

# PHARMACEUTICAL POLICY CHANGE AND THE SAFETY OF NEW DRUGS\*

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## ABSTRACT

Policy reforms in the Food and Drug Administration (FDA) have led to substantial increases in the speed of new-drug review. While data show that FDA review times for new drugs have fallen as much as 50 percent, other data show that several new drugs have been withdrawn from the market for safety reasons. This flurry of new-drug withdrawals raises a question. Have increases in the speed of new-drug review had an adverse effect on new-drug safety? This analysis uses adverse drug reaction (ADR) data from the FDA's Spontaneous Reporting System to examine this question. Specifically, ADR counts for newly approved drugs are estimated as a function of drug characteristics, patient characteristics, and regulatory factors (such as the speed of new-drug review) using negative binomial regression analysis. The primary result is that reductions in new-drug review times are associated with increases in both ADRs requiring hospitalization and ADRs resulting in death.

## I. INTRODUCTION

**P**HARMACEUTICAL regulation must balance two competing policy objectives: ensuring product safety and facilitating access to useful new drugs by patients. While stringent regulation designed to ensure safety may save lives because dangerous or ineffective drugs are kept off the market, such regulation may also delay patients' access to useful new drugs. Historically, U.S. pharmaceutical policy has reflected a concern for product safety over access. One consequence has been increased delay in the approval of new drugs. In response to rising political pressure (from AIDS activists and others) to reduce this delay, Congress passed legislation in 1992 that introduced user fees for new-drug review. The reform led regulators to accelerate new-drug review in an effort to facilitate access to new medicines. The question of interest in this analysis is whether the policies that result in faster new-drug reviews have led to reductions in new-drug safety.

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Reductions in new-drug safety may occur if the political pressures to accelerate approval also lead regulators to assume more risk in new-drug approval. In assuming such risk, regulators may accept more uncertainty at the time of approval for the purposes of accelerating new-drug review. These changes in regulatory behavior may translate into increased risks for patients who take new medicines. However, patients with serious conditions and few therapeutic alternatives may want faster access to such drugs even if the risks are higher. Unfortunately, there has been little empirical research that has examined the trade-off between safety and access in new-drug approval because of data limitations. Without an understanding of how changes in the speed of new-drug review affect new-drug safety, it is difficult to evaluate the effect of the User Fee Act.

Several new drugs recently withdrawn from the market have raised concerns about new-drug safety. Duract, approved in July 1997, was withdrawn in June 1998 after four patients died and eight others required liver transplants. Antiobesity drugs Redux and Pondimin were withdrawn in September 1997 after they were linked to cardiac valvular disease.<sup>1</sup> Posicor, a blood-pressure medication, was withdrawn in June 1998 because of serious interaction effects with other drugs. Raxar, a fluoroquinolone antibiotic first marketed in 1997, was withdrawn from the market in November 1999 after its use was associated with heart rhythm abnormalities. In March 2000, two more drug withdrawals were announced. Rezulin, a diabetes drug approved in 1997, was found to cause severe liver toxicity, and Propulsid, a drug for nighttime heartburn approved in 1993, was linked to 341 reports of heart rhythm abnormalities and 80 deaths. In November 2000, Lotronex, a drug approved in February 2000 for irritable bowel syndrome, was withdrawn from the market after five reported deaths and several serious cases of intestinal damage.<sup>2</sup> In March 2001, Raplon, an injectable anesthesia drug approved in 1999, was also withdrawn because of unexpectedly severe adverse drug reactions. Finally, Baycol, a cholesterol-lowering product approved in 1997, was withdrawn from the market in August 2001 after reports of severe muscle adverse reactions including 31 deaths.

These actions represent a total of 10 drugs approved by the Food and Drug Administration (FDA) that were withdrawn from the market in 4 years, September 1997 to August 2001. In contrast, O. M. Bakke and coauthors note that in the 20-year period from 1974 to 1993, only 10 FDA-approved drugs were discontinued or withdrawn from the U.S. market because of safety

<sup>1</sup> Pondimin was first approved in 1973 but not utilized extensively until the 1990s, when it was used in an off-label combined treatment with Redux (approved in 1996 for use as an appetite suppressant) for weight loss.

<sup>2</sup> In June 2002, the FDA and the drug's manufacturer agreed to allow Lotronex back on the market under marketing restrictions that will severely limit its use. See Naomi Aoki, FDA Walks Fine Line on Drug Approvals: Battle over Irritable-Bowel Medication's Risks, Benefits Illustrates Pressures Facing Regulators, *Boston Globe*, June 26, 2002, at C1.

concerns.<sup>3</sup> The jump in the number of withdrawn drugs suggests that the balance between safety and access in new-drug review may have shifted.

Michael Friedman and coauthors argue that product safety has not been compromised by the reform.<sup>4</sup> They suggest that the trends in withdrawn drugs over time are not related to increases in the speed of new-drug review. Unfortunately, the number of withdrawn drugs is not particularly useful as a proxy for new-drug safety. The reason is that this measure lacks sufficient variation over time to perform statistical analyses because of the relative infrequency of drugs withdrawn from the market. Furthermore, this measure provides no information about the safety or risks associated with drugs that remain in the market. A richer measure of new-drug safety is needed to empirically examine the effect of user fees on new-drug safety. In previous research that examined the health effects of mandatory prescriptions, Sam Peltzman used Vital Statistics data for the incidence of drug-related poisonings that resulted in death to proxy for drug safety.<sup>5</sup> While drug-related poisonings occur more frequently than the withdrawal of FDA-approved drugs, this measure has some drawbacks. First, poisoning deaths often reflect the misuse of drugs. Second, pharmaceuticals, even when taken as prescribed, may lead to many kinds of adverse effects on consumer health (that may or may not result in death) that would not be captured in the number of drug-related poisonings.

This study utilizes data from the FDA's Spontaneous Reporting System (SRS) of adverse drug reactions (ADRs) to measure reported new-drug safety. Adverse drug reaction reports are typically filed by a physician or other health professional when patients experience adverse health effects while taking prescribed medicines. These reports provide a richer and more continuous measure of information about new-drug safety than the drug-poisoning data. This analysis uses ADR data to examine how FDA review times and regulatory policy changes may have affected reported new-drug safety. In particular, three ADR counts are calculated for each new drug approved between 1990 and 1995: total ADRs, ADRs that required hospitalization, and ADRs that resulted in death. Controlling for other important determinants of ADR reporting, the analysis considers the effect of a drug's review time and the user-fee reform on these ADR counts using negative binomial regression analysis.

Results show that reductions in a drug's review time are associated with an increase in a drug's ADRs that result in hospitalization and in death. The

<sup>3</sup> O. M. Bakke *et al.*, Drug Safety Discontinuations in the United Kingdom, the United States, and Spain from 1974 through 1993: A Regulatory Perspective, 58 *Clinical Pharmacology & Therapeutics* 108 (1995).

<sup>4</sup> Michael A. Friedman *et al.*, The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There Is a Problem? 281 *JAMA* 1728 (1999).

<sup>5</sup> Sam Peltzman, The Health Effects of Mandatory Prescriptions, 30 *J. Law & Econ.* 207 (1987).

result suggests that there may be a trade-off between the speed of FDA review and the reported risks associated with newly approved drugs. The analysis also estimates the consequences of faster new-drug reviews in terms of incremental ADR reports. In addition, results show that the user-fee reform is associated with increases in ADR hospitalizations among drugs approved in the user-fee era even after controlling for the speed of new-drug review. However, when the analysis focuses on user-fee drugs instead of all drugs approved in the user-fee era, this effect disappears. This suggests that reported new-drug safety was primarily affected by changes in the speed of new-drug review and not other reform-specific factors.

The paper is organized as follows. Section II elaborates on the regulatory trade-offs in new-drug approval and hypothesizes how user fees may have altered these trade-offs. Section III describes the ADR data and their limitations as a proxy for new-drug safety. Section IV discusses factors that affect new-drug safety or ADR over time. The methodology and data for the analysis are discussed in Section V. Section VI presents the results, and Section VII offers some concluding remarks.

