PDUFA AND INITIAL U.S. DRUG LAUNCHES

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In the 1970s and 1980s, many pharmaceutical firms launched new drugs abroad prior to gaining U.S. approval. Consequently, U.S. patients often faced delays in accessing important new medicines. High regulatory barriers to entry, such as a stringent regulation and a lengthy drug review process, contributed to this problem. This Article examines the impact of the Prescription Drug User Fee Act (PDUFA), and subsequent increases in the speed of FDA review, on the likelihood of initial U.S. drug launches. These factors are hypothesized to lower regulatory barriers to entry in the U.S. pharmaceutical market. The results show that increased drug review speed and other reform-related changes, such as those affecting drug development times or the probability of approval, have increased the likelihood of initial U.S. drug launches. Overall, the results suggest that PDUFA did improve U.S. patients' access to new medicines by encouraging more first drug launches in the U.S. market.

I. Introduction

In the global pharmaceutical market, patients' access to new medicines often depends on the drug launch strategies adopted by firms. By

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all accounts, the United States should be an attractive place to first launch innovative new drug therapies, particularly given the size of the U.S. market and the absence of price controls. Yet, in the 1970s and the 1980s, many new drugs were first launched abroad prior to U.S. approval.[1] Consequently, U.S. patients' access to innovative new medicines lagged behind other countries.[2] Many attributed the stringency and length of the Food and Drug Administration's (FDA) drug approval process as the source of the problem.[3] In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA) to help accelerate FDA drug reviews and improve U.S. patients' access to new drugs.[4] Under PDUFA, the speed of FDA review has increased substantially.[5] Changes in regulation may also impact firm strategies about where to first launch new drugs. Given that PDUFA was introduced to help improve drug access, it is important to examine the effects of these changes on initial U.S. drug launches. In particular, to what extent have faster FDA reviews and PDUFA led firms to target more first drug launches in the United States?

First drug launches are particularly interesting to study because they are a direct measure of U.S. patient access to innovative new drugs relative to other countries. Even if new drugs continue to be launched abroad first, reducing the lag time between the first global drug launch and the date of FDA approval will improve patients' access to new drugs. Given the impact that innovative drugs can have on public health, the stakes for improving drug access are high.[6] For this reason, it is important to understand how changes in regulatory policy and the speed of drug review may affect the likelihood of an initial U.S. drug launch.

A recent study reports that first drug launches among new chemical entities in the United States increased from 44 during the 1982–1992 period to 156 in the 1993–2003 period, while first drug launches in the

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1.   *See* William M. Wardell, *The Drug Lag Revisited: Comparison by Therapeutic Area of Patterns of Drugs Marketed in the United States and Great Britain from 1972 Through 1976*, 24 Clinical Pharmacology & Therapeutics 499 (1978).

2.   *See* Kenneth I. Kaitin et al., *The Drug Lag: An Update of New Drug Introductions in the United States and in the United Kingdom, 1977 Through 1987*, 46 Clinical Pharmacology & Therapeutics 121–38 (1989). Their analysis found that the United States lagged behind the United Kingdom in the availability of new drugs in every therapeutic category. The greatest lags were observed for respiratory (5.1 years), cardiovascular (3.2 years), central nervous system (3.2 years), and anticancer (2.9 years) drugs. *Id.*

3.   *See* Ronald W. Hasen, *FDA Regulation of the Pharmaceutical Industry*, *in* Hazardous to Our Health 19 (Robert Higgs, ed., 1995); Kenneth I. Kaitin & Jeffrey S. Brown, *A Drug Lag Update*, 29 Drug Info. J. 361, 362 (1995).

4.   Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491 (codified as amended at 21 U.S.C. § 379).

5.   *See infra* Part III.

6.   Frank R. Lichtenberg, *Pharmaceutical Knowledge-Capital Accumulation and Longevity*, *in* Measuring Capital in the New Economy 237–69 (C. Corrado, J. Haltiwanger & D. Sichel eds., 2005).

European Union declined from 260 to 151 during the same time frame.[7] Although the overall number of first drug launches are roughly similar in the United States and the European Union from 1993–2003, the shifts noted are particularly striking because the European Union also undertook efforts in the 1990s to help facilitate drug access and reduce regulatory barriers to drug launch through global harmonization.[8] These trends lead to questions about PDUFA's impact on firms' drug launch strategies.

