

DO FASTER FDA DRUG REVIEWS ADVERSELY AFFECT PATIENT SAFETY?  
AN ANALYSIS OF THE 1992 PRESCRIPTION DRUG USER FEE ACT\*

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## Abstract

With the recent withdrawal of Vioxx and other high-profile products, there have been increasing concerns on drug safety especially the role of FDA review time, which was greatly reduced with the passage of PDUFA in 1992. Combining several comprehensive databases, we analyze how FDA review time, drug novelty, and US launch lag affect the occurrence of post-marketing, serious adverse events in the US during 1993-2003. While we find that more novel drugs and shorter US launch lags result in a larger number of serious adverse events, there is no association between FDA review time and adverse events after controlling for these and other factors. We also find that many novel products with significant anticipated benefits and risks carry black box warnings at the time of product launch. Since many adverse events involve rare occurrences and are necessarily unanticipated, various policy options for improving post-marketing surveillance should be considered including dedicating user fees to drug safety issues.

## I. INTRODUCTION

Do faster new drug reviews adversely affect patient safety? This has become an important regulatory policy issue. The 1992 Prescription Drug User Fee Act (PDUFA) has resulted in a substantial reduction in approval times for new molecular entities (NMEs), particularly for novel drugs receiving the FDA's priority rating (Berndt, et al, 2005). However, the withdrawal of Vioxx and some other high profile drug products in recent years has focused attention on whether faster reviews have adverse consequences.

Previous work offers mixed evidence on the question of whether faster reviews have negatively affected drug safety. Olson (2002) found that the reductions in FDA review times between 1990 and 1995 were associated with increases in serious adverse drug reactions (ADRs), i.e., those resulting in death or hospitalization. She also found that novel drugs receiving priority review by the FDA posed greater risk of serious ADRs compared with standard drugs in the same time period (Olson, 2004).<sup>1</sup> On the other hand, Berndt, et al (2005) found that the proportion of NME withdrawals remains unchanged in the periods before and after the implementation of PDUFA in 1992. Similar findings on new drug withdrawal were reported by the FDA's Center for Drug Evaluation and Research (2005) and the Tufts Center for the Study of Drug Development (2005).

From a conceptual standpoint, PDUFA's impacts on drug safety are subject to countervailing effects. On the one hand, FDA staff and resources increased with the introduction of user fees under PDUFA. Furthermore, the mean number of patients in clinical trials for NMEs receiving FDA approval also increased significantly in the post-PDUFA period. On the other hand, the increased speed of FDA approval under PDUFA (Berndt, et al, 2005) may have introduced unknown safety risks. Furthermore, the United States is less likely to benefit from

post-marketing experiences of other countries now that there has been a reversal of the drug lag phenomenon that characterized the pre-PDUFA period. (Grabowski and Wang, 2006).

In this paper, we examine the role of faster reviews and several other explanatory variables influencing drug safety. Our analysis utilizes a negative binomial regression model for the new drugs introduced over the period 1992 to 2002. The dependent variable is the number of serious adverse events reported after a product's introduction, including those resulting in hospitalization and death. Explanatory variables include FDA review times, global launch lags (i.e., the number of months a drug is available prior to the US introduction) and whether a black box warning is required at the time of the approval. Other explanatory variables include indicators of a drug's novelty, its degree of utilization, the nature of the patient population, therapeutic class, mode of delivery, and time on the market.

This paper is organized as follows: The next section of the paper discusses the evolution of the FDA's approach to drug safety and the implementation of PDUFA. Sections III and IV describe our principal hypotheses as well as the data and methods. Section V presents the results from the negative binomial regression model. The final section discusses our findings and their policy implications.

## II. HISTORICAL DEVELOPMENT OF FDA REGULATION

### A. *The FDA Regulatory Process and Issues*

The submission of statistical evidence on safety and efficacy obtained from randomized controlled clinical trials has long been the cornerstone of the drug regulatory process.<sup>2</sup> Clinical testing normally occurs over three distinct phases, each of which offers different information

about efficacy and safety. The final clinical development phase (Phase III) involves large-scale human trials and these represent the pivotal studies of the drug's efficacy. Phase III studies are designed with sufficient statistical power (i.e. with large enough groups of test and control subjects) to validate the preliminary evidence of efficacy developed in phase II.

Because several thousand individuals are commonly enrolled in phase III trials, testing is also useful in detecting infrequent adverse reactions. However, at this level of exposure, clinical trials normally would not detect events that occur in as few as 1 per 1,000 patients. Furthermore, significant interactions with other drugs and medicines could go unobserved in clinical trials since these trials are done under highly controlled conditions with selective patient populations. The regulatory process relies on post-marketing surveillance to detect rare or complex interactions events that are undetectable in phase III trials.

All drugs involve a benefit to risk evaluation, and regulators must make explicit or implicit trade-offs on this score in deciding when enough evidence is available to approve a drug. Historically, U.S. drug regulation has been characterized by risk averse behavior and very long development and regulatory review times.<sup>3</sup> Several researchers have argued that the FDA's risk aversion stemmed from the disproportionate costs regulators bear from making a type one error (i.e., approving a drug that later needs to be recalled on safety grounds) compared to making a type two error (i.e., not approving or unnecessarily delaying access to a drug whose benefits exceed the risks for patients). The latter error is less transparent and it does not have the same damaging effects on a regulator's professional reputation.

There is a lengthy literature on how the FDA regulation of pharmaceuticals affects R&D times and costs (for a recent review, see Danzon and Kueffel, 2005). A historical manifestation of the FDA's risk averse behavior was a significant U.S. "drug lag" in the introduction of new

entities relative to other advanced economies (Kaithin and Brown, 1995). By the late 1980s, DiMasi found that the typical new drug took more than 12 years from initial synthesis to FDA approval, and that the FDA review process by itself took 2.6 years (DiMasi, 1995).

During the 1980s, pressures for changes in FDA's behavior began to build from the AIDS activists and other groups to obtain faster access to new medicines. After a number of well publicized events involving activists, the agency and Congress, FDA implemented some important initiatives targeted to life-threatening diseases.<sup>4</sup> First, AIDS drugs were put on a super fast-track process in NDA review (so-called "AA" status). Second, the FDA established in 1988 the possibility of an expedited development process for life-threatening and seriously debilitating diseases that had no satisfactory therapeutic alternatives (the Subpart E Program).<sup>5</sup> These initiatives were followed in 1992 by "accelerated approval," another regulatory program of broader scope to speed the development and approval of new drugs for serious or life-threatening diseases with unmet needs. In particular, the accelerated approval program allowed firms to gain approval on the basis of a surrogate endpoint that is reasonably likely to predict ultimate clinical benefit (e.g. time to progression of a tumor instead of long-term patient survival). The FDA could require drugs approved under this program to undergo additional post-approval clinical trials or restrict distribution and usage to certain physician specialty groups.<sup>6</sup>

The expedited development/accelerated approval programs represented a significant departure in agency behavior. In particular, the FDA allowed speedier access and increased risk for life-threatening and seriously debilitating illness on an explicit "medical risk benefit analysis." At the same time, these programs were targeted to a relatively small number of disease categories—notably AIDS and certain types of cancer.

*B. The Prescription Drug User Act (PDUFA)*

In 1992 Congress passed PDUFA with the objective of changing the incentives for speedier review across the full spectrum of new drug applications. In addition, PDUFA introduced a new mechanism, user fees, to increase the resources to undertake that task. In particular, PDUFA required drug sponsors to pay a one-time fee for a new drug application (NDA) or a biological licensing application (BLA) with clinical data (\$573,500 in fiscal 2004). The contributed fees were dedicated to new drug reviews rather than other FDA tasks.

In exchange for these user fees, the FDA agreed to review and act on NDA/BLA within a specified time period. In particular, NDA/BLAs are assigned a standard or priority status at the time of NDA submission, depending in part on the FDA's assessment of the novelty of the agent and potential therapeutic benefits. Under PDUFA, FDA is expected to deliver a complete review of 90% of priority applications within six months. Correspondingly, the FDA is expected to review 90% of standard applications within 12 months (now 10 months under PDUFA III). In particular, on or before the action date mandated by PDUFA, the FDA is expected to issue one of three outcome letters—the NDA is approved, approvable, or not-approvable. In the case of an approved letter, the company has the right to market the drug. For an approvable outcome, the NDA/BLA can be approved if certain deficiencies and issues are appropriately addressed. Finally, a not-approvable letter means that the company has not satisfied the FDA's standards for safety and efficacy with the evidence submitted in its NDA/BLA.

Several researchers have found that PDUFA has resulted in significantly shorter FDA review times. In the most comprehensive study to date, Berndt, et. al. (2005) found that PDUFA significantly accelerated a downward trend in review times that was already occurring before the passage of PDUFA. In particular, they found that review times declined from 24.2 months in

1992 to 14.2 months in 2002. Using a statistical regression model, they estimated that approximately two-thirds of this decline could be attributed to PDUFA.

The original PDUFA legislation covered a five-year period. The law was renewed in 1997 and again in 2002. The size of the user fees have increased over time. The targets on review times have been reduced to 10 months from 12 months in the most recent renewal of the law (PDUFA III). The Act is up for renewal in 2007 and there is considerable debate about whether the user fee should be maintained or modified in structure.