## II. NEW-DRUG APPROVAL AND REGULATORY TRADE-OFFS

### A. *Food and Drug Administration Regulation and Drug Safety*

Firms must provide evidence that a new drug is both safe and effective for its intended use. Even though firms spend many years and invest millions of dollars to gather this evidence, it is impossible to resolve all uncertainty about drug safety (or effectiveness) at the time of FDA approval. Because clinical trials have inherent limitations (small patient samples, eligibility restrictions, relatively short duration, and underrepresented populations), there is always some uncertainty about all the benefits and risks associated with new drugs at the time of FDA approval. Given such uncertainty, there is always a positive probability that regulators will either mistakenly approve a dangerous or ineffective drug (type I error) or mistakenly fail to approve a beneficial drug (type II error).<sup>6</sup> These mistakes characterize the trade-offs that face regulators in the evaluation of new drugs. Regulatory policy must find a balance between safety and access in the timing of new-drug approval. While policies designed to reduce type I error may promote safety because dangerous drugs are kept off the market, such policies may also increase the prospect of type II error or regulatory delay that may limit patient access to effective new therapies.

The regulatory literature that focuses on the FDA has found that regulators have historically emphasized safety over access. Mary Olson empirically

<sup>6</sup> The maintained hypothesis is that a drug is dangerous. This classification is consistent with a regulatory standard in which the burden of proof falls on firms to show that new drugs are safe and effective.

examines the relative weighting of consumer, industry, and congressional interests reflected in FDA approval decisions between 1971 and 1991 and finds that consumer safety interests receive the highest weight in new-drug approval decisions.<sup>7</sup> Paul Quirk argues that such behavior arises because FDA regulators are concerned about their professional reputations and the reputation of the agency.<sup>8</sup> Drug tragedies, in which consumers die or are harmed by FDA-approved drugs, damage both these reputations. However, why is it that deaths that result from type I error are considered to be reputationally worse for professionals or the agency than deaths that result from type II error? The political environment plays an important role in affecting this determination.

Drug-related tragedies in the 1930s (elixir sulphanilamide) and in the early 1960s (Thalidomide) have contributed to this policy bias. One reason is that the FDA is held politically accountable when consumers die from taking FDA-approved drugs. Drug-related tragedies make the agency the object of public criticism and scrutiny by politicians. Such scrutiny may result in congressional oversight hearings, congressional investigations, new legislation (as in 1938 and in 1962), restrictions on agency authority, or cuts in the agency's budget. Regulators want to avoid such scrutiny because it may limit agency autonomy, damage the agency's reputation, and create other political costs for the agency.

In contrast, failure to approve beneficial drugs has not generated the same type of accountability or consequences for the agency. While the delays caused by type II errors may cause pain, suffering, and sometimes death for individuals who could have benefited from new drug treatments, the ultimate cause of the pain, suffering, and so on, is the individual's illness, not the bureaucrat's approval decision, as in the case of type I error. In addition, there have traditionally been few, if any, political or agency rewards for expediting the review of beneficial drugs. The asymmetry in the political consequences of type I and type II errors has contributed to the regulatory caution observed in the approval of new drugs.

The above discussion implies that changes in the political consequences associated with type I and type II errors or changes in the factors that contribute to reputational gains or losses for the agency may lead to changes in FDA behavior in the approval of new drugs. An example of such change is discussed below.

In the 1980s and early 1990s, increased demands for FDA product approval and budget cuts at the agency exacerbated the problem of regulatory delay

<sup>7</sup> Mary K. Olson, *Regulatory Agency Discretion among Competing Industries: Inside the FDA*, 11 *J. L. Econ. & Org.* 379 (1995).

<sup>8</sup> Paul J. Quirk, *Food and Drug Administration*, in *The Politics of Regulation* (James Q. Wilson ed. 1980).

in new-drug review.<sup>9</sup> Regulatory delays led to pressure from pharmaceutical firms, politicians, and some patient groups (AIDS) to reduce the delay and accelerate new-drug approval. The introduction of user fees for new-drug review was policy makers' response to this political pressure. The 1992 Prescription Drug User Fee Act required pharmaceutical manufacturers to pay a fee for each new-drug application (NDA) (\$208,000 in 1995) submitted to the FDA. The revenue from user fees can be used only to help expedite the review and approval of new drugs. Studies have found that the introduction of user fees has reduced new-drug review times by as much as 50 percent.<sup>10</sup> Since the political spotlight has focused primarily on the speed of new-drug review, these studies suggest that the user-fee reform has been a success. However, there has been little to no investigation of the effect of the reform or review speed on product safety.

Although new pharmaceuticals offer health benefits, they also pose health risks for patients. Risks that are detected in clinical trials (known side-effects) are acknowledged by regulators at the time of approval and are incorporated into a drug's labeling. However, new drugs in particular may have additional sources of risk such as rare or unanticipated side-effects not observed in clinical trials.<sup>11</sup> Such health risks may not be detected until a drug is sold in the general patient population. To improve understanding about both types of health risks, regulators conduct postmarketing surveillance of adverse drug reactions using the Spontaneous Reporting System. This system relies primarily on health professionals such as physicians to file reports when patients experience an adverse reaction to a drug.

The FDA's Center for Drug Evaluation and Research reports that adverse drug reactions increased from 83,310 in 1990 to 243,342 in 1997.<sup>12</sup> These numbers reflect an increasing stock of drugs and include reports about known side-effects as well as unanticipated side-effects. In 1998, the FDA received 71,464 reports of serious, unanticipated adverse drug reactions out of a total of 232,470 suspected drug-related adverse event reports. Firms and regulators rely on these data to learn more about the safety of new drugs. Information from these reports can lead to revisions in product labeling or the subsequent

<sup>9</sup> Olson, *supra* note 7.

<sup>10</sup> Sheila Shulman & Kenneth I. Kaitin, The Prescription Drug User Fee Act of 1992: A 5-Year Experiment for Industry and the FDA, 9 *PharmacoEconomics* 121 (1996); and K. I. Kaitin, The Prescription Drug User Fee Act of 1992 and the New Drug Development Process, 4 *Am. J. Therapeutics* 167 (1997). In addition, Mary K. Olson, Regulatory Reform and Bureaucratic Responsiveness to Firms: The Impact of User Fees in the FDA, 9 *J. Econ. Mgmt. Strategy* 363 (2000), finds that FDA reviewers became less responsive to the differences among firms and that user fees have led to more equity in the FDA review process.

<sup>11</sup> Other risks or uncertainties may arise from long-term exposure to drugs, from drug effects in understudied populations (such as pregnant women and children), or from drug interactions.

<sup>12</sup> U.S. Department of Health & Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, CDER 1998 Report to the Nation: Improving Public Health through Human Drugs 23 (1998) (<http://www.fda.gov/cder/reports/rptntn98.pdf>).

withdrawal of FDA-approved drugs from patient markets. The trends in ADRs along with the jump in new-drug withdrawals discussed earlier suggest that the risks associated with new drugs may have increased after the user-fee reform.

This paper hypothesizes that the user-fee reform increased the political costs associated with regulatory delay and increased the political benefits arising from faster new-drug approval. The addition of these new political consequences associated with accelerated approval altered the trade-offs confronting regulators. As these trade-offs changed, regulatory concern shifted from type I to type II error. While this shift may have allowed regulators to accelerate new-drug approval, it may have also increased the risks associated with taking new drugs. The next subsection describes the ways in which the user-fee reform may have altered new-drug safety.

#### *B. How User Fees May Affect New-Drug Safety*

There are some key features of the reform that may be helpful in understanding how regulator motivations may have been changed. First, the reform altered agency financing by providing additional user-fee revenue to supplement the agency's budget. This revenue, approximately 10 percent of the agency's budget, can be used only to expedite the review of new drugs.<sup>13</sup> In effect, the majority of fee revenue goes to the FDA division responsible for reviewing new-drug applications, the Center for Drug Evaluation and Research (CDER). Second, in return for the new revenue, the FDA promised to meet new performance goals outlined in the legislation. The performance goals set review targets of 6 months for the most therapeutically novel drugs and 12 months for all other drugs. These performance goals represent quite an ambitious change in the speed of FDA review. In contrast, for new chemical entities (NCEs) approved between 1990 and 1992, the average FDA review time was 31 months.<sup>14</sup>

Third, the reform increased reporting requirements for the agency. The agency must prepare annual performance reports and financial reports that are then used to evaluate the agency's progress in meeting the performance goals. Both politicians and firms have shown a keen interest in this oversight. Fourth, the user-fee program has a fixed term of 5 years. Program renewal requires new legislation that allows all interested parties to revisit the issue. Politicians and firms have indicated that continued support for this program is conditioned on the agency's ability to meet its performance goals.