Less time spent in the FDA review process can shorten or eliminate U.S. launch lags, holding all else equal. In addition, quicker FDA reviews effectively lower regulatory barriers to the U.S. market. Faster drug reviews allow firms to enjoy longer periods of market exclusivity, which increases the expected profitability of new drugs.[9] Consequently, higher expected profits for U.S. drug launches may lead firms to target more drugs for first launch in the United States. However, liability concerns and other competitive market considerations[10] may create disincentives for initial U.S. drug launches for some drugs even though regulatory barriers, namely lengthy drug review times, have fallen. The impact of this regulatory change, relative to other possible determinants of initial U.S. drug launches, is not clear. Even with faster drug review times, firms may continue to pursue initial drug launches abroad rather than in the United States.

This Article empirically examines the impact of PDUFA and the speed of FDA review on the likelihood of initial U.S. drug launches among new drugs approved from 1990 to 2001. This study differs from previous studies of the determinants of global drug launches by focusing only on the determinants of initial U.S. drug launches and by considering the impact of PDUFA and faster drug reviews along with other important determinants.[11] The primary result of this study is that both faster FDA reviews and other PDUFA-related changes have increased the probability of initial U.S. drug launches over time. The results suggest

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7.   *See* Henry Grabowski & Y. Richard Wang, *The Quantity and Quality of Worldwide New Drug Introductions, 1982–2003*, 25 Health Aff. 452–60 (2006).

8.   *See* Elaine M. Healy & Kenneth I. Kaitin, *The European Agency for the Evaluation of Medicinal Products' Centralized Procedure for Product Approval: Current Status*, 33 Drug Info. J. 969 (1999). The European Agency for the Evaluation of Medicinal Products (EMEA) implemented a centralized procedure for drug approval in the European Union and created performance goals for the timely review and approval of new products. *Id.*

9.   This occurs since firms typically patent new drugs during the development process and prior to FDA submission. Consequently, regulatory delay reduces the effective patent lives of drugs. *See* Martin M. Eisman & William M. Wardell, *The Decline in Effective Patent Life of New Drugs*, Res. Mgmt., Jan. 1981, at 18–21.

10.   These other considerations include the number of competing drugs in a therapeutic class.

11.   These determinants include several firm and drug characteristics.

that over this period, declining FDA review times have led to a 14 percent increase in the likelihood of initial U.S. drug launches. Other PDUFA-related reforms, such as those reducing drug development times or increasing the probability of approval, have also increased the likelihood initial U.S. drug launches 31 percent by the end of PDUFA I and 27 percent by the end of PDUFA II. Overall, these results suggest that PDUFA I and PDUFA II were successful in improving drug access for U.S. patients by raising the probability of initial U.S. drug launches.

Part II of this Article provides some background on FDA regulation of the drug industry and on the regulatory barriers facing pharmaceutical firms. Part III describes PDUFA and its impact and discusses the factors that may influence firms' initial drug launch strategies. Part IV presents the data and methods that are used in the analysis. Part V reports the study results; and Part VI presents some concluding remarks.

II. FDA Regulation, Entry Barriers, and Drug Access

The process of bringing new innovative pharmaceuticals to the U.S. market is characterized by high entry barriers. FDA regulation plays an important role in creating and maintaining these entry barriers. Firms must obtain FDA approval before marketing a new drug in the United States. The process of gaining approval is both time consuming and costly.[12] FDA approval requires clinical evidence of a drug's safety and efficacy.[13] There is a multi-stage process used to gather the evidence. It begins with pre-clinical laboratory and animal studies to ensure that drugs are safe for humans. Next, firms must complete three phases of clinical testing in human subjects to learn more about a drug's risks and benefits and determine whether the drug is effective for its intended use.[14] On average, clinical trials typically involve between 600 and 3000 human subjects and can take between two to ten years to complete.[15] Once completed, the firm submits a new drug application to the FDA for review, which consists of all the raw data and clinical test results.[16]

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12.   Studies suggest that it takes eight to twelve years to get a drug from the lab to the market and costs approximately $802 million (in 2001 dollars) per FDA-approved drug. Joseph A. DiMasi, Ronald W. Hansen, & Harry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. Health Econ. 151, 166 (2003).