### III. THE FDA REVIEW PROCESS AND DRUG SAFETY—THEORETICAL CONSIDERATIONS AND HYPOTHESES

From a conceptual standpoint, the system of user fees and performance targets under PDUFA could operate to increase or decrease drug risk. On one hand, critics have argued that PDUFA has caused FDA reviewers to undertake more risks in order to meet performance targets. On the other hand, PDUFA also produced a large infusion of new resources to evaluate a drug's benefits and risks in a timely manner.

The potential impact on drug risks from these countervailing forces is illustrated in Figure 1. In particular, one can model the potential incentive effects of PDUFA on FDA's willingness to undertake more risks as a leftward movement along a negatively sloped risk-review time tradeoff curve. Depending on the shape and location of this curve, the effect of a shorter review time could be substantial or negligible in value. At the same time, PDUFA also results in a downward shift in the curve as a result of the increased resources from user fees.



A reduction in review time from  $T_1$  to  $T_2$  results in a movement from point A on the pre-PDUFA curve to point C on post-PDUFA curve. Consequently, one cannot say whether the representative new drug will be characterized by more or less risk as a result of PDUFA. It depends on the size of the negative slope of the risk-review time curve over the relevant region of change as well as the magnitude of the downward shift in this curve from expanded resources at the FDA. Determining the effects of PDUFA on drug safety is essentially an empirical issue.

A number of other regulatory and non-regulatory factors also impact drug safety. In particular, given that approval decisions are based primarily on the outcomes of controlled clinical trials, the number of subjects and the duration of these trials will have an important effect on the ability of the FDA to discern risks prior to approval. The average number of patients studied in clinical trials for approved new molecular entities has grown significantly since the early 1990s.<sup>7</sup> This causes the risk-return curve in Figure 1 to shift downward over time.

While clinical trial sizes have been increasing, rare but serious side effects (i.e., risks involving 1 or fewer incidents in 1,000 patients) generally require information based on post-marketing experience. Prior to the mid-1990s, most new drugs were introduced into Europe and other countries before the United States. This provided spillover knowledge inputs to U.S. regulators. This has changed in recent years, both due to shorter regulatory reviews in the United States as well as the movement to harmonize regulatory procedures between the United States and the EU. The fact that many commercially important new drugs are introduced first in the United States, or simultaneously with other countries, results in a shift of the risk-review time curve upward in Figure 1. In assessing the level of risks associated with review times pre- and post-PDUFA, it is therefore important to consider whether a drug has been marketed outside the

United States prior to U.S. approval. This is one of the control variables included in our empirical analysis.

Novel drugs are also expected to incur above-average risks. As discussed, the Subpart E and accelerated approval programs which began in the 1990s target drug treatments for serious and/or life threatening diseases with large unmet medical burden. These programs, by design, allow for expedited development schedules and approval based on surrogate endpoints. The FDA, in effect, has made a policy decision to accept greater risks to speed the availability of new drugs with large potential benefits in areas of unmet medical need. Consequently, it is reasonable to expect higher post-launch risks for drugs that meet the criteria for these programs.

Priority drugs are another class of specially designated drugs by the FDA. As discussed, when a firm submits a new drug application (NDA) to the FDA for review, the drug is classified as priority or standard. Priority drugs go to the head of the queue in terms of FDA resources and have the shortest review time targets—six months under PDUFA. According to the Center for Drug Evaluation and Research (CDER), a priority designation is given to products that have the likelihood of providing a significant therapeutic advance compared to marketed products, either because of increased effectiveness, safety, or patient tolerability and compliance.<sup>8</sup> Since many priority drugs rely on a novel mechanism of action, they are also subject to greater uncertainty about safety risks. Consequently, it is reasonable to expect higher risk levels for priority drugs. Olson (2004) has found evidence to support this hypothesis.

Biological drugs are another class of novel agents that have grown in importance since the early 1990s. Most biologicals are reviewed by the Center for Biological Evaluation and Research (CBER). In contrast to the criteria for new chemical entities, biological entities only receive priority review by CBER when they offer the potential of a significant therapeutic

advance for life threatening diseases or conditions.<sup>9</sup> In a recent paper, Grabowski and Wang (2006) found new biological entities are focused particularly on cancer and other life-threatening disease categories. They also found that new biologicals have accounted for a disproportionate share of first-in-class drugs since 1993. Given these characteristics, we expect biologicals also to be subject to above average risks.<sup>10</sup>

An important distinction in FDA decision making is known (or anticipated) risks versus unknown (or unanticipated) risks. Through a product's labeling at the time of approval, the FDA can signal a known risk of a serious nature to the physicians and patients. In particular, when the FDA decides to approve a new drug where the expected therapeutic benefits outweigh a known safety risk of a serious nature, it can require a black box warning in the initial label. An example of such a case is the drug Herceptin. This drug was approved by the FDA in 1998 with a review time of slightly less than five months. Herceptin constitutes an important advance in the treatment of breast cancer patients that express excessive HER-2 protein. However, treatment with Herceptin also significantly increases the risk of congestive heart failure.<sup>11</sup> Consequently, the drug was given both a priority review as well as a black box warning at the time of initial approval.

It is reasonable to postulate that drugs which receive a black box warning at initial approval will be subject to above average risks after launch. A situation, however, in which this might not be the case involves black box warnings targeted to particular sub-populations for whom the drug is counter-indicated (e.g., pregnant women). For example, the class of ACE inhibitors/angiotensin receptor blockers are widely utilized drug treatments for hypertension. The complete class carries a black box warning associated with the increased risk of birth defects for pregnant women in their second and third trimester. If this type of this black box warning is

effective in causing pregnant women to substitute other anti-hypertensive treatment regimes, it wouldn't necessarily be associated with above average risks after launch.

The primary objective of this study is to understand how speedier reviews under PDUFA and other regulatory programs and developments have affected drug safety. Safety risks are measured by the incidence of adverse events after product approval. Our empirical analyses examines how several regulatory and non-regulatory determinant variables have affected the drug safety of the new molecular entities introduced between 1992 and 2002. In particular, with respect to the regulatory variables, we focus on the following hypotheses:

- (1) Novel drugs, i.e., those subject to accelerated approval or priority review, are expected to be riskier to patients.
- (2) Biological drugs are expected to be riskier on the basis of both novelty and an emphasis on indications with high disease burden and unmet need.
- (3) Drugs subject to initial black box warnings generally involve cases of high benefits and risks. Therefore, they are expected to experience more adverse events after approval, unless the black box warning is directed to a particular sub-population or demographic group for which the drug is counter-indicated.
- (4) Knowledge spillovers associated with U.S. launch lags are expected to reduce safety risks, especially in cases where data become available from a large population abroad over an extended period prior to U.S. approval.
- (5) Controlling for these and other determinant factors, shorter FDA review times under PDUFA may or may not be associated with greater safety risks, given the countervailing effects of PDUFA presented above.

## IV. METHODOLOGY AND DATA

### A. *Model Specification*

The negative binomial model is typically employed where the dependent variable involves counts that are over-dispersed and do not fit the Poisson distribution. (Cameron and Trivedi, 1998) Given this is the case here, we employ the negative binomial model to model the occurrence of adverse events for new molecular entities introduced between 1992 and 2002.<sup>12</sup>

The basic specification for the negative binomial regression model in the current analysis is

$$E(ADR_{it}) = \exp(\alpha R_{it} + \beta N_{it} + \gamma P_{it} + \epsilon_{it}) \quad (1)$$

where  $E(ADR_{it})$  is the expected value of the counts of adverse drug reactions,  $R_{it}$  are the regulatory related variables,  $N_{it}$  are the NME characteristic variables, and  $P_{it}$  are the patient specific variables. Separate models are estimated for serious ADRs, hospitalization ADRs, and death ADRs. The data sources and definitions for all the explanatory variables are discussed in the next two sections.

### B. *Adverse Drug Reactions*

The dependent variable in equation 1 is the count of ADRs in the year of launch and the first two years after launch. We identified the annual number of adverse events for 1992-2002 NMEs using the Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS) databases maintained by the FDA (Rodriguez, Staffa and Graham, 2001; Wysowski and Swartz, 2005).<sup>13</sup> The ADRs in this database are voluntary, spontaneous reports filed primarily by health care professionals such as clinicians, physicians, and pharmacists. We focused in

particular on serious ADRs defined as those resulting in hospitalization, death, disability, or determined to be life threatening or require intervention to prevent permanent impairment/damage.

A strength of this database is its broad coverage of all patient populations and all use, including approved indications and possibly off-label use. It is particularly useful for detecting rare ADRs that are not captured in clinical trials and for detecting drug-drug interactions. The ADRs reported in a drug's initial years on the market are the main basis for revisions in a drug's label, including new warnings and counter indications. In extreme cases these ADR reports can also result in a product's withdrawal.

Some of the recognized limitations of the ADR databases are its under-reporting of ADRs, uncertainty about causation, and the fact that there is no risk-adjustment for utilization and other factors. We structured our analysis in various ways to deal with these different concerns. First, with respect to the under-reporting issue, we focused on an NME's annual number of serious ADRs within three years of marketing. The reporting of adverse events is highest in the first two years after approval (Rodriguez, Staffa and Graham, 2001; Lasser et al, 2002).<sup>14</sup> With respect to the causation issue, we considered only ADRs labeled with suspected drugs by health professionals.<sup>15</sup>

We address concerns about the role of drug exposure and other factors affecting ADR reports by employing a multivariate regression framework described in equation 1 above. In particular, the set of determinant variables include a drug's exposure in terms of physical unit sales, whether the drug is a biological or chemical entity, its product formulation (oral, injectible, or other), its therapeutic class, its patient user characteristics, and so forth. These determinant variables are discussed in detail in the sections which follow.

