, respectively, in 2005 $US). However, PhRMA-member firms themselves are only a subset of the entire industry (albeit a very large subset), and many medium- to small-sized biotechnology companies are not members. In a recently completed analysis for PhRMA, Burrill & Company estimated that total industry pharmaceutical R&D in 2005 was approximately $51.3 billion, of which PhRMA members accounted for $39.4 billion, or 76.8% (Pharmaceutical Industry Profile 2006, PhRMA, Washington DC, March, 2006). Thus, it may be cautiously concluded that the effects of PDUFA on pharmaceutical R&D spending and new drug innovation are likely to be greater than the estimates we generated based upon our sample of 7 firms from 1990 to 1999.

While the pooling of multiple empirical estimates in this manner must be considered with caution, it does appear likely that PDUFA has generated, and continues to generate, social welfare in terms of the Act’s contribution to pharmaceutical innovation.

5. Conclusions

In this paper we employed 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 on measures of profitability and prices to capture the expected returns to pharmaceutical R&D. We argue that an additional element of expected returns may be captured using FDA approval times as an explanatory variable. For top-decile selling drugs brought to market in the early 1990s, it has been estimated that present value net sales equaled about $16 billion; clearly, the
benefit to firms of moving this life-cycle cash-flow profile backward 6 months (ignoring other plausible 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.

Using multiple model specifications and data from 7 large, U.S-based pharmaceutical firms between 1990 and 1999, we find that FDA approval times exerted a robust and economically meaningful impact on firm-level pharmaceutical R&D expenditures. Based upon the theoretically most appropriate models, we estimate an R&D elasticity range (with respect to approval times) from -0.09 to -0.17. This suggests a 10% reduction (increase) in FDA-approval times will lead to an increase (reduction) in pharmaceutical R&D by between 0.9% and 1.7%, ceteris paribus. Combining our analyses with previous research on the effect PDUFA had on FDA approval times, we estimate that PDUFA increased pharmaceutical R&D spending by the firms in our sample by between 2.7% and 5.7%, or by approximately $1.8 billion to $3.6 billion. While it would be inappropriate to generalize these findings beyond our sample to the industry at large, the following facts suggest the $1.8 billion-$3.6 billion range may be conservative: (1) in the current study, we measure incremental R&D spending attributable to PDUFA up to 1999 only (the last year in our sample). Presumably, PDUFA continued to incentivize additional R&D after 1999; in fact, it may still be incentivizing R&D spending on the margin if counterfactual FDA approval times continue to exceed observed approval times; and (2) the fact that the firms in our sample represented only about one-half of total PhRMA-member R&D expenditures in 1999 and
PhRMA-member R&D is currently about three-fourths of industry-wide pharmaceutical R&D spending.

In light of these facts, and considering the research on the productivity of pharmaceutical R&D in terms of its contribution to human health (e.g., Lichtenberg, 2003), the social benefits of PDUFA from increased levels of pharmaceutical R&D spending may be substantial.
REFERENCES