13.   Federal Food, Drug, and Cosmetic Act § 505, 21 U.S.C. § 355 (2008).

14.   *See* 21 C.F.R. § 312.21 (2008).

15.   Committee on the Assessment of the US Drug Safety System, The Future of Drug Safety: Promoting and Protecting the Health of the Public 36, 37 (Alina Baciu et al. eds., 2007).

16.   21 U.S.C. § 355(b)(1); 21 C.F.R. § 314.50.

   In addition to the costs of clinical testing, delays in the FDA's review process also contribute to the high entry barriers facing firms. Long FDA reviews delay the realization of monopoly drug profits for firms because new drug compounds are typically patented prior to FDA review.[17] Consequently, long regulatory reviews for patented drug products not only delay market launch but can also reduce the period of market exclusivity remaining after FDA approval. Regulatory delay was particularly severe in the 1980s and early 1990s when the average review time for a new FDA-approved drug was about 31 months.[18] When one considers that a new blockbuster drug can generate sales of more than $1 billion per year,[19] a 31-month reduction in a patented drug's period of exclusivity represents a substantial cost to firms and a significant regulatory barrier to entry.

   Increases in regulatory delays have hindered drug access for U.S. patients. Previous research found that stringent FDA regulation contributed to U.S. drug launch lags in the late 1960s and 1970s.[20] Policymakers' concern about U.S. launch lags continued into the 1970s and 1980s as regulatory delay increased.[21] In general, positive U.S. launch lags indicate that drugs were often launched abroad prior to FDA approval.[22] Research found that the United Kingdom, a country with comparable regulation, led the United States in the introduction of new drugs by 27.7 months.[23] However, legislative efforts to combat the effects of regulatory delay in 1984 focused instead on restoring effective patent lives for new drug products.[24] The Waxman-Hatch Act of 1984 addressed some of the

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   17.   Eisman & Wardell, *supra* note 9.
   18.   *See* Mary K. Olson, *Managing Delegation with User Fees: Reducing Delay in New Drug Review*, 29 J. HEALTH POL. POL'Y & L. 397, 406 (2004).
   19.   *See* Michael S. Rosen, *New Data on Blockbuster Drugs: A Clear Measure of Global Pharma Success*, MIDWESTBUSINESS.COM, Aug. 11, 2008, http://www.midwestbusiness.com/news/viewnews.asp?newsletterID=19369.
   20.   *See* Sam Peltzman, *An Evaluation of Consumer Protection Legislation: 1962 Drug Amendments*, 81 J. POL. ECON. 1049–91 (1973). *See also* Henry G. Grabowski et al., *Estimating the Effects of Regulation on Innovation: An International Comparative Analysis of the Pharmaceutical Industry*, 21 J.L. & ECON. 133 (1978).
   21.   In 1979, Congress held hearings on the drug lag problem. *See Hearings on the FDA's Drug Approval Process Before the H. Subcommittee on Science, Research, and Technology*, 96th Cong. (1979).
   22.   Kenneth I. Kaitin et. al., *The New Drug Approvals of 1987, 1988, and 1989: Trends in Drug Development*, 31 J. CLINICAL PHARMACOLOGY 116–22 (1991), [hereinafter Kaitin et al., *The New Drug Approvals of 1987, 1988, and 1989*]; Kenneth I. Kaitin et. al., *The New Drug Approvals of 1990, 1991, and 1992: Trends in Drug Development*, 34 J. CLINICAL PHARMACOLOGY 120–27 (1994) [hereinafter Kaitin et al., *The New Drug Approvals of 1990, 1991, and 1992*].
   23.   *See* Kaitin et al., *supra* note 2, at 126.
   24.   *See* Drug Price Competition and Patent Term Restoration (Waxman-Hatch) Act of 1984, 35 U.S.C.A. § 156 (West 2009) (allowing firms to extend the patent lives of brand-name drugs for up to five years to offset delay in the FDA review process as long as the total patent

adverse effects of delay on firms, but did little to reduce the actual causes of delay in the review process. Hence, delays persisted and most drugs continued to be launched abroad prior to FDA approval.[25]