### *C. The NME Sample*

There were 328 new biological and new chemical entities approved between 1992 and 2002. This information is taken from the FDA database of NME approvals. Our analysis specifically excludes NMEs classified as vaccines, diagnostic agents, radiopharmaceuticals, OTC products, combination products or any new formulations of existing products over the 1992-2002 period. In addition, 35 NMEs were excluded on the grounds of missing information in SRS/AERS database or in one of the other databases used to construct the explanatory variables in the analysis.<sup>16</sup> Our final sample consisted of 293 unique NMEs and 823 NME-year observations.

We focused on NMEs approved between 1992 and 2002 based on the time series information available in the different databases. We excluded NMEs approved prior to 1992 because our sales volume data (used to adjust for patient exposure) started in 1993. Since adverse event reporting is highest in the first two years after approval, it wasn't feasible to include NMEs approved before 1992. Correspondingly, our last year with complete data on adverse events was 2003, so we excluded all NMEs approved after 2002.<sup>17</sup>

Our sample includes the withdrawn NMEs that were approved between 1992 and 2002. The lone exception is Omniflox which was approved and withdrawn in 1992 (therefore excluded because of missing sales data and an incomplete ADR profile). Furthermore, 54 of the 293 NMEs in our sample were approved with an initial label requiring a black box warning.

Following the FDA, we defined PDUFA NMEs as those NDAs or BLAs submitted on or after October 1, 1992. Using this definition, 18% of our NME-year observations are pre-PDUFA and the remaining 82% are PDUFA NME-year observations.

#### *D. Explanatory Variables*

The key explanatory variables of interest relate to the bundle of regulatory variables. Information was obtained from the FDA on each drug's speed of review (the time between NDA or BLA filing and approval). We also obtained data from the FDA on which NMEs received FDA's priority or standard ratings. We obtained the lists of accelerated approvals from the FDA website (<http://www.fda.gov/cder/rdmt/>) and defined accelerated approvals as NDAs approved under Subpart H [21CFR 314.510] and BLAs approved under Subpart E [21CFR 601.42]; our study sample included 27 accelerated approvals.<sup>18</sup>

Data on whether an NME's label required a black box warning at the time of approval were obtained from the FDA's website and annual editions of the Physician's Desk Reference.<sup>19</sup> Furthermore, the warning labels were analyzed as to whether they involved restrictions on a specific sub-population of patients. In particular, 11 of the 54 NMEs with black box warnings at the time of approval were contra-indicated for pregnant women due to the risk of birth defects but carried no other black box warnings for the general population. These NMEs were treated as a separate category from the other NMEs with black box warnings. The more general category of black box warnings consisted largely of NMEs for life threatening diseases and conditions, especially cancer (n=15) and AIDS (n=11). The 11 drugs contra-indicated for pregnancy included nine anti-hypertensive agents, one oncology drug, and one drug for rheumatoid arthritis.

We used the MIDAS database provided by IMS Health to obtain information on the first world-wide launch date, formulation (oral, injectable, or others), therapeutic class, and sales volume. Therapeutic class was defined as the four-level Anatomical Therapeutic Classification (ATC) code, developed and maintained by the European Pharmaceutical Marketing Research



Association (<http://www.ephmra.org/main.asp?page=465>). This information from MIDAS was used to construct a U.S. launch lag variable (i.e., elapsed time from an NME's first launch worldwide).

We also used MIDAS to estimate the annual US sales volume for the combined retail and hospital channels for each NME. MIDAS reports quarterly sales volume in standard units. This is defined by IMS Health, for example, as one tablet, one capsule, five milliliter of oral liquid, one ampoule, etcetera.<sup>20</sup> We constructed separate sales measures for oral, injectible, and other forms, given the units of measurement are different for these forms. As injectible products are mainly consumed in the hospital setting, it is important that we include the hospital channel to accurately measure patient exposure to these products.<sup>21</sup>

Finally, we used the 2003 National Disease Therapeutic Index (NDTI) database, also provided by IMS Health, to estimate the age and sex distribution of patients treated by a NME. The NDTI is a nationally representative survey of ambulatory medical care visits in the United States. Using the 2003 NDTI, we estimated for a certain therapeutic class, the percentages of patients treated who were under 20 years of age, at or above 65 years of age, and those who were female. These therapeutic-class-level variables were used as proxies to reflect the demographic characteristics of patients treated by a NME.

## V. RESULTS

### A. *Summary Statistics*

As mentioned before, our final sample consisted of 293 NMEs including 12 withdrawn products that were approved between 1992 and 2002. Figure 2 presents the distribution of these NMEs by year of approval and also by withdrawal status, with the most approvals in 1996

(n=47) and the most withdrawals approved in 1997 (n=5). Figure 3 shows that these NCEs belong to 14 therapeutic areas (the first level of ATC classification). The greatest number of products are in the central nervous system (n=49), oncology (n=45), and systemic anti-infectives (n=41) categories. The fewest products are for hormone therapy (n=3), parasitology (n=4), and the miscellaneous (various other) categories (n=5). Of the 293 NMEs, 31 were biological products and 44 were orphan drugs.

Variable definition and characteristics of the 823 NME-year observations are presented in Table 1. Noticeably, the distributions of adverse events, FDA review time, U.S. launch lag, and sales volume are highly skewed. In the negative binomial models, we used natural log specifications for FDA review time and U.S. launch lag.<sup>22</sup> This log transformation was used because the distributions are highly right-skewed, and also because we expect their marginal effects to decrease with longer time. In addition, the sales volume variables for oral, injectable, and other formulations were specified as natural logs due to the skewed distribution.

PDUFA NMEs account for 82% of the observations. Priority drugs, accelerated approvals, and biological products account for 42%, 9%, and 10% of the observations respectively. The predominant formulation is oral, followed by injectable and the others. Note that product age is defined as the number of full calendar years after launch, with the year of launch designated as zero. Also note that the year of launch may differ from the year of approval.

In Table 2, we compared characteristics of standard NMEs, priority NMEs, and accelerated approvals using data from the first year of positive sales.<sup>23</sup> In this table, the three categories are mutually exclusive. In particular, the 27 accelerated approvals include 25 priority NMEs and two standard NMEs. In absolute numbers, the mean number of serious adverse events is highest for priority drugs, followed by accelerated approvals, and lowest for standard

drugs. Once adjusted for sales volume (in thousands of standard units), accelerated approvals become the highest in the number of serious adverse events because its mean sales volume is less than  $\frac{1}{4}$  of priority drugs and  $\frac{1}{2}$  of standard drugs. The above holds true for hospitalization ADRs and death ADRs and remains true if the medians instead of the means are compared.

Table 2 also shows that the percentages of biological and orphan products increase for priority products and accelerated approvals. The mean FDA review time decreases for priority products and accelerated approvals. Due to a few outliers, the mean US launch lag is longest for priority drugs – the median US launch lag is three months for standard drugs and zero months for priority drugs and accelerated approvals.

The group of drugs with black box warning labels at time of initial approval is disproportionately concentrated in the priority and accelerated approval categories. Only 5 percent of standard approvals receive these black box warnings. By contrast, 24 percent of priority drugs and 44 percent of accelerated approvals receive black box warnings. This option is therefore utilized primarily for novel drugs with large expected therapeutic benefits. The pattern of black box warnings is very different for the special group involving counter-indications for pregnant women. The vast majority of these drugs are standard drugs. Nine of these 11 drugs have a standard rating, with the other two receiving a priority rating.

We also separated the NME data in Table 2 into observations for the pre-PDUFA and PDUFA periods. As expected, the major differences between the two samples are in the FDA review times. In particular, the mean FDA review times for standard NMEs was 43 months pre-PDUFA (n = 30) and 19 months post-PDUFA (n = 145). The mean review times for priority NMEs in Table 2 was 29 months pre-PDUFA (n = 21) and 10 months post-PDUFA (n = 70).

The mean values for the accelerated approval were similar to those for priority drugs—26 months pre-PDUFA (n = 2) and 10 months post- PDUFA (n = 25).

*B. The Negative Binomial Regression Model*

We estimated the negative binomial models using the GENMOD procedure in SAS version 8.1, with the REPEATED statement to adjust for multiple observations from the same NME over time. The SAS GENMOD procedure derives the generalized estimating equation estimates using the maximum likelihood method. As a sensitivity analysis, we also repeated the negative binomial models using only PDUFA NMEs.

We present the negative binomial model estimates for the full sample of NME-year observations in Table 3. We estimated separate regression models for serious, hospitalization, and death ADRs.<sup>24</sup> All three dependent variables exhibit a skewed distribution. As shown in Table 2, however, the counts of death ADRs exhibit a particularly large dispersion as reflected in the difference between the mean (n=12) and median (n=2) in Table 1. This is reflected in our estimated equations. The dispersion coefficient is substantially higher for the death ADR estimated equations than that for serious ADRs' equations or hospitalized ADRs (Tables 3 and 5).<sup>25</sup> As expected, death ADRs also occur much less frequently than serious or hospital ADRs, (with a substantial number of observations with zero counts).