This reform creates new rewards for accelerating new-drug review that were not present in the agency prior to the reform: the addition of user-fee

<sup>13</sup> Firms pay half of the fee when an application is submitted and the remainder after the agency makes its approval decision.

<sup>14</sup> Olson, *supra* note 10.

revenues to supplement the agency's budget.<sup>15</sup> Larger budgets mean a larger agency, more funding for regulatory activities, increased regulatory power, and, perhaps, greater autonomy.<sup>16</sup> For instance, the FDA has devoted over 50 percent of its user-fee revenues to expanding the size of its review staff. The agency also faces new costs if regulatory delay is not reduced over time because program renewal and the continued stream of fee revenues depends on agency performance. The Center for Drug Evaluation and Research, in particular, has the greatest incentive to ensure that its reviewers meet the performance goals because it receives a majority of the fee revenue. This financing arrangement and the increase in monitoring of new-drug review activities may have altered the trade-offs that face FDA regulators and increased the administrative pressures inside the agency to accelerate new-drug review.

User-fee revenues provide the FDA with new funds to hire more reviewers and update information-processing equipment. Both these changes may lead to faster FDA review times. As long as the revenue from user fees does not affect the risk level assumed by regulators, user fees need not have an adverse effect on product safety. However, heightened political pressures and new administrative pressures inside the agency that arise from the desire to meet user-fee performance goals may have led regulators to assume more risk in the approval of new drugs. Also, new reviewers hired with user-fee revenues may have risk preferences that differ from those of existing reviewers. If the level of risk assumed by FDA regulators increases, this could lead to a reduction in new-drug safety.

In assuming such risk, regulators may accept more uncertainty at the time of approval to help accelerate new-drug review. For instance, prior to user fees, regulators often requested additional information from firms during the review process if they had concerns about the safety and efficacy evidence presented in an NDA. Some requests may require firms to perform additional clinical tests that they would then have to resubmit as an amendment to an existing NDA.<sup>17</sup> While such information could alleviate regulator uncertainty in the approval of new drugs, these requests also increase regulatory delay in new-drug approval. User fees may have reduced reviewer incentives to

<sup>15</sup> The act prevents Congress from reducing the agency's budget in response to increased fee revenue. Also, any extra fee revenues that the agency does not spend in a given fiscal year can be carried over to future fiscal years. This feature is very atypical of government bureaucracies because it essentially allows the agency to retain any savings from increased efficiency in the new-drug review process over time.

<sup>16</sup> William A. Niskanen, *Bureaucracy and Representative Government* (1971), has argued that agencies will engage in actions to maximize their budgets.

<sup>17</sup> There is evidence that regulators made many such requests in the 1980s. U.S. Congress, Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks and Rewards* 147 (February 1993) ([http://www.wws.princeton.edu/~ota/disk1/1993/9336\\_n.html](http://www.wws.princeton.edu/~ota/disk1/1993/9336_n.html)), reports that for the 68 NDAs for new molecular entities submitted to the FDA in 1984 and 1985, the sponsoring firms filed a total of 1,141 amendments (at 147).

demand such information given the new costs associated with regulatory delay.

Another way in which user fees may have affected new-drug safety is through a reduction in informational spillovers from other countries. A country that approves drugs more slowly may benefit from the safety information that becomes available from other countries where the drugs are already approved. In the case of Thalidomide in the early 1960s, the United States, which had not yet approved Thalidomide, clearly benefited from the safety information from Europe and Canada, where the drug was already approved. Data showed that this drug, which was given to pregnant women as a sedative, caused severe birth defects. Because of this information, the drug did not receive FDA approval and the United States largely avoided the Thalidomide tragedy. This strategy of deliberate regulatory slowness reduces the probability that an unsafe drug will be approved and hence may reduce the incidence of new-drug safety problems. As the review process speeds up, the likelihood of benefiting from such informational spillovers is reduced.

The alternative hypothesis is that user fees generate additional resources for the agency that help them to increase the speed of review without influencing the level of risk assumed by regulators. If extra resources, not changing risk assumptions, are responsible for the changes in regulatory behavior, then increases in the speed of review may not be expected to affect new-drug safety. Since restrictions in the user-fee act prevent any fee revenue from being used for purposes other than the review and approval of new drugs (such as improvements in adverse drug surveillance or monitoring), user-fee revenues are not expected to generate any improvements in new-drug safety or prevent adverse drug effects during this period.<sup>18</sup>

An issue not yet addressed is the possibility that changes observed in new-drug safety may result from changes in firms' decisions instead of changes in regulatory behavior. Because the application fee is small relative to the cost of developing a new drug, \$802 million in 2000 dollars, user fees are not expected to affect a firm's drug development strategies.<sup>19</sup> Furthermore, the long lags required to develop a new drug further suggest that the pipeline of new drugs being approved in the years immediately following the reform is also unaffected by introduction of user fees. It takes approximately 9.5 years for firms to develop a drug and collect all of the evidence needed to submit a new-drug application to the FDA. For the same reason, user fees

<sup>18</sup> Fee revenues cannot be used for generic drug review, medical device review, postmarketing drug surveillance (prior to 2002), or enforcement or inspection activities not related to new-drug review. Politicians, firms, and regulators jointly determined the list of activities to which user-fee revenues could be directed.

<sup>19</sup> Tufts Center for the Study of Drug Development, Tufts Center for the Study of Drug Development Pegs Cost of a New Prescription Medicine at \$802 Million (news release, November 30, 2001) (<http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=6>).

are not expected to alter the set of firms that submit new-drug applications during this period.<sup>20</sup>

This discussion suggests that more empirical investigation of the relationship between review speed and new-drug safety is warranted to evaluate the effect of this policy. Proponents of accelerated approval argue that the agency is too cautious in its review decisions because the gains in consumer safety from regulatory delay are minimal. They believe that residual uncertainty about new-drug safety can be resolved only when such drugs are prescribed in the general patient population. If true, then efforts to reduce regulatory delay for such drugs may not be expected to lead to reductions in new-drug safety over time. However, critics of accelerated approval worry that political pressures associated with user fees may lead regulators to assume more risk in new-drug review and, consequently, result in a reduction in new-drug safety. Whether the changes caused by any reform affect new-drug safety is ultimately an empirical question. It is a question that motivates this analysis.

### III. ADVERSE DRUG REACTIONS

This study uses ADR data from the FDA's Spontaneous Reporting System in its postmarketing surveillance program to explore the relationship between new-drug review speed and reported new-drug safety. Health professionals file most ADR reports when a patient experiences an adverse reaction to a drug. The FDA especially encourages ADR reporting in cases of serious reactions such as those that are fatal, life threatening, permanently disabling, or that require hospitalization. Reports include clinical information about the adverse outcome, whether the drug was suspected of causing the outcome, and characteristics of the patients who experience each ADR. The reports may be sent to the drug's manufacturer (who must legally report them to the FDA) or directly to the FDA. All reports are then entered into this database.

Adverse drug reactions represent an important source of information about the adverse health effects of new drugs on consumers. Although the FDA, clinicians, and pharmaceutical firms have used ADR data to detect unanticipated safety problems or other adverse effects of new drugs, these data have not been utilized by economists.<sup>21</sup> Economists may use such data to examine changes in reported product safety in the pharmaceutical industry over time.

It is important to recognize some important limitations of these data. First,

<sup>20</sup> In the future, perhaps, since faster reviews also generate quicker financial payoffs, this arrangement may increase the attractiveness of developing drugs for conditions that have proved difficult to address with drug therapy. Such changes in firm strategies regarding drug development may have consequences for understanding the pattern of ADRs observed in the future.

<sup>21</sup> One exception is Mary K. Olson, *Substitution in Regulatory Agencies: FDA Enforcement Alternatives*, 12 *J. L. Econ. & Org.* 376 (1996), which examined how the changes in the annual number of ADR reports affected FDA drug inspection policy over time.

many ADRs go unreported. Particularly in spontaneous reporting systems such as the FDA's, underreporting may be severe. While pharmaceutical manufacturers and distributors have mandatory reporting requirements, reporting by physicians and other health professionals is voluntary. Hence, the ADRs in this data set most likely represent an underestimate of the true number of ADRs. Second, variation in the reporting of ADR information can be influenced by the length of time that a drug has been on the market. Reporting tends to be the highest in the first 2 years after a drug enters the market and then tends to decline thereafter. Uncertainty about pharmaceutical risk is greatest when a drug is first approved. Hence, health professionals may have greater incentives to report ADRs early in a drug's marketing because such reports can lead to better information about pharmaceutical risks and subsequent improvements in product labeling.