Things began to change in the 1990s with the advent of the AIDS crisis. AIDS brought new political pressure and urgency for addressing the problem of drug lag and drug access for AIDS patients, and AIDS activists aggressively lobbied the FDA to speed up the review of new AIDS drugs.[26] The FDA responded to this pressure by introducing new programs to accelerate the approval of new AIDS drugs.[27] Unfortunately, these programs did not extend more broadly, as regulatory delays in the review of other drugs persisted. The success that the FDA had in speeding up the approval of AIDS drugs brought new pressure from other patient groups and the drug industry to accelerate the approval of all drugs.[28]

III. The Prescription Drug User Fee Act

The Prescription Drug User Fee Act (PDUFA) of 1992 was passed to help combat regulatory delay in the review process and improve drug access.[29] The legislation required firms to pay fees to the FDA to help cover the cost of drug review.[30] The fee revenues, which were designed to supplement existing agency appropriations, were then used to hire more staff and build infrastructure to help speed reviews.[31] In return, the agency promised to accelerate drug reviews according to a series of deadlines established in the legislation and to report annually to Congress on the status of meeting those deadlines.[32] The agency was to review and act on 90 percent of priority drug applications within six

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life with the extension does not exceed 14 years); *see also* Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 Mich. Telecomm. & Tech. L. Rev. 345, 356–59 (2007).

25.   *See* Kaitin et al., *The New Drug Approvals of 1987, 1988, and 1989*, *supra* note 22, *at* 116–22; Kaitin et al., *The New Drug Approvals of 1990, 1991, and 1992*, *supra* note 22, *at* 120–27.

26.   *See* Steven Epstein, Impure Science: AIDS, Activism, and the Politics of Knowledge (Univ. of Cal. Press 1996).

27.   *See* Sheila R. Shulman & Jeffrey S. Brown, *The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked?*, 50 Food & Drug L.J. 503 (1995).

28.   *See* Mary K. Olson, *Pharmaceutical Policy Change and the Safety of New Drugs*, 45 J.L. & Econ. 615 (2002).

29.   Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491 (codified at 21 U.S.C. §§ 379g, 379h) [hereinafter PDUFA I].

30.   *Id.*

31.   *See id.*

32.   *Id.*

months and 90 percent of standard drug applications within 12 months.[33] The agency was also supposed to eliminate the backlog of un-reviewed applications within 24 months of the establishment of the user fee program.[34] PDUFA had a five-year fixed term so that its stakeholders[35] could revisit the program and reassess the agency's performance prior to its renewal.[36] Since new legislation was required to reauthorize PDUFA, this allowed industry to give feedback on the program and on the agency's performance. Under this arrangement, FDA would have to show that they were meeting the review deadlines to justify program renewal.[37]

At the end of its first term, the user fee program was viewed by its stakeholders as a success.[38] The FDA had gained more resources for its drug review division and firms had faster drug reviews.[39] Data from PDUFA performance reports to Congress showed that the agency was quite successful in meeting the drug review deadlines.[40] Thus, Congress decided to build on the program's success with additional reforms of the drug review process. The 1997 Food and Drug Administration Modernization Act (PDUFA II) renewed the user fee program for another five years and increased user fee revenue targets for the FDA.[41] The program continued its focus on decreasing drug review times by lowering the review deadline for standard rated drugs from 12 months to 10 months.[42] However, PDUFA II also introduced extra performance metrics designed to reduce the period of drug development and clinical testing, which had changed little over time. A new series of procedural timetables were established to schedule meetings requested by industry, to resolve disputes

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33.   See Letter from David A. Kessler, M.D., Comm. of Food and Drugs, to Rep. John D. Dingell & Rep. Norman Lent (Sept. 14, 1992), 138 Cong. Rec. H9099–100 (daily ed. Sept. 22, 1992).

34.   *Id.*

35.   Stakeholders included doctors, patients, disease-based interest groups, and consumer safety advocates.

36.   *See* Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 Va. L. Rev. 1753, 1796 (1996).