As we hypothesized, more novel drugs, including priority products, accelerated approvals, and biological products, lead to more serious adverse events (all  $p < 0.05$ ), except for accelerated approvals in the case of death ADRs. For these indicator variables, the marginal effect is the coefficient times the mean of the dependent variable. For example, the mean is 60 for serious ADRs in Table 1. Therefore, *ceteris paribus*, a priority product leads to 57 more

serious ADRs annually, an accelerated approval product leads to 35 more serious ADRs, and a biological product leads to 75 more serious ADRs. In contrast, orphan products are not associated with more serious adverse events in any of the specifications.<sup>26</sup>

We estimated both a log and linear variant of the FDA review time variable. Given the skewed nature of the distribution of review times, a logarithmic specification was the preferred variant utilized in the basic model. While this coefficient was negative, it was statistically insignificant for all three dependent variables, indicating that shorter review times, *ceteris paribus*, have not lead to more serious adverse events.

The linear formulation for review times was also statistically insignificant, except in the case of death ADRs. For this latter case, the estimated coefficient on the linear review time variable implies a one year reduction in review times would be associated with 1.2 more death ADRs per year. However, this observed effect may be the result of a few outlier observations, given that the logarithmic formulation of the review time variable is insignificant.<sup>27</sup> As noted, death ADRs are subject to many fewer observations with much greater dispersion than serious ADRs or hospital ADRs. Neither the linear nor logarithmic variants of review time are significant when the dependent variable is the more frequently observed serious ADRs, or those requiring hospitalization.

In contrast to the review time variable, US launch lag has a negative and significant effect on the occurrence of serious ADRs in all specifications. In particular, *ceteris paribus*, if one compares the case of first launch in the United States with the situation where the U.S. experiences a launch lag of 12 months, the marginal impact is 20 fewer serious adverse events annually with the lagged introduction. We also tried two variations of this variable – a population weighted launch lag and a simple indicator variable on whether drug was introduced

abroad first or not. The launch lag variable and its population weighted alternative performed comparably. They were statistically significant ( $p < .02$ ) in all cases.<sup>28</sup> The simple indicator variable was negative, but not statistically significant, indicating that the length of the lag mattered.

The two black box warning variables exhibit opposite signs. The general black box warning has the expected negative sign and is statistically significant except for the death ADRs' case. This is consistent with our hypothesis that many drugs have both large anticipated benefits and risks. The FDA employs a black box warning to signal this situation to physicians and patients. A large percentage of these compounds came from the cancer and AIDS categories.

By contrast, the black box warning pertaining only to risks for pregnant women has a negative sign. It is statistically significant in all three specifications. A plausible interpretation of this negative sign is that the warning appears to be successful in causing pregnant women to substitute other medications, and that these drugs have below average relative risks for populations other than pregnant women. As discussed, nine of the 11 drugs in this group are anti-hypertensives from the ACE inhibitor/ARB class. This black box warning has been in effect for many years for the entire therapeutic class. There are also a large number of substitute anti-hypertensives without these risks for pregnant women.

A drug's sales volume is a strong predictor of the level of its ADRs. All three product type formulations have sales coefficient estimates with  $p$  values significant at the 1% level. The higher coefficient observed for unit sales of injectibles could reflect higher risks for these products. Alternatively, it could be the result of differences in dosing or more adverse event reporting for products dispensed primarily in hospitals. Other positive and significant predictors of adverse events include drugs targeted to older patients (patients over 65 years) and to female

patients. As expected, product age is negatively associated with its level of reported ADRs. Therapeutic class and event year indicator variables are included in all specifications but not separately reported.

It is unknown the extent to which the voluntary reporting nature of the SRS/AERS database affects our findings. For example, physicians may be more motivated (scientific curiosity) to report adverse events caused by novel drugs, and this will lead to an upward bias for novel drugs.<sup>29</sup> For another example, similar to Olson (2002; 2004), we find that female patients are more likely to experience adverse events. While this could be caused by less clinical trial testing on female patients prior to marketing approval, another possible explanation is that female patients are more likely to seek medical care, therefore report the adverse events. These questions can be answered in large-scale, head-to-head comparison trials, but such trials are expensive to conduct in a systematic way.

### *C. Sensitivity Analyses*

We performed a number of sensitivity analyses designed to consider interaction and other potential effects of PDUFA on drug safety. First, we entered a PDUFA indicator variable, based on whether or not the submission date of the NME to the FDA was after the passage of PDUFA, into all the estimated equations in Table 3. This was done separately, i.e., without the FDA review time variables present, and in combination with the review time variables. This PDUFA variable was always statistically insignificant. Hence there is no evidence that the implementation of the PDUFA program caused a regime shift in which there was an increase in safety risks across the spectrum of review times.<sup>30</sup> It should also be noted that the coefficient

estimates on the other variables remain essentially unchanged when the review time (log-linear or linear) variable is omitted.

We also tried various specifications in which the PDUFA variable was interacted with the FDA review time and U.S. launch lag variables. None of these variables were statistically significant. Since simple shift and interaction variables may not adequately capture all the changes in the post-PDUFA period, we also estimated our negative binomial model on the PDUFA –only sample of NMEs to test its robustness. Table 4 provides some summary statistics while Table 5 presents the coefficient estimates for the sample of PDUFA NMEs.

The results in Table 5 for the negative binomial regression model using only the PDUFA sample (i.e., NMEs filed on or after October 1, 1992) are little changed from the estimates in Table 3. A few variables have reduced coefficients and statistical significance (most notably the accelerated approval variable). As previously was the case, priority drugs, biological products, and drugs with shorter U.S. launch lags experience more serious adverse events ( $p \leq .05$ ). Other variables that are statistically significant predictors of adverse events include the three sales variables, the patient demographic variables, and product age. None of the review time variables, including all the linear review time specifications, are statistically significant.

We then tested the interactions between FDA review time and three drug novelty variables, i.e., priority products, accelerated approvals, and biological products, to see whether the effect of FDA review time differs by drug novelty. None of the interactions are significantly negative, indicating that an increase in FDA review time will not reduce serious adverse events for novel drugs. In fact, the interaction term between FDA review time and priority review is positive statistically significantly ( $p < .05$ ) in the case of death ADRs, suggesting that the staff at



FDA may spend more time reviewing novel but potentially dangerous drugs in the PDUFA period.<sup>31</sup>

We next investigated the general sensitivity of our results to outliers and in particular whether this positive interaction term between novelty and review time was driven by outliers. In Figure 4, which covers the PDUFA time period, we show a plot of annual serious ADRs per standard unit (SU) on the Y axis versus FDA review time in months on the X axis. One obvious outlier is the priority rated and acceleratedly approved drug, Mifiprex (generic name mifepristone), also known as RU-486, which is indicated for medical termination of early pregnancy or within 49 days (Table 6). This drug was subject to political controversy and it took 54 months to gain approval after its submission date in March 1996. The regimen for this drug is also one pill per prescription for each patient, leading to a potentially high number of adverse events per standard unit. These facts are consistent with its strong outlier status in Figure 4.

Table 6 presents the characteristics of eight outliers with annual serious ADRs per SU above mean plus 1 standard deviation, with four NMEs (Mifeprex, Flolan, Ontak, and Mylotarg) above mean plus 2 standard deviations. In addition to the fact that these drugs are indicated primarily for serious, life-threatening conditions, six of these products have black box warnings at approval, six are priority products (plus 1 standard product under accelerated approval), and four are orphan products. The positive interaction between priority and log-transformed FDA review time was sensitive to the exclusion of outliers in Table 6. It became insignificant when all eight outliers above mean plus 1 standard deviation were excluded. Furthermore, the findings of the other variables in Table 5 were generally unaffected by exclusion of these eight outliers.<sup>32</sup>

This analysis sheds some further insights into the issue of anticipated risks versus unanticipated risks. In particular, the eight NMEs that were observed to have the highest *expost*

risk (per unit of utilization) consisted primarily of drugs for life threatening diseases with the presence of black box warnings in their initial label. The presence of black box warnings in the initial label suggests that the FDA was aware *ex ante* that these drugs pose much higher risks than other NMEs, but these compounds were assessed to have important potential benefits that outweighed the risks. The issue of anticipated versus unanticipated risks as reflected in the utilization and timing of black box warnings, warrants further research.

Finally, we tested the interactions between product age (years after FDA approval) and the three novelty variables to see whether the difference between novel products and less novel ones narrows over time. None are significant, indicating that novel drugs remained riskier throughout the product life cycle.

## VI. DISCUSSION

Our findings are generally consistent with previous research by Berndt, et. al (2005), the Tufts University CSCD (2005), and the FDA (2005), which found no significant effect of PDUFA or shorter review times on the rate of withdrawals of new drug approvals, pre-and post-enactment of the law. However, drug withdrawals are an infrequent event. ADRs are a measure of drug safety risks that is more amenable to statistical analysis and inference. The only prior analysis of PDUFA employing ADRs is by Olson (2002) (2004). She found a negative statistical relationship between ADRs and FDA review times. Her analysis employs a negative binomial framework for new chemical entities approved between 1990 to 1995.

Compositional factors undoubtedly play some role in explaining the differences in Olson's results with our findings.<sup>33</sup> However we believe the most important differentiating

features of our work from Olson's involve the additional variables that characterize the regulatory intervention process. In particular, besides FDA review time, we include a "drug lag" variable measuring whether and how long a new molecule has been available abroad before the U.S. Furthermore, our analysis includes an indicator variable on whether a black box warning is present in the initial label to distinguish serious risks of an anticipated versus unanticipated nature.

We find that earlier U.S. introductions relative to other countries, and the presence of a black box warning variable at approval, are positively associated with drug safety risks. However, after controlling for these and other variables, FDA review times are not significantly related to ADRs.<sup>34</sup> Our findings, therefore, do not support the hypothesis that the performance targets on review time under PDUFA have resulted in more risky behavior by FDA reviewers.