Third, an ADR report does not require or provide evidence of causation. Health professionals need only to suspect that a serious adverse reaction was associated with a drug to report an ADR. There may be uncertainty surrounding the causal relationship between a drug and the noted adverse reaction at the time the report is made.

Fourth, ADRs provide information only about patients who report adverse drug effects, not about the actual number of individuals who were exposed to a drug. The absence of drug utilization data is perhaps the greatest limitation of the FDA's ADR database. Since drug utilization will affect ADR reporting, failure to control for differences in drug utilization could lead to misleading inferences about new-drug safety. Also, other factors unrelated to product risk (such as patient age) may also affect ADRs. For these two reasons, simple ADR counts may not be good measures of the relative riskiness among different drugs.

This analysis addresses these concerns in the following ways. The first two limitations influence the construction of the dependent variable for the analysis. The dependent variable is a count of ADRs reported for each new drug during the first 2 years after its FDA approval date. This 2-year interval was chosen to lessen the problems of underreporting noted above since it is during this period that the incentives to report ADRs are the highest. In addition, this interval reduces the bias arising from differential reporting trends during a drug's time on the market. For each new drug  $i$  approved in year  $t$ , ADR counts per drug will include ADRs received in years  $t + 1$  and  $t + 2$ . This measure  $ADR_{it}$  is then used to explore the sources of variation in reported ADRs among newly approved drugs between 1990 and 1995.

To address the third limitation, the analysis will examine the set of ADRs in which the individual who files the report identifies the drug suspected of causing the reaction. The drug suspected of causing an ADR is indicated by an "S" for suspect drug in the data record. Although reports do not require evidence of causation, suspect status reflects some information about the reporter's or health professional's belief about causation. These results will

be compared to an analysis that includes all ADR reports that mention a drug.

To address the fourth limitation, the analysis includes control variables that proxy for drug utilization as well as other control variables for factors, unrelated to drug risk, that may affect ADR reporting. With these control variables, the analysis examines the effect of drug review times and the user-fee reform on reported new-drug safety.

#### IV. EXPLAINING VARIATION IN ADVERSE DRUG REACTIONS

There are several factors that may help explain variation in ADR counts among new drugs. The first is the therapeutic novelty of a drug. Therapeutically novel drugs offer significant therapeutic gains over existing remedies. Since the mid-1970s, the FDA has used a rating system to identify such drugs for the purpose of expediting their approval.<sup>22</sup> Currently, regulators assign each drug a rating: "P" for priority, which indicates a significant therapeutic gain over existing remedies, and "S" for standard, which indicates little to no therapeutic gain.<sup>23</sup> Regulators may be willing to assume greater risk in the approval of therapeutically novel drugs because of the potential benefits to patients from accelerated access. If patients do not have access to effective drug therapies, they may also be more willing to trade safety for faster access to such drugs. AZT provides an example. Given the absence of therapies for AIDS, regulators may have been more willing to tolerate greater risk in the approval of the first AIDS drug. If regulators assume greater risk for priority drugs by approving them faster than other drugs, then these drugs may be associated with more ADRs.

There are alternative reasons why therapeutically novel drugs may be associated with increased ADR reporting. First, since therapeutically novel drugs often represent the first of their kind in a particular drug class, both physicians and patients may have less experience with such drugs. This lack of experience may translate into more ADRs. Second, since therapeutically novel drugs may also be heavily promoted, such promotion may also have a separate effect on ADR reporting. Third, the patients who receive novel drugs may have conditions that place them at greater risk of having an ADR. In any event, it is important to control for the therapeutic novelty of a drug because novel drugs may be associated with higher ADR counts.

A second variable that may explain variation in ADR counts among drugs

<sup>22</sup> Until 1992, regulators assigned an A rating to the most therapeutically novel drugs, a B rating to drugs that offer modest therapeutic gains, and a C rating for drugs that offer little to no therapeutic gain. In 1987 regulators introduced the AA rating specifically for AIDS drugs to help expedite their approval. See K. I. Kaitin *et al.*, Therapeutic Ratings and End-of-Phase II Conferences: Initiatives to Accelerate the Availability of Important New Drugs, 31 *J. Clinical Pharmacology* 17 (1991).

<sup>23</sup> Center for Drug Evaluation and Research, FDA, Priority Review Policy, in the Manual of Policies and Procedures, MAPP 6020.3 (1996) (<http://www.fda.gov/cder/mapp/6020-3.pdf>).

is the therapeutic category of a drug. The reason is that some classes of drugs may entail different risks and complexities depending on the way in which they function in the human body (acting on the cardiovascular system or the central nervous system, for instance). Since some classes of drugs raise greater safety concerns than do others, it will be important to control for the therapeutic category of a drug. New drugs in any particular class may also be judged relative to preexisting drugs available in that class. There may be systematic influences on ADR levels that arise from either the science or the historical trends of drug therapies in specific therapeutic categories.

The size of the patient population exposed to any drug will also affect adverse drug reaction counts. Drugs taken by large patient populations will generate more adverse drug reactions than drugs taken by small patient populations even if the drugs have the same underlying riskiness. Failure to control for differences in drug utilization will result in misleading inferences about the risks or safety of new drugs. For this reason, it is important to control for differences in the size of the patient population that utilizes a drug.

Patient characteristics may also affect ADR levels. Two important characteristics are the age and the gender of patients experiencing adverse drug reactions. Age may be a proxy for patient health. Patients in poor health may be more likely to experience adverse drug effects. In addition, older patients may be taking more medications that could affect the likelihood of experiencing adverse drug reactions. In either case, older patients may experience more adverse drug effects. Gender may proxy for differences in either the tendency to report ADRs or differences in the way drugs affect men and women. Data from the FDA (1998) show that the number of ADR reports for women is greater than the number of ADR reports for men. In addition, patient conditions may also affect ADR levels, in that patients with certain conditions such as heart disease may be at greater risk of an ADR.

Finally regulatory variables may help explain variation in reported new-drug safety or ADR levels. First, a drug's FDA review time may systematically be related to its ADR count. The reason is that regulators may assume more risk to help accelerate new-drug review and approval. If so, then drugs with shorter FDA review times may be associated with increased pharmaceutical risks and increased adverse drug reactions. In addition to the speed of new-drug review, the user-fee reform may have led to other changes in regulatory behavior or agency process that influenced pharmaceutical risks and new-drug safety. A regime shift variable (for the reform) may detect any discrete increases in the ADRs associated with new drugs approved in the user-fee era.

Although a user-fee variable captures time-relevant variation in ADR counts following the reform, there may be other time-relevant considerations (secular trends) that affect ADR reporting. To address this issue, yearly dummy variables, in addition to the regime shift variable, should help control

for the idiosyncratic year-specific effects that may affect ADR reporting over time. The next section describes the empirical methods and data used to perform this analysis.

## V. METHODOLOGY AND DATA

Adverse drug reaction data have important similarities to other types of accident data in that they are discrete data represented by nonnegative integers that are often modeled using Poisson regression. However, the distribution of the dependent variable, the 2-year sum of ADRs for new drugs, is highly skewed. These data violate the Poisson assumption that the conditional mean equals the conditional variance. Instead, the variance of this distribution is several times greater than the mean, which indicates overdispersion. Overdispersion causes a downward bias in the standard errors resulting from a Poisson regression. To avoid this bias, maximum-likelihood estimation of a negative binomial model is used. The variance of the distribution,  $\sigma^2$ , under the negative binomial model is a quadratic function of the mean,  $E[Y_i] = \mu$ , so that  $\sigma^2 = \mu + \alpha\mu^2$ , where  $\alpha$  is the dispersion parameter.<sup>24</sup>

The empirical analysis models variation in the ADR count

$$Y_i = \sum_{j=1}^2 \text{ADR}_{i,t+j}$$

for drug  $i$  approved in year  $t$  as a function of drug-specific  $X_{i,t}$ , patient-specific  $P_{i,t}$ , and regulatory factors  $R_{i,t}$  believed to affect drug safety or ADR levels:

$$E[Y_i] = \exp(\beta X_{i,t} + \delta P_{i,t} + \gamma R_{i,t} + \epsilon_{i,t}). \quad (1)$$

The coefficients  $\beta$ ,  $\delta$ , and  $\gamma$  will measure the extent to which ADR counts represented by  $Y_i$  are influenced by drug-specific, patient-specific, and regulatory factors, respectively.