37.   Olson, *supra* note 18, at 426.

38.   *See* Anonymous, *Prospects for PDUFA*, Pharm. Executive, Dec. 1996, at 59; Tufts Ctr. for the Study of Drug Development, Impact Report: User Fees Credited with 51% Drop in Average Approval Times Since 1993 (2000), http://csdd.tufts.edu/_documents/www/Doc_309_18_892.pdf.

39.   *See* Figure 1; *see also* Olson, *supra* note 18, at 406.

40.   U.S. Food & Drug Admin., Prescription Drug User Fee Act Reports and Plans, http://www.fda.gov/oc/pdufa/reports.html#performance (last visited Apr. 13, 2009) (PDUFA annual performance reports).

41.   The Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 103, 111 Stat. 2296 (codified as amended in scattered sections of 21 U.S.C.) [hereinafter FDAMA].

42.   *See* 143 Cong. Rec. S12,653 (1997) (Letter from Donna E. Shalala, Sec'y of DHHS, to Sen. James M. Jeffords (Nov. 12, 1997)); 143 Cong. Rec. H10,886 (1997) (Letter from Donna E. Shalala, Sec'y of DHHS, to Rep. Thomas J. Bliley, Jr. (Nov. 13, 1997)).

with industry, to respond to industry questions about study protocols, and to develop agency guidelines for the industry.[43] In addition, market incentives were introduced for firms to conduct pediatric studies ("pediatric exclusivity") and a provision was included to allow FDA to accept a single well-controlled clinical study under certain conditions.[44] Since clinical studies can take several years to complete,[45] this last provision in particular had great potential to reduce drug development times.

At the end of the PDUFA II's term in 2002, review time reductions were observed in both the approval phase and the clinical phases of drug development. Among the most innovative drugs, new molecular entities, review times had fallen from an average of 31 months in 1990–1992 to an average of 17 months in 1999–2001.[46] The average clinical testing phase among such drugs also declined from a high of 7.2 years in 1993–1995 to 5.5 years in 1999–2001.[47] It is also interesting that, although PDUFA performance reports focused on agency actions and response times, the probability of product approval also increased from 66 percent prior to PDUFA to 80 percent in the post PDUFA era.[48] While no one disputed the fact that review speed had increased substantially under PDUFA, concerns about drug safety and industry influence in the review process created some conflict over the program's renewal.[49] However, these concerns did not derail political support for the program among its stakeholders.

PDUFA III was enacted as part of the Public Health Security and Bioterrorism Preparedness and Response Act (2002).[50] Drug safety concerns were addressed by allowing a small portion of user fee funds to be

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43.   *See* 143 Cong. Rec. S12,653 (1997); 143 Cong. Rec. H10,886 (1997).

44.   *See* 143 Cong. Rec. S12,653 (1997); 143 Cong. Rec. H10,886. (1997); *see also* FDAMA § 115(a), 111 Stat. at 2313. This provision introduced the concept that establishing efficacy does not always require two or more trials. *Id.*

45.   *See* DiMasi, Hansen, & Grabowski, *supra* note 12, at 101–42.

46.   Kenneth I. Kaitin & Catherine Cairns, *The New Drug Approvals of 1999, 2000, and 2001: Drug Development Trends a Decade After the Passage of the Prescription Drug User Fee Act of 1992*, 37 Drug Info. J. 357 (2003).

47.   *Id.*

48.   U.S. Food and Drug Admin., FY 2000 Performance Financial Report for the Prescription Drug User Fee Act of 1992 as Authorized and Amended by the Food and Drug Modernization Act of 1997 4 (2000), http://www.fda.gov/ope/pdufa/report2000/PDUFA2000.pdf.

49.   *See* David Willman, *How a New Policy Led to Seven Deadly Drugs*, L.A. Times, Dec. 20, 2000, at A1; *see also* U.S. Food & Drug Administration, Executive Summary of PDUFA FDA and Stakeholders Meeting (2000), http://www.fda.gov/oc/pdufa2/meeting2000/meeting2000summ.html.