Some additional risk is associated with the fact that more new drug entities, especially novel drugs, are now introduced first or simultaneously in the United States and Europe. (Grabowski and Wang, 2006). However, these additional risks need to be evaluated against the increased benefits to patients from earlier U.S. launches. Our analysis indicates that the spillover benefits from launch delays are relatively modest in size—e.g., a 12 month delay, other things equal, would lead to approximately 20 fewer serious ADRs per year compared to the case of first launch in the United States. From a policy perspective, there is a movement toward harmonization of regulatory procedures and approvals between the United States and the EU. This would lessen the opportunities for spillover benefits from launch lags as regulators and firms move toward a more global approach to new product introductions.

It is also important to consider the effects of regulatory delays on the availability of new drugs, and incentives for drug innovation. R&D costs have been increasing significantly in real

terms while the rate of new drug approvals has been on a declining path in recent years (Grabowski, 2004).<sup>35</sup> Analyses of the returns to R&D indicate that the length of FDA reviews is an important parameter affecting R&D costs and returns. For example, prior research indicates that a one year delay in approval could lead to a 9-10% increase in capitalized R&D costs and negatively impact the returns for the representative compound in a significant fashion (Grabowski, Vernon, and DiMasi, 2002; DiMasi, Hansen, and Grabowski, 2003).

Our results confirm prior findings that more novel products—those receiving priority rating at the FDA—are subject to a much higher level of serious ADRs (Olson, 2002; 2004). In addition, two other categories of novel drugs not previously analyzed, accelerated approvals and biological products, were found to be subject to higher levels of serious ADRs in our work. It is important, however, to balance the increased risks from novel therapies with the benefits of early access. The net benefits from the timely availability of novel drugs appear to be particularly large (Lichtenberg, 2005; Olson, 2004; Philipson et. al., 2005).

To the extent that risks can be anticipated based on clinical trials, the FDA has the option of approving a product with large potential benefits and risks with a black box warning in the label. Our analysis indicates that many of the important drug advances for life-threatening diseases, those that received high priority and accelerated approval, carried black box warnings in their initial labels. The FDA should be encouraged to continue to make these benefit-risk tradeoffs in an objective and timely manner.

Our results indicate that a return to the long delays of the pre-PDUFA period would have few apparent benefits and many undesirable consequences. Policymakers instead should focus on establishing a diligent post-marketing surveillance program to monitor risks and to inform physicians and patients as new knowledge becomes available. Although some serious adverse

events can be anticipated from clinical trials, many tend to be rare, and consequently largely unknown at the time of approval. An improved post-marketing surveillance program could be financed through user fees similar to PDUFA (Carpenter, 2005). At the current time, both the FDA and pharmaceutical firms devote very modest resources to post-marketing monitoring and surveillance compared to pre-approval clinical trials and R&D activities (Ridley, et. al, 2006). The introduction of the Medicare Part D program in January 2006 also creates opportunities for significant improvements in the current U.S. post-marketing surveillance program.

Table 1. Variable definition and characteristics of NME-year observations (n=823).

Variable	Definition	Mean	STD	Median	Min	Max
Serious ADRs	Number of serious ADRs in a year	60	121	19	0	1433
Hospitalization ADRs	Number of hospitalization ADRs in a year	43	92	13	0	1155
Death ADRs	Number of death ADRs in a year	10	26	2	0	279
Priority review	FDA designated priority review	0.40	0.49	0	0	1
Accelerated approval	FDA designated accelerated approval	0.09	0.29	0	0	1
Biological product	FDA designated biological product	0.10	0.31	0	0	1
Orphan product	FDA designated orphan product	0.15	0.36	0	0	1
FDA review	FDA review time in month	19	16	14	1	122
Log (FDA review)	Log transformed FDA review time	2.67	0.75	2.64	-0.53	4.81
BB warning	Black box warning at time of approval (except pregnancy cases)	0.14	0.35	0	0	1
BB/pregnancies	Black box warning – counter indicated for pregnant women	0.04	0.19	0	0	1
PDUFA NME	Its NDA or BLA submitted on or after 10/01/1992	0.82	0.38	1	0	1
Percent <20 years	Percent of treated patients under 20 years old	0.13	0.19	0.05	0	1
Percent ≥65 years	Percent of treated patients 65 years or older	0.33	0.23	0.30	0	0.95
Percent female	Percent of treated patients who are female	0.54	0.20	0.56	0	1
US launch lag	Lag in month between the first launch and the US launch	20	49	0	0	432
Log (US launch lag)	Log transformed US launch lag plus 1	1.43	1.73	0.00	0	6.07
Oral sales volume	Oral formulation sales in thousands of standard units in a year	47145	134068	1268	0	1550542
Log (Oral sales)	Log transformed oral sales volume plus 1	5.63	5.07	7.15	0	14.25
Injectable sales volume	Injectable formulation sales in thousands of standard units in a year	169	693	0	0	9237
Log (Injectable sales)	Log transformed injectable sales volume plus 1	1.44	2.42	0	0	9.1
Other sales volume	Other formulation sales in thousands of standard units in a year	10651	56122	0	0	651924
Log (Other sales)	Log transformed other sales volume plus 1	1.22	3.31	0	0	13.4
Product age	Years on the market (0 in the year of launch)	0.99	0.81	1	0	2

Source: Authors

Table 2. Characteristics of standard, priority, and accelerated approval NMEs in the first year of positive sales.

NME Type	Standard (n=175)*					Priority (n=91)*					Accelerated Approval (n=27)				
	Mean	STD	Median	Min	Max	Mean	STD	Median	Min	Max	Mean	STD	Median	Min	Max
<b>Serious ADRs</b>	29	65	6	0	610	89	170	22	0	1020	46	62	20	1	290
<b>Hospitalization ADRs</b>	20	40	4	0	283	63	121	16	0	774	36	51	18	1	244
<b>Death ADRs</b>	4	9	1	0	60	16	38	5	0	238	8	9	3	0	34
<b>Biological product</b>	0.10	0.30	0	0	1	0.11	0.31	0	0	1	0.15	0.36	0	0	1
<b>Orphan product</b>	0.06	0.24	0	0	1	0.26	0.44	0	0	1	0.33	0.48	0	0	1
<b>BB Warning</b>	0.05	0.22	0	0	1	0.24	0.43	0	0	1	0.44	0.51	0	0	1
<b>BB/pregnancies</b>	0.05	0.22	0	0	1	0.02	0.15	0	0	1	0	0	0	0	0
<b>FDA review time</b>	23	16	18	7	122	14	15	8	1	100	11	12	7	1	54
<b>PDUFA NME</b>	0.83	0.38	1	0	1	0.77	0.42	1	0	1	0.93	0.27	1	0	1
<b>Percent &lt;20 years</b>	0.15	0.21	0.06	0	1	0.12	0.19	0.04	0	1	0.04	0.06	0.02	0	0.24
<b>Percent &gt;=65 years</b>	0.32	0.23	0.27	0	0.95	0.36	0.23	0.35	0	0.95	0.33	0.25	0.38	0.06	0.89
<b>Percent female</b>	0.56	0.19	0.56	0	1	0.53	0.21	0.56	0	0.99	0.42	0.24	0.43	0	0.99
<b>US launch lag</b>	18	36	3	0	272	23	63	0	0	432	14	56	0	0	290
<b>Sales volume</b>	18076	36895	2713	1	266042	34251	101754	2402	1	843876	7847	19979	203	1	94938
<b>Percent oral</b>	0.62	0.49	1	0	1	0.50	0.50	0.74	0	1	0.63	0.49	1	0	1
<b>Percent injectable</b>	0.25	0.43	0	0	1	0.34	0.47	0	0	1	0.37	0.49	0	0	1
<b>Percent others</b>	0.13	0.34	0	0	1	0.16	0.36	0	0	1	0	0	0	0	0

\* The 27 accelerated approvals were excluded from standard NMEs (n=2) or priority NMEs (n=25).

Notes: For the 12 NMEs launched in 1992, the first available data in 1993 were used.