The analysis is performed for three different ADR count measures: Total, the total number of ADRs per drug; Hospital, the number of ADRs per drug in which the patients require hospitalization; and Death, the number of ADRs that result in the death of the patient. Deaths reflect the most serious and objective measure of patient harm. Hospitalizations, which are more frequent than deaths, are another objective measure of patient harm in that the adverse effect was serious enough to warrant hospitalization. Adverse effects that require hospitalization may also be more likely to be reported than adverse effects that do not require hospitalization. A breakdown of the results for each ADR category will provide more specific information about the health effects of the FDA policy change.

<sup>24</sup> Colin A. Cameron & Pravin K. Trivedi, *Regression Analysis of Count Data* (1998).

Adverse drug reactions in which the new drug is considered to be the drug suspected of causing the reaction will be analyzed first. A second analysis will be performed using all ADRs in which a drug is mentioned but not necessarily identified as the suspect drug.

#### A. *Explanatory Variables*

The explanatory variables fall into the three general categories: regulatory factors, drug characteristics, and patient characteristics. The discussion below describes each variable and discusses its relationship to the dependent variable.

The vector of regulatory factors includes two variables that may proxy for changes in FDA behavior. The first variable, *Revtim*, represents the time (in months) between the date of submission of a new-drug application to the agency and the date of a drug's FDA approval. This period includes the time that regulators spend reviewing the application and the time that firms take to respond to regulator requests for additional information to support the application. This is the key variable that specifically links the speed of FDA review to new-drug safety. The coefficient for this variable will measure the extent to which drugs with faster FDA review times generate more adverse effects among patients. A predicted negative coefficient for this variable suggests that a decrease in a drug's FDA review time leads to an increase in the adverse drug effects associated with a drug.<sup>25</sup>

A second regulatory variable is a regime shift variable, *Userfee*, equal to one for all drugs approved after the introduction of user fees and zero otherwise. The regime shift variable will measure the effect of other changes associated with the reform that may have affected new-drug safety. If user fees affect new-drug safety only through the speed of new-drug review, then this coefficient when included with *Revtim* is not expected to be significantly different from zero. However, if the reform led to other changes in FDA behavior (besides the speed of review) that affected new-drug safety, then the predicted sign of the coefficient for *Userfee* is positive.<sup>26</sup>

The vector of drug-specific factors includes several variables. First, the variable *Priority* is a dummy variable equal to one for drugs rated by the FDA as therapeutically novel.<sup>27</sup> For drugs that offer greater therapeutic benefits to patients, regulators may be willing to assume more risk. Alternatively, patients who take novel drugs may have conditions that place them at greater

<sup>25</sup> An alternative estimation will explore whether there are any nonlinear effects of a drug's FDA review time on the ADR variables.

<sup>26</sup> An alternative specification will include a regime variable that equals one for all user-fee drugs to determine whether the changes in regulatory behavior were specifically confined to user-fee drugs.

<sup>27</sup> This includes all drugs receiving either a P rating during 1992–95 or an A, AA, or B rating in preceding years.

risk of an ADR. Also, lack of physician and patient experience with therapeutically novel drugs may result in more ADRs. The sign of the coefficient for Priority will reflect the extent to which therapeutically novel drugs generate more adverse drug reactions than drugs that offer little to no therapeutic gains.

Six variables are included to control for differences in the therapeutic classes among drugs. They are Cardio for cardiovascular drugs, CNS for central nervous system drugs, Analges for anesthetic/analgesic drugs, Infect for anti-infective drugs, Endo for endocrine drugs, and Neopl for anti-neoplastics or cancer drugs. The coefficients for these variables will measure the extent to which drugs in different therapeutic classes are associated with either greater or fewer adverse drug reactions in patients either because of the way the drug works in the body or because of historical trends in ADRs within a particular drug class.

Two variables are included to proxy for differences in drug utilization. The variable  $\log(\text{Utilization})$  is defined as the logarithm of the number of prescriptions associated with each drug. Prescription drug utilization data are obtained from the 1996 Medical Expenditure Panel Survey (MEPS). The coefficient for the utilization variable is expected to be positive because drugs taken by more patients are expected to generate more ADRs. Because some drugs intended for very small patient populations are not contained in the MEPS survey, namely, some orphan drugs, a second variable, Orphan, is also included in the analysis. This variable is set equal to one for drugs designated as orphan drugs by the FDA and hence intended for small patient populations (that is, fewer than 200,000 patients per year). The coefficient for Orphan is expected to be negative because drugs intended for small patient populations are expected to generate fewer ADRs.

The vector of patient characteristics includes two variables. The first variable, Age, is the average age of the patients who experience adverse drug reactions. For Total, Hospital, and Death, the average ages of the patients in each ADR category are represented by  $\text{Age}(t)$ ,  $\text{Age}(h)$ , and  $\text{Age}(d)$ , respectively. The signs of the coefficients for Age will indicate the extent to which age is linked to the level of ADRs reflected in the count. A positive coefficient suggests that an increase in the mean age of patients results in a higher ADR count. The second variable, Female, is the percentage of female patients reflected in each drug's ADR count. For each ADR category, Total, Hospital, and Death, this percentage is represented by  $\text{Female}(t)$ ,  $\text{Female}(h)$ , and  $\text{Female}(d)$ , respectively. The signs of these coefficients indicate the extent to which increases in the percentage of women who experience ADRs are associated with higher ADR counts.

The age and gender variables described above may not capture the effect of different patient conditions on ADR counts. However, the drug class and drug novelty variables may proxy for some important differences in patient conditions. The drug class variables will control for broad differences in the

diseases being treated (that is, cardiovascular drugs for cardiovascular disease, neoplastic drugs for cancer). If patients with cardiovascular disease are at greater risk of an ADR than patients with other diseases, then a drug class variable for cardiovascular should help capture such variation. If the patients who take therapeutically novel drugs have conditions that place them at greater risk of an ADR, then the drug novelty variable Priority should help control for that source of variation.

Finally, the analysis includes yearly dummy variables to control for secular trends or other idiosyncratic year-specific effects that may affect ADR reporting over time.

One empirical issue to address is the possible endogeneity of the variable *Revtim*, the length of new-drug review. To investigate this issue, an omitted-variable version of the Hausman test is performed.<sup>28</sup> For all ADR counts, a Hausman test cannot reject the null hypothesis (exogeneity of *Revtim*).

### B. Data

This analysis utilizes ADRs for the 141 new chemical entities (NCEs) approved by the FDA between 1990 and 1995.<sup>29</sup> Adverse drug reaction counts per drug are constructed by aggregating all ADR reports received during the first 2 years following a drug's FDA approval year, so a drug approved in 1990 will include ADRs reported in 1991 and 1992 for Total, Hospital, and Death. Since generic versions of these drugs are not available until after patent expiration, ADR reports that cite a particular drug can be attributed to the brand-name drug. All ADR data come from the FDA's Spontaneous Reporting System. The age and gender variables are also collected from the ADR reports. For each ADR category, the average age of the patients who experience an ADR and the percent of patients who are female are constructed from these reports.

In addition to the ADR data, the analysis also requires drug-specific data such as the names of 141 new molecular entities approved by the FDA between 1990 and 1995, the review times for each drug, the approval dates,

<sup>28</sup> Peter Kennedy, *A Guide to Econometrics* (3d ed. 1992), describes this test. Estimates of review time, *Revtim* are formed from instruments including firm and drug characteristics expected to affect the length of new-drug review (as in Olson, *supra* note 10, and the explanatory variables in (1)). Instruments include firm research intensity, firm specialization in pharmaceutical sales, firm size, measures of firm experience with the FDA, drug class, drug novelty, a user-fee reform variable, and the other exogenous variables in (1). Then the ADR count variable is regressed on all the variables listed in (1) including *Revtim* and *Revtim*. The coefficient for *Revtim* is then tested against zero to determine if there is contemporaneous correlation between the regressor and the error in each ADR expression.