50.   Public Health Security and Bioterrorism Preparedness and Response Act of 2002, tit. 5, Pub. L. No. 107-188, 116 Stat. 594 (2002).

used for a limited range of post-marketing drug safety monitoring.[51] No reforms were introduced to address the drug industry's influence in the FDA process or in PDUFA renegotiations. PDUFA III maintained the deadlines for drug review times and the timetables for sponsor meetings, and it further expanded the FDA's interactions and communication with firms during both the pre-submission clinical testing period and the review cycle.[52] The rationale for these changes was that enhanced communication between regulators and firms during these periods could further reduce delays in the drug development and product review phases.[53]

A. *PDUFA's Effect on Entry Barriers*

To understand the impact of PDUFA on firms, it is useful to consider how these regulatory changes affected barriers to entry in the U.S. drug market. On one hand, PDUFA created new fees for firms to market new drugs in the United States. In 2007, the submission fee for a new drug application with clinical evidence was $896,200.[54] On the other hand, user fees reduced delay in the development process and expedited review times so that firms could bring drugs to market earlier in their patent lives, thus gaining longer periods of market exclusivity. An extra month or two of effective patent life gained by reducing development or review times translates into tens of millions of dollars for firms.[55] Given that PDUFA resulted in a 50 percent increase in review speed since the 1990–1992 period,[56] the return to firms is likely to be even greater. This suggests that the gains to firms from reducing delay in drug development and review are likely to far exceed the amount of the user fee. One study suggests that PDUFA raised the private surplus of producers by $7 to $11 billion.[57] Hence, the net impact of PDUFA and faster drug review times is likely to represent lower entry barriers for firms.

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51.   User fee funding could be used for post-marketing drug safety monitoring of drugs approved after 2002 in their first 2 to 3 years on the market. User fee funds could not, however, be used for the safety monitoring for drugs approved prior to 2002 or for long-term safety monitoring. *See* 148 CONG. REC. S5,195–204 (2002) (Letter from Tommy S. Thompson, Sec'y of DHHS, to Sen. Edward M. Kennedy (June 6, 2002)).

52.   *See id.*; U.S. FOOD & DRUG ADMIN., PDUFA III FIVE YEAR PLAN 2003 (2003), http://www.fda.gov/oc/pdufa3/2003plan/default.htm.

53.   U.S. FOOD & DRUG ADMIN., *supra* note 52.

54.   Some small firms and some orphan drugs may receive exemptions. SUSAN THAUL, PRESCRIPTION DRUG USER FREE ACT (PDUFA): BACKGROUND AND ISSUES FOR PDUFA IV REAUTHORIZATION, CRS REPORT FOR CONGRESS 11 (2007).

55.   Tomas Philipson et al., *Cost-Benefit Analysis of the FDA: The Case of the Prescription Drug User Fee Acts,* 92 J. PUB. ECON. 1306, 1308 (2008).

56.   *See supra* note 38.

57.   Philipson et al., *supra* note 55, at 1308.

Smaller entry barriers can lead to more first drug launches in the United States for two reasons. First, drugs in the pipeline will move through more quickly, holding all else equal. Second, more drugs may be targeted for the U.S. market because of the reduction in entry barriers. Lower entry barriers raise the expected profitability of an initial U.S. drug launch and may consequently lead more firms to shift their initial drug launch strategies from foreign countries to the U.S. market. In both instances, drug access for U.S. patients should improve.

However, data suggest that there has been a decline in drug and bio-logic submissions to the FDA in the ten years following PDUFA. For instance, new molecular entity submissions declined from 44 in 1996 and 44 in 1997 to 22 in 2002 and 26 in 2003.[58] New molecular entity approvals declined from 53 in 1996 and 39 in 1997 to 17 in 2002 and 21 in 2003.[59] While these trends may signal declining innovation and other hurdles in the road to drug discovery, they also raise questions about the extent to which PDUFA impacted drug access and U.S. drug launches. Although U.S. regulatory barriers have fallen, there may continue to be benefits associated with a first launch abroad for some drugs. For instance, seeking drug approval where a firm's cost of entry is lower can provide the firm with revenue to help pay for the costs of the FDA's drug approval process. Also, first launches outside the U.S. may allow firms to gain more information and data about a drug's effects under conditions of normal use, which may help support its case for FDA approval. Beyond regulatory factors, other important considerations may influence the likelihood of initial U.S. drug launches.