Source: Authors

**Table 3:** Negative binomial model results on the determinants of adverse drug reactions (ADRs) (n=823).

ADR Type Specifications	Serious				Hospitalization				Deaths			
	Basic		Alternative		Basic		Alternative		Basic		Alternative	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	-0.44	0.49	-0.54	0.46	-0.84 <sup>+</sup>	0.46	-0.97 <sup>*</sup>	0.43	-1.53 <sup>+</sup>	0.82	-1.63 <sup>*</sup>	0.82
Priority review	0.96 <sup>**</sup>	0.20	0.95 <sup>**</sup>	0.19	0.98 <sup>**</sup>	0.21	0.98 <sup>**</sup>	0.19	1.20 <sup>**</sup>	0.34	1.18 <sup>**</sup>	0.31
Accelerated approval	0.59 <sup>*</sup>	0.30	0.61 <sup>*</sup>	0.29	0.59 <sup>*</sup>	0.30	0.62 <sup>*</sup>	0.29	0.67	0.51	0.67	0.50
Biological product	1.25 <sup>**</sup>	0.22	1.24 <sup>**</sup>	0.22	1.30 <sup>**</sup>	0.21	1.28 <sup>**</sup>	0.21	1.02 <sup>**</sup>	0.37	1.00 <sup>**</sup>	0.36
Orphan product	0.16	0.21	0.14	0.21	0.20	0.23	0.18	0.23	0.23	0.33	0.23	0.33
Log (FDA review)	-0.08	0.09			-0.10	0.09			-0.12	0.13		
FDA review			-0.006	0.004			-0.006	0.004			-0.01 <sup>*</sup>	0.005
BB warning	0.66 <sup>*</sup>	0.27	0.65 <sup>*</sup>	0.27	0.58 <sup>*</sup>	0.27	0.57 <sup>*</sup>	0.27	0.58	0.43	0.56	0.43
BB/Pregnancies	-1.29 <sup>**</sup>	0.44	1.32 <sup>**</sup>	0.44	-1.13 <sup>*</sup>	0.45	-1.16 <sup>*</sup>	0.45	-1.44 <sup>*</sup>	0.59	1.49 <sup>*</sup>	0.59
Percent<20 years	0.37	0.40	0.38	0.39	0.57	0.40	0.57	0.41	0.58	0.57	0.58	0.57
Percent≥65 years	0.96 <sup>**</sup>	0.27	0.93 <sup>**</sup>	0.27	0.82 <sup>**</sup>	0.27	0.79 <sup>**</sup>	0.27	1.83 <sup>**</sup>	0.41	1.75 <sup>**</sup>	0.41
Percent female	0.62 <sup>+</sup>	0.35	0.62 <sup>+</sup>	0.34	0.87 <sup>**</sup>	0.34	0.86 <sup>*</sup>	0.33	0.23	0.53	0.20	0.52
Log (US launch lag)	-0.13 <sup>**</sup>	0.03	-0.13 <sup>**</sup>	0.03	-0.10 <sup>**</sup>	0.04	-0.10 <sup>**</sup>	0.04	-0.12 <sup>**</sup>	0.05	-0.12 <sup>*</sup>	0.05
Log (oral sales)	0.34 <sup>**</sup>	0.02	0.34 <sup>**</sup>	0.02	0.36 <sup>**</sup>	0.02	0.36 <sup>**</sup>	0.02	0.26 <sup>**</sup>	0.03	0.26 <sup>**</sup>	0.03
Log (Injectable sales)	0.50 <sup>**</sup>	0.03	0.50 <sup>**</sup>	0.03	0.51 <sup>**</sup>	0.04	0.51 <sup>**</sup>	0.04	0.41 <sup>**</sup>	0.04	0.42 <sup>**</sup>	0.04
Log (Other sales)	0.22 <sup>**</sup>	0.03	0.22 <sup>**</sup>	0.03	0.22 <sup>**</sup>	0.04	0.22 <sup>**</sup>	0.04	0.18 <sup>**</sup>	0.05	0.18 <sup>**</sup>	0.05
Product age	-0.15 <sup>**</sup>	0.05	-0.15 <sup>**</sup>	0.05	-0.17 <sup>**</sup>	0.05	-0.17 <sup>**</sup>	0.05	-0.06	0.08	-0.06	0.08
Event year indicators	Yes		Yes		Yes		Yes		Yes		Yes	
Therapeutic area indicators	Yes		Yes		Yes		Yes		Yes		Yes	
Dispersion	1.09		1.09		1.07		1.06		1.71		1.67	

Notes: <sup>+</sup> significant at the 0.1 level  
<sup>\*</sup> significant at the 0.05 level  
<sup>\*\*</sup> significant at the 0.01 level

Source: Authors



Table 4. Characteristics of PDUFA NME-year observations (n=678).

Variable	Mean	STD	Median	Min	Max
Serious ADRs	61	128	19	0	1433
Hospitalization ADRs	44	97	13	0	1155
Death ADRs	10	26	2	0	279
Priority review	0.40	0.49	0	0	1
Accelerated approval	0.11	0.31	0	0	1
Biological product	0.12	0.32	0	0	1
Orphan product	0.14	0.34	0	0	1
FDA review	15	10	12	1	54
Log (FDA review)	2.51	0.66	2.48	-0.53	3.99
BB warning	0.15	0.36	0	0	1
BB/pregnancies	0.04	0.20	0	0	1
Percent <20 years	0.12	0.20	0.03	0	1
Percent ≥65 years	0.35	0.24	0.31	0	0.95
Percent female	0.54	0.21	0.56	0	1
US launch lag	19	51	0	0	432
Log (US launch lag)	1.27	1.67	0	0	6.07
Oral sales volume	46652	142228	754	0	1550542
Log (Oral sales)	5.49	5.03	6.63	0	14.25
Injectable sales volume	156	664	0	0	9237
Log (Injectable sales)	1.48	2.40	0	0	9.13
Other sales volume	7690	47727.8	0	0	651924
Log (Other sales)	1.06	3.04	0	0	13.38768
Product age	0.97	0.81	1	0	2

Source: Authors

**Table 5:** Negative binomial model results on the determinants of adverse drug reactions (ADRs) for PDUFA NME-year observations

ADR Type Specifications	Serious				Hospitalization				Deaths			
	Basic		Alternative		Basic		Alternative		Basic		Alternative	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	-1.01 <sup>+</sup>	0.52	-0.95	0.47	-1.52 <sup>**</sup>	0.50	-1.50 <sup>**</sup>	0.43	1.91 <sup>*</sup>	0.77	-1.82 <sup>*</sup>	0.77
Priority review	1.12 <sup>**</sup>	0.23	1.10 <sup>**</sup>	0.22	1.18 <sup>**</sup>	0.23	1.16 <sup>**</sup>	0.22	1.28 <sup>**</sup>	0.41	1.21 <sup>**</sup>	0.38
Accelerated approval	0.41	0.28	0.41	0.27	0.37	0.27	0.38	0.27	0.44	0.48	0.45	0.48
Biological product	1.10 <sup>**</sup>	0.23	1.10 <sup>**</sup>	0.23	1.11 <sup>**</sup>	0.21	1.11 <sup>**</sup>	0.21	0.90 <sup>*</sup>	0.37	0.90 <sup>*</sup>	0.36
Orphan product	0.24	0.24	0.24	0.24	0.30	0.25	0.30	0.26	0.39	0.38	0.41	0.38
Log (FDA review)	0.02	0.13			-0.002	0.122			-0.009	0.182		
FDA review			-0.002	0.009			-0.003	0.008			-0.01	-0.01
BB warning	0.79 <sup>**</sup>	0.27	0.78 <sup>**</sup>	0.27	0.74 <sup>**</sup>	0.26	0.74 <sup>**</sup>	0.26	0.66	0.41	0.65	0.42
BB/Pregnancies	-1.38 <sup>**</sup>	0.50	-1.38 <sup>**</sup>	0.50	-1.23 <sup>*</sup>	1.53	-1.23 <sup>*</sup>	0.53	-1.51 <sup>*</sup>	0.67	-1.52 <sup>*</sup>	0.67
Percent<20 years	0.62	0.40	0.63	0.40	0.88 <sup>*</sup>	0.40	0.89 <sup>*</sup>	0.40	0.86	0.60	0.90	0.58
Percent>=65 years	0.90 <sup>**</sup>	0.27	0.93 <sup>**</sup>	0.27	0.80 <sup>**</sup>	0.26	0.81 <sup>**</sup>	0.27	1.46 <sup>**</sup>	0.39	1.50 <sup>**</sup>	0.40
Percent female	0.65 <sup>+</sup>	0.34	0.68 <sup>*</sup>	0.34	0.90 <sup>**</sup>	0.32	0.92 <sup>*</sup>	0.33	0.22	0.56	0.26	0.56
Log (US launch lag)	-0.14 <sup>**</sup>	0.04	-0.14 <sup>**</sup>	0.04	-0.11 <sup>**</sup>	0.04	-0.11 <sup>**</sup>	0.04	-0.13 <sup>**</sup>	0.05	-0.11 <sup>*</sup>	0.05
Log (oral sales)	0.36 <sup>**</sup>	0.02	0.36 <sup>**</sup>	0.02	0.38 <sup>**</sup>	0.02	0.38 <sup>**</sup>	0.02	0.28 <sup>**</sup>	0.03	0.28 <sup>**</sup>	0.03
Log (Injectable sales)	0.53 <sup>**</sup>	0.04	0.53 <sup>**</sup>	0.04	0.55 <sup>**</sup>	0.04	0.55 <sup>**</sup>	0.04	0.44 <sup>**</sup>	0.04	0.45 <sup>**</sup>	0.04
Log (Other sales)	0.24 <sup>**</sup>	0.05	0.24 <sup>**</sup>	0.05	0.24 <sup>**</sup>	0.05	0.24 <sup>**</sup>	0.05	0.15 <sup>+</sup>	0.08	0.15 <sup>+</sup>	0.08
Product age	-0.15 <sup>**</sup>	0.06	-0.15 <sup>**</sup>	0.06	-0.18 <sup>**</sup>	0.06	-0.18 <sup>**</sup>	0.06	-0.05	0.08	-0.07	0.08
Event year indicators	Yes		Yes		Yes		Yes		Yes		Yes	
Therapeutic area indicators	Yes		Yes		Yes		Yes		Yes		Yes	
Dispersion	1.09		1.09		1.05		1.05		1.67		1.66	

Notes: <sup>+</sup> significant at the 0.1 level  
<sup>\*</sup> significant at the 0.05 level  
<sup>\*\*</sup> significant at the 0.01 level

Source: Authors

Table 6. Characteristics of PDUFA NME outliers.