<sup>29</sup> A new chemical entity is defined by K. I. Kaitin *et al.*, *The New-Drug Approvals of 1990, 1991, and 1992: Trends in Drug Development*, 34 *J. Clinical Pharmacology* 120 (1994), "as any new molecular compound not previously approved in the United States, excluding biologics, vaccines, and diagnostic agents. New salts, esters, and dosage forms of previously approved compounds are also excluded."

the therapeutic ratings assigned by the FDA, orphan drug status, and the therapeutic drug classes associated with each new drug. All of this information (except the therapeutic drug class) is contained in two published articles.<sup>30</sup> On request, the author also provided the therapeutic drug classes associated with each drug. Drug utilization data are obtained from the 1996 MEPS.

## VI. RESULTS

### A. Summary Statistics

This section provides the summary statistics and discusses the characteristics of the data used in the analysis. The data include ADRs in which a drug suspected of causing the adverse reaction was identified and ADRs in which a drug was taken but was not specifically identified as a suspect drug in the report. In the 2 years following each drug's approval, the 141 new drugs approved between 1990 and 1995 generated 64,729 total ADRs (52,946, or 82 percent identified a suspect drug), 16,148 ADRs requiring hospitalization (12,800, or 79 percent identified a suspect drug), and 5,243 ADR deaths (4,494, or 86 percent identified a suspect drug).

Summary statistics are presented in Table 1 for ADR reports that list a suspect drug. For comparison, Table 1 also provides summary statistics for all ADRs both for drugs identified as the suspect drug and for other drugs listed but not identified as the suspect drug. Among the ADR reports that list suspect drugs, the data show that the average number of ADRs per drug is 376 in the 2 years following a drug's FDA approval. Within this group, ADRs that require hospitalization are less frequent, with an average of 91 per drug. Deaths, as expected, occur with the least frequency, an average of 32 per drug in the first 2 years of marketing. The corresponding standard deviations for these data indicate that there is substantial variation within each ADR category as well as overdispersion in these data.

The degree of overdispersion for Death, Hospital, and Total among ADRs for suspect drugs is seen in the frequency distributions presented in Figures 1, 2, and 3, respectively. Figure 1 shows that 71 drugs (50 percent) have between one and 20 ADRs that result in death. Figure 2 shows that 56 drugs (40 percent) have between one and 40 ADRs requiring hospitalization. However, both figures show that the data are highly skewed. In Figure 1, 14 drugs (10 percent) have 80 or more ADRs that result in death. In Figure 2, 22 drugs (16 percent) have 200 or more ADRs requiring hospitalization. A similar pattern is evident in Figure 3, where 56 drugs (40 percent) have

<sup>30</sup> *Id.*; and K. I. Kaitin & M. A. Manocchia, The New-Drug Approvals of 1993, 1994, and 1995: Trends in Drug Development, 4 *Am. J. Therapeutics* 46 (1997).

TABLE 1  
SUMMARY STATISTICS: NEW-DRUG APPROVALS IN 1990-95

Variable	Definition	Mean	SD
ADRs in which suspect drug is identified:			
Total	Number of total ADRs per drug	376	629
Hospital	Number of hospitalizations per drug	91	123
Death	Number of deaths per drug	32	65
Age(t)	Average age for total ADR count	48	19
Age(h)	Average age for ADR hospital count	46	21
Age(d)	Average age for ADR death count	46	25
Female(t)	% female for total ADR count	44	22
Female(h)	% female for ADR hospital count	42	23
Female(d)	% female for ADR death count	36	26
ADRs experienced while taking a drug:			
Total	Number of total ADRs per drug	459	693
Hospital	Number of hospitalizations per drug	115	148
Death	Number of deaths per drug	37	69
Age(t)	Average age for total ADR count	49	18
Age(h)	Average age for ADR hospital count	47	21
Age(d)	Average age for ADR death count	47	24
Female(t)	% female for total ADR count	46	21
Female(h)	% female for ADR hospital count	44	24
Female(d)	% female for ADR death count	38	26
Summary statistics for the 141 drugs in the sample:			
Revtim	FDA review time (in months)	28	23
Userfee	Equals 1 for drugs approved after user fees	.48	.50
Priority	Equals 1 for drugs with priority rating	.48	.50
log(Utilization)	log of the number of prescriptions	2.55	2.45
Orphan	Equals 1 for orphan drugs	.25	.43
Cardio	Equals 1 for cardiovascular drugs	.24	.43
Neopl	Equals 1 for neoplastic drugs	.11	.32
Infect	Equals 1 for anti-infective drugs	.20	.40
CNS	Equals 1 for central nervous system drugs	.11	.32
Analges	Equals 1 for anesthetic/analgesia drugs	.13	.34
Endo	Equals 1 for endocrine drugs	.08	.27

NOTE.—*N* = 141. ADR = adverse drug reaction; FDA = Food and Drug Administration.

between one and 100 total ADRs in the 2 years following FDA approval; however, 16 drugs (11 percent) have more than 800 total ADRs.

While the mean age of patients experiencing ADRs is mid- to late-40s in each ADR category, the standard deviations are quite large, ranging from 19 years for all ADRs to 25 years for ADRs that result in death. Finally, among the ADRs for suspect drugs, the data show that the average percentage of women reflected in the ADR counts is 44 percent among total ADRs, 42 percent among ADR hospitalizations, and 36 percent of ADR deaths per drug. The standard deviations indicate that there is large variation in the percentage of females who experience ADRs among the newly approved drugs in the sample.

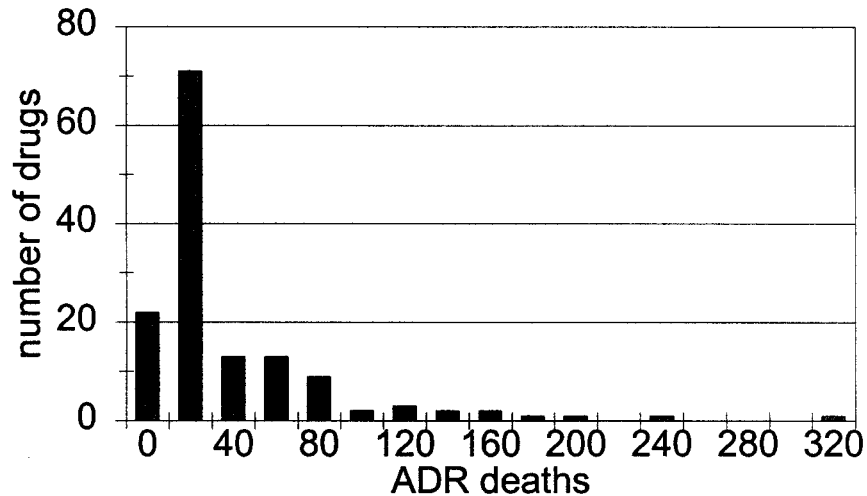


FIGURE 1.—Frequency distribution of adverse drug reaction death counts: 1990–95 new chemical entities.

Table 1 also provides summary statistics for the 141 drugs in the sample. The data indicate that the mean review time among these drugs is 28 months. For new drugs approved between 1990 and 1992, the mean review time was 31 months. For new drugs approved between 1993 and 1995, the mean review time fell to 24 months. The table shows that 48 percent of the drugs were approved after the introduction of user fees, 48 percent of the drugs represent therapeutically novel drugs, and 25 percent of the drugs are classified as orphan drugs that affect small patient populations. The therapeutic drug class variables show the percentages of drugs approved in each drug class, with cardiovascular and anti-infective categories representing the classes with the most new-drug approvals.

#### B. Negative Binomial Regression Results

Results from the estimation of (1) for the set of ADRs in which a drug is suspected of causing the reaction are presented in Table 2. The first column presents the coefficients from the expression for total ADRs, the second column presents the coefficients from the expression for ADR hospitalizations, and the third column presents the coefficients from the expression for ADR deaths.<sup>31</sup>

<sup>31</sup> Since less severe ADRs are aggregated with more severe ADRs in the total ADR counts per drug, this measure is expected to contain the most noise of the three proxies for reported new-drug safety. Measures of ADR hospitalizations and ADR deaths are expected to be less noisy proxies for new-drug safety because there is less variation in ADR severity within each group.