B. *Other Drug Launch Determinants*

Previous research shows that drug launch decisions in global pharmaceutical markets are influenced by firm and market characteristics as well as price regulation.[60] A firm's domestic status and past experience

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58.   U.S. Food & Drug Admin., Innovation Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products 2 (2004), http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf.

59.   U.S. Food & Drug Admin., FDA Facts: The Center for Drug Evaluation and Research, http://www.fda.gov/bbs/topics/NEWS/2006/NEW01342/Fact_Sheet_CDER.pdf. Total approvals are the sum of priority and standard NMEs.

60.   *See* Patricia Danzon et al., *The Impact of Price Regulation on the Launch Delay of New Drugs—Evidence from Twenty-Five Major Markets in 1990s*, 14 Health Econ. 269, 271 (2005); Margaret K. Kyle, *Pharmaceutical Price Controls and Entry Strategies*, 89 Rev. Econ. & Stat. 88 (2007) [hereinafter Kyle, *Pharmaceutical Price Controls*]; Margaret K. Kyle, *The Role of Firm Characteristics in Pharmaceutical Product Launches*, 37 RAND J. Econ. 602, 614 (2006) [hereinafter Kyle, *Role of Firm Characteristics*]; Jean O. Lanjow, Patents, Price Controls and Access to New Drugs: How Policy Affects Global Market Entry 6–7 (Ctr. for Global Dev., Working Paper No. 61, 2005).

with regulators, in particular, increase the likelihood of a drug launch in a given country.[61] Domestic status could be associated with more knowledge about local markets or be indicative of lower regulatory barriers which produce a home-court advantage for these firms. Firms which have past experience with a country's regulatory process may face lower regulatory barriers than firms without such experience.[62] Other research shows that regulatory policies that restrict drug prices also influence drug launch strategies. Several studies find that firms delay drug launches in countries that have price controls.[63] While this research characterizes the determinants of a drug launch in general, it does not examine their influence on initial drug launch decisions. These studies also do not examine the impact of the regulatory changes associated with PDUFA on first drug launches in the United States.

The Orphan Drug Act (1983) is another important policy that may have affected the likelihood of initial U.S. launches of orphan drug products.[64] Orphan drugs are drugs intended for diseases that affect fewer than 200,000 patients. The Orphan Drug Act strengthened incentives for firms to develop and market drugs to treat rare diseases.[65] This Act included incentives for research and development in the form of a targeted tax credit and a seven-year market exclusivity provision once drugs were approved.[66] While the tax credit lowers the cost of developing new orphan drugs, the exclusivity provision increases the expected profits of marketing orphan drugs. Together, these incentives are expected to lead to an increase in the number of orphan drugs developed and first launched in the United States.

Given the impact that new innovative drugs can have on public health, all countries may share an interest in reducing launch lags and improving drug access for their citizens. Efforts toward global harmonization occurred in the mid-1990s, concurrent with PDUFA. One example of these harmonization efforts was the establishment of the European Agency for the Evaluation of Medicinal Products (EMEA) in 1993. This agency was designed to encourage faster drug launches and improved drug access in European Union.[67] Since these efforts may lower regulatory barriers for firms who want to introduce drugs in the European

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61.   *See* Kyle, *Role of Firm Characteristics*, *supra* note 60.

62.   Firms having prior experience with the regulatory process in a country will have more information and familiarity with that process.

63.   *See* Danzon et al., *supra* note 60, at 271; Kyle, *Pharmaceutical Price Controls*, *supra* note 60; Lanjow, *supra* note 60.

64.   Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983).

65.   *See* Sheila R. Shulman & Michael Manocchia, *The U.S. Orphan Drug Program: 1983–1995*, 12 PharmacoEconomics 312, 314–15 (1997).

66.   Orphan Drug Act § 527.

67.   *See* Healy & Kaitin, *supra* note 8, at 970.

Union, they may affect firms' initial drug launch strategies, and therefore U.S. drug access.[68] Overall, whether PDUFA and increased review speed improved U.S. patient access to new drugs relative to other countries remains an important empirical question. If firms target initial drug launches abroad prior to U.S. approval as they have done in the past, launch lags will persist. However, if PDUFA creates incentives for firms to seek more initial drug launches in the United States (because entry barriers have fallen relative to other countries), then patient access to innovative new drugs will be improved.