Product	Indication	Black box Warning	Route	NDA Submission Date	FDA Review (month)	Priority Review	Accelerated Approval	Biological Product	Orphan Product	Highest Annual Serious ADRs per SU**
Mifeprex	Medical termination of intrauterine pregnancy through 49 days' pregnancy	Yes	Oral	3/18/1996	54	Yes	Yes	No	No	0.0675
Flolan	Long-term treatment of primary pulmonary hypertension in NYHA Class III and IV patients	No	Injection	2/28/1994	19	Yes	No	No	Yes	0.0163
Ontak	Treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor	Yes	Injection	12/9/1997	14	Yes	Yes	Yes	Yes	0.0130
Mylotarg	Treatment of patients with CD33 positive acute myeloid leukemia in first relapse who are $\geq 60$ years of age and who are not considered candidates for cytotoxic chemotherapy	Yes	Injection	10/29/1999	7	Yes	Yes	No	Yes	0.0099
Vistide	Treatment of cytomegalovirus retinitis in patients with AIDS	Yes	Injection	10/4/1995	9	No	No	No	No	0.0069
Ellence	As a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer	Yes	Injection	12/15/1998	9	Yes	No	No	No	0.0066
Rituxan	Treatment of patients with relapsed or refractory low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma	No	Injection	2/28/1997	9	Yes	No	Yes	No	0.0060
Tracleer	Treatment of pulmonary arterial hypertension in patients with WHO Class III or IV symptoms	Yes	Oral	11/17/2000	12	No	Yes	No	Yes	0.0042

\* Black box warning in the FDA approved label at the time of initial introduction

\*\* For annual serious adverse drug reactions (ADRs) per standard unit (SU), mean plus 2 standard deviations equals to 0.0070; mean plus 1 standard deviation equals to 0.0037.

Source: US Food and Drug Administration

**Figure 1. Trade-offs between Drug Safety Risks and Review Times Pre- and Post-PDUFA.**

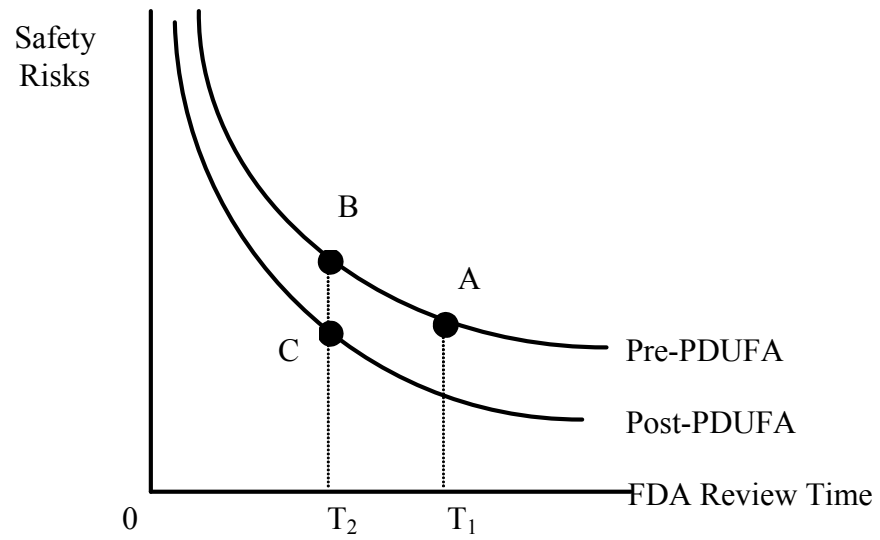


Figure 2. Distribution of sample NMEs by year of FDA approval and withdrawn status.

Source: Authors

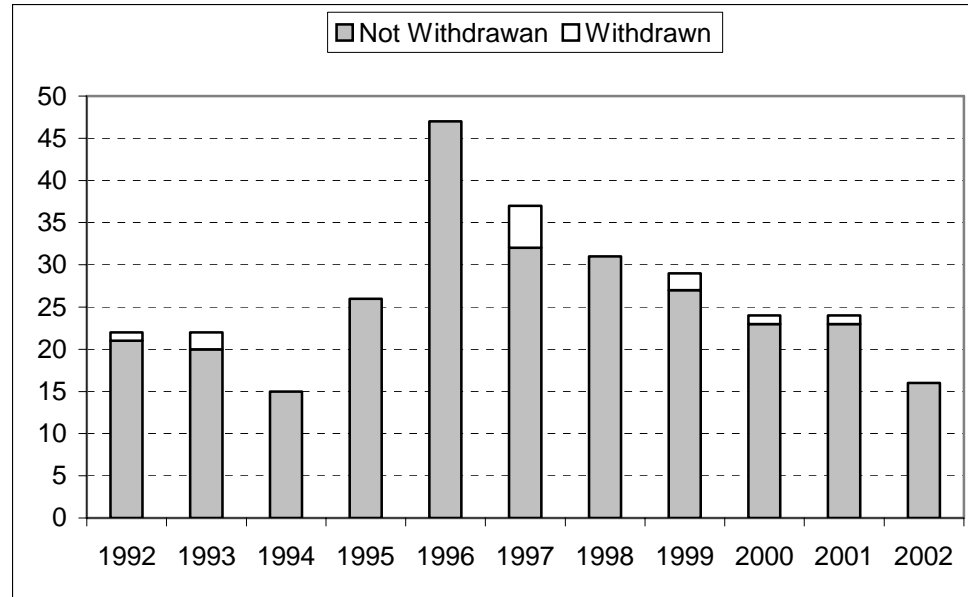
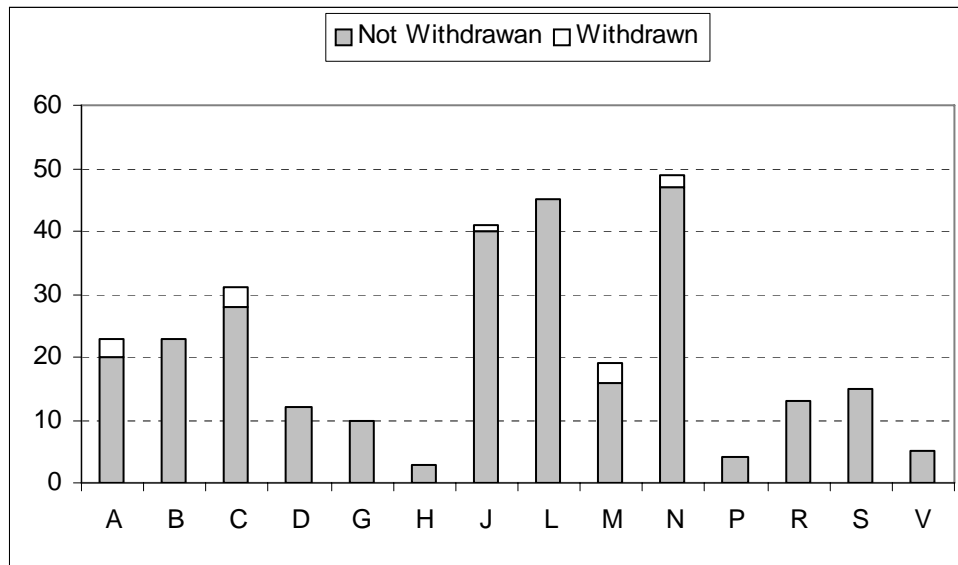


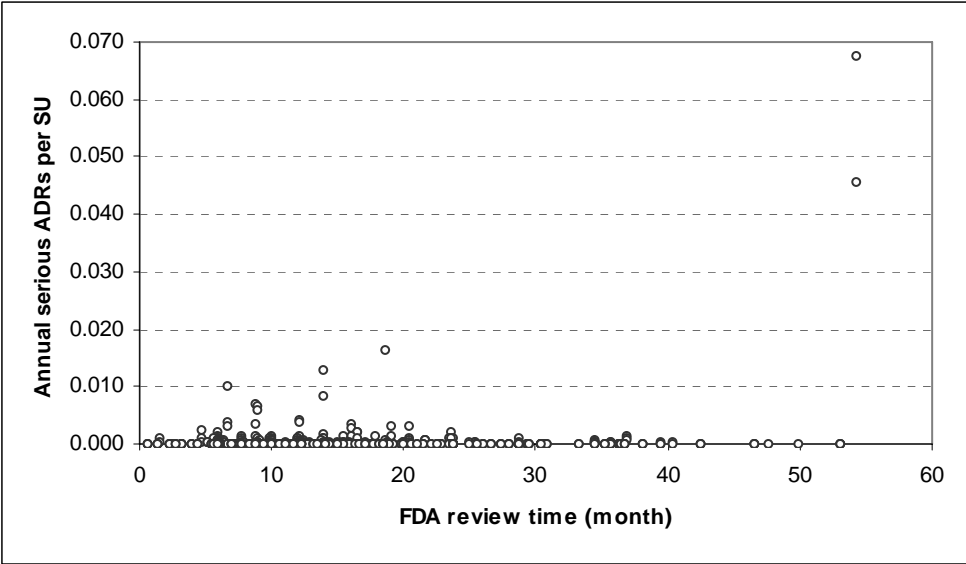
Figure 3. Distribution of sample NMEs by therapeutic area and withdrawn status.



Notes: A Alimentary Tract & Metabolism; B Blood & Blood Forming Organs; C Cardiovascular System; D Dermatologicals; G Genital Urinary System & Sex Hormones; H Hormone Therapy; J Systemic Anti-Infectives; L Oncology; M Musculo-Skeletal System; N Central Nervous System; P Parasitology; R Respiratory System; S Sensory System; V Various Others.