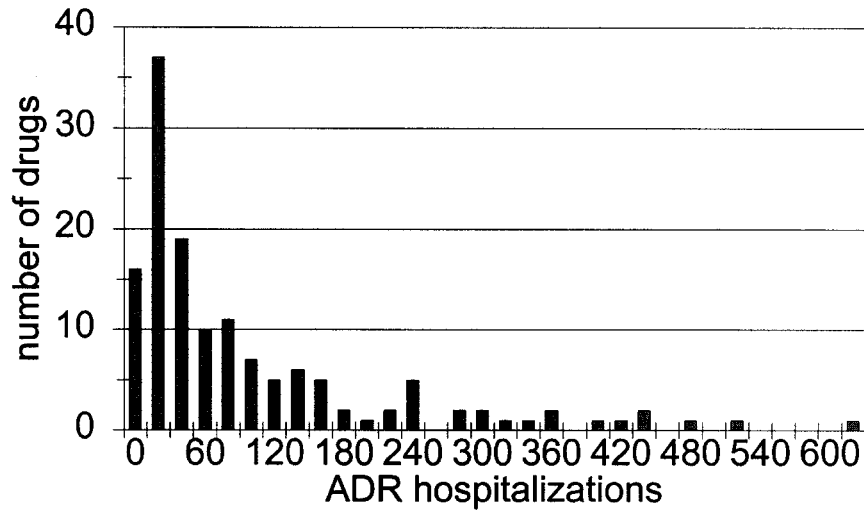


FIGURE 2.—Frequency distribution of adverse drug reaction hospitalization counts: 1990–95 new chemical entities.

Among the regulatory variables, the length of new-drug review is related to all ADR count measures. The coefficient for the review time variable is negative, but only marginally significant (.1 level) in the expression for total ADRs in the first column. In the second column, the coefficient for the length of new-drug review is negative and significant at the .05 level, which suggests that reductions in new-drug review times are associated with increases in ADRs that require hospitalization. The magnitude of the coefficient indicates that a 1-month reduction in a drug's FDA review time leads to a 1 percent increase in expected ADR hospitalizations. Evaluated at the mean, a 12-month reduction in the speed of new-drug review on average is associated with an increase of 10.92 ADR hospitalizations per drug.<sup>32</sup>

The coefficient for the length of new-drug review in the third column is also negative and significant at the .01 level, which suggests that reductions in new-drug review times are associated with increases in ADRs resulting in death. The magnitude of this coefficient indicates that a 1-month reduction in a drug's FDA review time leads to a 2 percent increase in expected ADR deaths. Evaluated at the mean, a 12-month reduction on average is associated with an additional 7.68 ADR deaths per drug. These results suggest that there is a regulatory trade-off between reported new-drug safety and the speed of new-drug review.

<sup>32</sup> An alternative estimation included a squared review time variable in each estimation to test for nonlinearities. In each ADR category, the coefficient for this variable was not significantly different from zero.

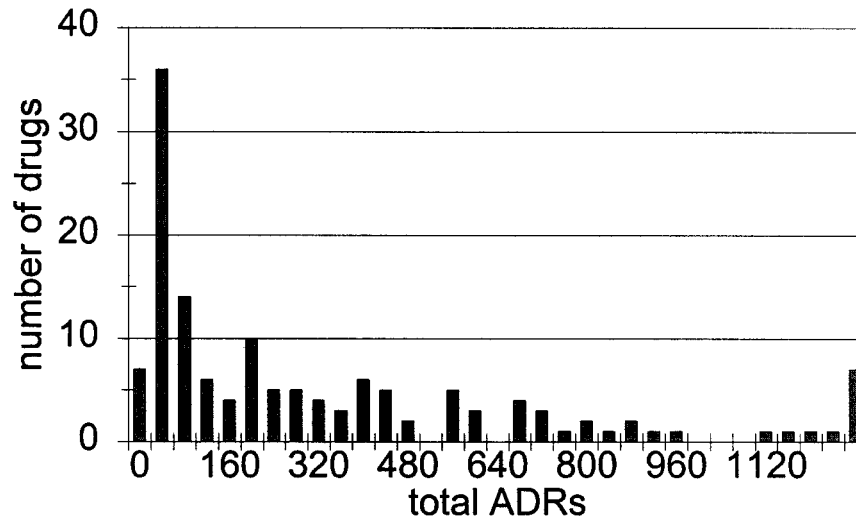


FIGURE 3.—Frequency distribution of total adverse drug reaction counts: 1990–95 new chemical entities.

The coefficient for the user-fee reform variable *Userfee* is positive and significant at the .01 level only in the second column. This result suggests that ADRs that require hospitalization increased following the reform even after controlling for changes in FDA review times. The adjusted relative risk corresponding to this coefficient indicates that the conditional mean ADR hospitalization count is 2.56 times greater in the user-fee era than prior to the reform. The coefficients for *Userfee* in the expression for total ADRs and ADR deaths were not significantly different from zero.

Because some drugs approved in 1993 to 1995 were submitted to the FDA prior to the reform, the inclusion of these drugs (pipeline NDAs) along with user-fee NDAs may create noise in the variable used to measure the effect of the regime shift. To examine the effects of user-fee drugs on reported new-drug safety (controlling for FDA review times), an alternative specification includes the variable *Feedrug*, which is equal to one only for user-fee drugs. When substituted for the regime shift variable *Userfee* in the analysis, this measure did not produce coefficients that were significantly different from zero. The coefficient for the *Feedrug* variable was .31, with a standard error equal to .51 for ADR hospitalizations. Hence, the results suggest that ADR hospitalization counts (along with ADR totals and ADR deaths) were not significantly different for user-fee drugs than for non-user-fee drugs after controlling for the length of FDA review.

Drug characteristics are also related to reported new-drug safety or ADR counts among new drugs. In particular, results show that drugs rated by the

TABLE 2  
 NEGATIVE BINOMIAL REGRESSION RESULTS: ADVERSE DRUG REACTIONS  
 FOR WHICH SUSPECT DRUGS ARE IDENTIFIED

Variable	Total	Hospital	Death
Revtim	-.01 <sup>+</sup> (.006)	-.01* (.005)	-.02** (.006)
Userfee	.08 (.42)	.94** (.37)	.25 (.41)
Priority	.55* (.24)	1.04** (.23)	1.45** (.26)
log(Utilization)	.27** (.05)	.24** (.05)	.14** (.05)
Orphan	-.73** (.31)	-.54 <sup>+</sup> (.29)	.03 (.32)
Age	.02* (.01)	.04** (.01)	.05** (.01)
Female	.01** (.006)	.02** (.005)	.01* (.005)
Cardio	-.90* (.47)	-.64 <sup>+</sup> (.38)	-.89* (.43)
CNS	.74 <sup>+</sup> (.43)	.53 (.39)	.03 (.45)
Analges	-.73 <sup>+</sup> (.43)	-.35 (.39)	-1.18** (.46)
Neopl	-.31 (.54)	-.22 (.46)	-1.00* (.50)
Infect	.11 (.40)	.41 (.37)	-1.19** (.42)
Endo	-.60 (.55)	-.37 (.45)	-1.48** (.57)
$\alpha$	1.33	1.02	1.26
Deviance	169	158	154
Deviance/(degrees of freedom)	1.37	1.29	1.25

NOTE.—Dependent variable: adverse drug reaction count per drug.  $N = 141$ . Standard errors are in parentheses. Year effects are included for all models. Degrees of freedom = 123 for all models.

<sup>+</sup> Significant at the .1 level.

\* Significant at the .05 level.

\*\* Significant at the .01 level.

FDA as therapeutically novel generate more ADRs in all ADR categories than nonnovel or standard drugs. The coefficients of Priority for Total, Hospital, and Death are all positive and significant at the .05, .01, and .01 levels, respectively. This suggests that drugs that offer therapeutical gains over existing drugs are associated with more total ADRs, more ADR hospitalizations, and more ADR deaths than drugs offering little to no therapeutic gains. The adjusted relative risks corresponding to these coefficients indicate that conditional mean count for (1) total ADRs is 1.73 times greater for priority drugs than for nonpriority drugs, (2) ADR hospitalizations is 2.83 times greater for priority drugs than for nonpriority drugs, and (3) ADR deaths is 4.26 times greater for priority drugs than for nonpriority drugs. These results suggest that priority drugs may entail greater pharmaceutical risk than nonpriority drugs. However, these results are also consistent with alternative explanations that suggest that lack of physician and patient experience with such drugs, or the conditions being treated with novel drugs, or increased drug promotion for such drugs may also contribute to higher ADR counts for novel drugs.

The coefficients for the drug utilization variables are also important determinants of ADR counts. The coefficient for log(Utilization) is positive and highly significant in each ADR category. This result shows that drugs with a higher utilization generate more ADRs for Total, Hospital, and Death.

The coefficient for Orphan that proxies for small patient populations is negative and significant in the Total and Hospital ADR categories. This suggests that drugs utilized by small patient populations generate fewer total ADRs and fewer ADR hospitalizations. The coefficient for Orphan in the third column (ADR deaths) is not significantly different from zero.

The therapeutic drug class variables show that there is some systematic variation in reported new-drug safety or ADR counts by drug class. Results show that central nervous system drugs generate more total ADRs than drugs in other drug classes. Cardiovascular drugs generate fewer total ADRs, fewer ADR hospitalizations, and fewer ADR deaths than drugs in other therapeutic classes. Several of the therapeutic class variables are significant determinants of ADR death counts. These results suggest that drugs in different therapeutic drug classes (or for different patient conditions) may pose differential safety risks for patients. More research is needed to explore these effects.

Finally, patient characteristics also help explain variation in reported new-drug safety or ADR counts. Patient age is positive and significant at the .01 level in all ADR categories, Total, Hospital, and Death. The result implies that an increase in the average age of patients who report ADRs is associated with higher ADR counts for ADR totals, ADR hospitalizations, and ADR deaths. These results are consistent with medical literature that suggests that age is a risk factor in the likelihood of experiencing an ADR. The patient gender variable, Female, is also positive and significant in each ADR category. The coefficient suggests that increases in the percentage of women who report ADRs are associated with higher ADR counts per drug in all three categories. This result implies that gender is related to ADR reporting rates or that gender is a risk factor for experiencing an ADR to a newly approved drug.

Table 3 presents the results from the estimation of (1) all ADRs, including ADRs for which a suspect drug is identified and those for which the reporter does not specifically identify the drug as the suspect drug. Even with the broader set of ADRs, most coefficients in Table 3 have the same sign and significance as those presented in Table 2. The key results are similar. Reductions in new-drug review times increase both ADR hospitalizations and ADR deaths. The user-fee reform is associated with a positive and significant increase in ADR hospitalizations. However, the result disappears when the analysis considers only user-fee drugs instead of all drugs approved after the reform.<sup>33</sup> Priority drugs generate more total ADRs, more ADR hospitalizations, and more ADR deaths. The only difference between the results in Tables 2 and 3 is the effect of the age and gender variables. While Female was positive and significant in all three ADR categories in Table 2, it is significant only for ADR hospitalizations in Table 3. While Age was positive

<sup>33</sup> The coefficient for the Feedrug variable in the expression for ADR hospitalizations is .34, with a standard error of .50.

TABLE 3  
NEGATIVE BINOMIAL REGRESSION RESULTS: ALL ADVERSE DRUG REACTIONS

Variable	Total	Hospital	Death
Revtim	-.007 (.005)	-.01* (.005)	-.015** (.005)
Userfee	.30 (.39)	1.18** (.38)	.33 (.39)
Priority	.53* (.23)	1.02** (.24)	1.36** (.25)
Log(Utilization)	.30** (.05)	.25** (.05)	.15** (.05)
Orphan	-.72* (.31)	-.61* (.30)	.13 (.32)
Age	.01 (.01)	.05** (.01)	.06** (.01)
Female	.006 (.005)	.02** (.005)	.008 (.005)
Cardio	-.47 (.45)	-.62 (.39)	-1.05* (.44)
CNS	.78* (.41)	.35 (.41)	-.10 (.45)
Analges	-.55 (.41)	-.63 (.40)	-1.48** (.46)
Neopl	.08 (.52)	-.17 (.47)	-1.20* (.50)
Infect	.40 (.39)	.53 (.38)	-1.06** (.42)
Endo	-.18 (.53)	-.67 (.47)	-1.67** (.56)
$\alpha$	1.23	1.11	1.25
Deviance	168	160	156
Deviance/(degrees of freedom)	1.36	1.30	1.27

NOTE.—Dependent variable: adverse drug reaction count per drug.  $N = 141$ . Year effects are included for all models. Degrees of freedom = 123 for all models.

\* Significant at the .05 level.

\*\* Significant at the .01 level.

and significant in all three ADR categories in Table 2, it is significant only for ADR hospitalizations and ADR deaths in Table 3.

An alternative specification considered whether there were any interaction effects between therapeutic novelty, Priority, and the two regulatory variables, Userfee and Revtim. This specification examines whether either of the regulatory variables had different effects among therapeutically novel drugs and less novel drugs. Two interaction variables were included in each of the six ADR estimations presented in Tables 2 and 3. The results show that none of the coefficients for these interaction terms was significantly different from zero.

Another specification examined whether the effect of a drug's review time on its ADR count differed in the pre- and post-user-fee periods. To examine this, the Userfee dummy variable was interacted with the review time variable Revtim. The coefficient for this interaction variable was not significantly different from zero in any ADR expression. However, when the variable Feedrug, a dummy variable equal to one for user-fee drugs, was interacted with Revtim, this interaction term was negative and significant in the expressions for total ADRs and ADR hospitalizations.<sup>34</sup> This suggests that reductions in the review times for user-fee drugs had a greater effect on ADR hospitalizations (and total ADRs) than for non-user-fee drugs. The effect of

<sup>34</sup> The coefficient (standard error) for Feedrug  $\times$  Revtim is  $-.07$  (.04) for total ADRs,  $-.08$  (.03) for ADR hospitalizations, and  $.004$  (.04) for ADR deaths.

review time on ADR deaths did not differ among user-fee and non-user-fee drugs.

## VII. CONCLUSIONS

There has been little empirical examination of the effect of pharmaceutical policies or FDA decisions on new-drug safety. One reason is the lack of data to measure new-drug safety. This paper uses adverse drug reaction data for all new drugs approved between 1990 and 1995 to examine whether faster new-drug reviews have altered reported new-drug safety. This paper hypothesizes that faster new-drug reviews may be associated with increases in reported pharmaceutical risks. The reason is that regulators may be assuming more risk to help accelerate new-drug review and approval.

The results show that reductions in new-drug review times are associated with increases in ADRs that result in hospitalization and in death. Estimates suggest that a 1-month reduction in a drug's review time is associated with a 1 percent increase in expected reports of ADR hospitalizations and a 2 percent increase in expected reports of ADR deaths. At the mean, a 12-month reduction in a drug's FDA review time is associated on average with an increase of 10.92 ADR hospitalizations and 7.68 ADR deaths per drug. These results suggest that there are some adverse consequences associated with faster new-drug reviews.

This evidence, however, does not necessarily imply that the FDA policy changes leading to faster new-drug reviews have made consumers worse off. Faster new-drug reviews also create health benefits for patients who gain quicker access to life-saving drugs. More information is needed about the health benefits of new drugs relative to existing treatments. With such information, policy makers can determine whether the expected health benefits associated with faster reviews exceed the expected health costs associated with adverse drug reactions. This kind of evaluation should help to bring new-drug safety back into the policy debate. It will also provide a more rational basis for making pharmaceutical policy reforms.

Alternatively, policy makers can search for ways to reduce the expected costs of faster new-drug reviews without eliminating the health benefits of quicker patient access to new drugs. Strategies to accomplish this objective might include improvements in both the monitoring and the communication of new-drug risks to physicians and patients. Since new drugs are being approved faster and since faster reviews are associated with more adverse drug effects, there is a greater rationale to ensure the timely completion of phase IV studies (postmarketing safety studies) by firms and, perhaps, move toward a more active surveillance program for new drugs when they are first

marketed.<sup>35</sup> Faster detection and communication of new-drug risk information that is revealed in the marketplace can help to reduce future adverse drug reactions.

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<sup>35</sup> Improved surveillance of recent drug approvals, in particular, is more likely to reveal new risk information than improvements in the surveillance of drugs that have been on the market for many years. One exception is adverse drug reactions that result from long-term use.

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