Source: Authors

Figure 4. The relationship between FDA review time and annual serious adverse drug reactions (ADRs) per standard unit (SU) for PDUFA NME-year observations (n=678).



Source: Authors

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## Endnotes

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<sup>1</sup> Rudholm (2004) found a similar negative relationship between approval times and number of adverse events for a small sample of new drug introductions in Sweden between 1972 and 1996.

<sup>2</sup> The new drug development paradigm has been discussed in detail elsewhere [U.S. FDA 1999; DiMasi, Hansen and Grabowski, 2003].

<sup>3</sup> Earlier analysis of FDA regulation were focused in particular on the impact of the 1962 amendments to the Food, Drug and Cosmetic Act on drug innovation. See for example, Peltzman (1973) Wardell and Lasagna (1975) and Grabowski, Vernon and Thomas (1978).

<sup>4</sup> See for example the discussion of various initiatives targeted to AIDS and other life threatening disease categories in Shulman and Brown (1995).

<sup>5</sup> This allowed approval to be granted at the earliest phase of development at which safety and efficacy can be reasonably inferred. This could be done, in some cases, on the basis of a single phase II trial involving hundreds rather than thousands of patients.

<sup>6</sup> In 1997 the expedited development and accelerated approval programs were consolidated into the FDA's Fast Track program (Tufts, 2001).

<sup>7</sup> See in particular the analysis of trends in this regard in DiMasi, Hansen and Grabowski (2003) p. 177 and footnote 41. In particular, the mean number of subjects for New Drug Applications in the 1998 to 2001 period exceeded 5,000 compared to just over 3,000 at the start of the 1990s.

<sup>8</sup> The FDA guidelines for a priority review are set forth in the Manual of Policies and Procedures, Center for Drug Evaluation and Research, 6020.3, p. 1-2.

<sup>9</sup> Ibid, p. 2.

<sup>10</sup> Some classes of biological drugs have experienced higher risks than others – e.g. monoclonal antibodies versus recombinant products. This is reflected in the black box warning variable discussed below. In particular, five of the nine monoclonal antibody products carry a black box warning at approval. This compares to 20% of the recombinant products (5 of 24).

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<sup>11</sup> See the discussion of these issues in Herbst, et. al. (2006). For breast cancer patients with excessive amounts of HER-2 protein (25% - 30% of patients), Herceptin cuts the risk of recurrence by half but also has the increased risk of congestive heart failure (the incidence of severe congestive heart failure or death from heart problems after three years in the first two trials: 2.9% to 4.1% for Herceptin versus 0.0% to 0.8% for the control group).

<sup>12</sup> The negative binomial model has been utilized in the analysis of adverse drug events by Olson (2002,2004) and Rudholm (2004).

<sup>13</sup> The SRS database, which was started in 1969, was later replaced by the AERS database in November 1997. Our SRS/AERS data were provided by Lincoln Technologies and ended in the third quarter of 2004. In both the SRS and AERS, adverse drug reactions (ADRs) could be reported under either brand or generic name. Therefore, using only the brand name to count ADRs potentially under-estimates the number of adverse events. Lincoln Technologies standardized the generic name for each reported drug in its data releases, making it easy to count all ADRs associated with a particular drug.

<sup>14</sup> We could not use smaller time units such as quarter because the event month variable is missing for a significant portion of ADRs. We excluded foreign and study ADRs, as the former were for non-US patients and the latter were for ADRs that occurred in post-marketing clinical studies (therefore not related to product consumption or commercial sales in the US).

<sup>15</sup> However, in contrast to Olson (2002; 2004), for an ADR with more than one suspected drug, we assigned an equal 1/N share of the ADR to each suspected drug.

<sup>16</sup> Of the 35 NMEs excluded because of missing data, there are 6 products without a unique generic name in the SRS/AERS, 12 products missing in the SRS/AERS, 11 products without sales volume information, 4 products belonging to two therapeutic classes without patient demographic information, 1 product withdrawn in 1992 and 1 product without priority or standard review designation.

<sup>17</sup> As the mandated reporting frequency is every quarter prior to a NME's third anniversary and every year afterwards, we also excluded 2003 observations for NMEs approved prior to 2000 to deal with the issue of reporting lag.

<sup>18</sup> The expedited development program (Subpart E for NCEs) was rarely used with the implementation of PDUFA and, to the best of our knowledge, the full list of expedited development approvals have not been made available by the FDA. Initially, however, it was not uncommon for NMEs to be jointly covered under both the accelerated approval and expedited development programs (Schulman and Brown, 1995). After 1997, both programs were incorporated into the Fast Track program.

<sup>19</sup> Two other sources were utilized as a check on our data for black box warning. Joyce Generali has compiled a comprehensive list of drugs with black box warnings ([www.formularyproduction.com](http://www.formularyproduction.com)). Also, Lasser, et. al. (2002) has examined the timing and addition of black box warnings for all new chemical entities approved between 1975 and 1999.

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<sup>20</sup> Our approach differs from those of Olson (2002 and 2004), which used the number of retail prescriptions in the single year 1996 for new drugs (biological products excluded) approved between 1990 and 1995.

<sup>21</sup> We have access to another IMS Health database called NPA Plus for the year 2003. NPA Plus reports the number of dispensed prescriptions through retail pharmacies in a given year. For the 275 NMEs that we could match with NPA Plus in 2003, the correlation ratio between our defined sales volume in standard units and NPA Plus reported number of retail prescriptions is 0.77 ( $p < 0.0001$ ).

<sup>22</sup> We added 1 to all observations for the therapeutic class lag, U.S. launch lag, and the sales volume variables, to avoid the log of zero problem.

<sup>23</sup> For the 12 NMEs launched in 1992, the first available sales data were 1993. In these cases, data for 1993 were used in Table 2.

<sup>24</sup> Because the biological products in our study sample were approved by the former CBER, we also ran separate analyses for NDAs and BLAs. The results were qualitatively similar and therefore all NMEs were combined in Table 3.

<sup>25</sup> In the negative binomial regression model, the variance of the distribution is a quadratic function of the mean with the coefficient on the quadratic term being denoted as the dispersion parameter (Cameron and Trivedi, 2005).

<sup>26</sup> It should be noted, however, that orphan products are disproportionately represented in the priority and accelerated approval categories which are associated with more adverse events.

<sup>27</sup> This interpretation also receives some support from the sensitivity analysis in the next section, where we estimate the model for the post-PDUFA period. There are significantly few outliers post-PDUFA. The maximum review time in the post-PDUFA period is 54 months (table 4). This compares to 122 months in the pre-PDUFA period (table 1) and there were also 10 NMEs in excess of 54 months. We find none of the linear FDA review variables are significant for the model estimates of the post-PDUFA period. Furthermore, there is a period in which a substantial downward trend in review times occurred (Berndt, et. al, 2005).

<sup>28</sup> Population weights provide only a rough measure of the number of patients exposed outside the United States, given differences across countries in utilization controls and disease burden. We constructed the population-weighted global launch lag variable for the U.S. using the New Product Focus database from IMS Health (Grabowski and Wang, 2006) which tracks the launch dates of new drugs in 22 major markets worldwide since the early 1980s. For an NME, we first calculated the U.S. launch lag with each of the other 21 countries (value equals 0 if U.S. launch earlier or at the same time). We then weighted this U.S. launch lag with that country's total population in 2004 and the sum of these weighted launch lags is that NME's population-weighted global launch lag for the U.S. Note that this variable is also log-transformed in the regressions.



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<sup>29</sup> Biological drugs in particular are generally dispensed as injectibles in hospitals and specialty clinics. These institutional settings may also contribute to higher ADR reporting.

<sup>30</sup> Some suggestions along these lines were presented in Olson (2002) but the results were mixed in support of this hypothesis, especially when drugs are classified based on year of submission rather than approval. The FDA has indicated the former classification is the more appropriate one.

<sup>31</sup> In particular, the coefficients on the interaction between priority and log-transformed FDA review time were 0.51 ( $p < 0.10$ ), 0.40 ( $p = .14$ ), and 0.77 ( $p < .05$ ) respectively for serious ADRs, hospital ADRs, and death ADRs. The results are quantitatively similar for the full sample (Table 3) but with substantially smaller coefficient estimates.

<sup>32</sup> The only exception was that the general black box warning became insignificant ( $p > .10$ ).

<sup>33</sup> From a compositional standpoint, Olson's analysis differs from our work in that it focuses on a relatively narrow time window before and after the Act was passed. The majority of the observations are in the pre-PDUFA period when classification is based on the date of a drug's submission to the FDA. Second, Olson's analysis focuses only on new chemical entities and omits biologicals as well as any analysis of novel NMEs in the accelerated approval program. Third, her controls for drug exposure are based on a single year of data from the MEPS survey. This is a weaker measure of exposure than annual unit sales from audit sources. This is reflected in the smaller coefficient estimates for these variables. Hospital products and drugs with small patient populations are particularly under represented in the MEPS survey.

<sup>34</sup> As discussed, the only exception is for death related ADRs when a linear rather than logarithmic version of review time variable is employed (table 3). Given the fact that review times are highly skewed, a logarithmic variable is preferred on statistical grounds. Furthermore, none of the review time variables, linear or logarithmic formulations, are significant in the post-PDUFA period regression (table 5).

<sup>35</sup> Among the key drivers of higher R&D costs are larger patient trials and an increased number of procedures per patient over time (DiMasi, Hansen, and Grabowski, 2003).