VI. Methods and Data

This empirical analysis examines the impact of PDUFA, drug review times, and other factors on the probability of initial U.S. drug launch. It considers all new chemical entities (NCE) approved by the FDA in 1990 to 2001. This period is interesting to study because it includes drugs submitted both before and after the introduction of PDUFA I and PDUFA II so that the impact of a changing regulatory environment on the likelihood of initial U.S. drug launches can be studied. Drugs which were never approved in the United States are excluded from this study.

The model below characterizes the factors that may be associated with first drug launch in the United States. Conditional upon FDA approval, the drug is either initially launched in the United States ($Y=1$) or it was initially launched abroad ($Y=0$). The model below estimates the probability of first drug launch in the United States ($Y=1$) as a logit.[69]

$$P(Y=1) = e^{\beta'x} / (1+e^{\beta'x})$$

The factors that influence this probability contained in the x-vector include regulatory factors, review time, PDUFA I, and PDUFA II, drug characteristics, and firm characteristics.

$$P(Y=1) = \alpha + \beta_1 \, review \, time_i + \beta_2 \, PDUFA \, I_i + \beta_3 \, PDUFA \, II_i$$

$$+ \beta_4 \, novel_i + \beta_5 \, orphan_i + \beta_{6j} \, drug \, class_{j,i}$$

$$+ \beta_7 \, U.S.firm_i + \beta_8 \, past \, approval_i + \beta_9 \, trend_i + \varepsilon_i \qquad (1)$$

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68.   Firms could be more likely to target the European Union, not the United States, for first launch, given the simplified procedures under harmonization.

69.   When there is a dichotomous dependent variable as above, a logit model is appropriate for modeling how the probability p of an event is affected by one or more explanatory variables. *See* William H. Greene, Econometric Analysis 871–947 (Prentice Hall, 3rd ed. 1997). Logistic regression is a statistical regression model for binary dependent variables. It can be considered as a generalized linear model that utilizes the logit as its link function, and has binomially distributed errors.

Three variables are included to examine the impact of regulatory factors on the likelihood of initial U.S. drug launch. The variable *review time* is defined as the time (in months) between the date of submission of a new drug application and the date of FDA approval.[70] The coefficient for this variable, β_i, will measure the extent to which faster drug reviews are associated with increased probability of initial U.S. drug launches. Shorter review times imply smaller regulatory entry barriers so that the predicted sign for this coefficient is negative. Two time-indexed variables, *PDUFA I* and *PDUFA II*, are included to control for the impact of additional reform-related factors in the PDUFA era, besides review speed, on the decision to first launch in the United States. The PDUFA era is divided into two periods to measure the separate impact of PDUFA II relative to PDUFA I. Unlike PDUFA I, PDUFA II included several provisions designed to help accelerate the process of developing new drug submissions. The variable *PDUFA I* is equal to 1 for drug submissions in the first fiscal year of the respective PDUFA program (actually, eleven months, 10/29/92 to 9/30/93), 2 for drug submissions in the second year of the program (10/1/93 to 9/30/94), 3 for drug submissions in the third year of the program, etcetera, up to and including 5 for drug submissions received in the fifth year of the program. To continue with time indexing in the PDUFA era, *PDUFA II* is defined as 6 for drug submissions in the first year of PDUFA II (10/01/97 to 9/30/98), 7 for drug submissions in the second year of PDUFA II (10/1/98 to 9/30/99), 8 for drug submissions in the third year of PDUFA II (10/1/99 to 9/30/00), 9 for drug submissions in the fourth year of PDUFA II (10/1/00 to 9/30/01), and 10 for drug submissions in the fifth year (10/1/01 to the end of the sample period 12/31/01).

Several drug characteristics are included. The first variable, *novel*, is defined by a drug's therapeutic novelty rating assigned by the FDA and is a proxy for drug quality. This variable equals 1 for drugs that are given a priority rating of P (indicating novelty) by the FDA and 0 for standard-rated drugs (indicating little to no therapeutic gain).[71] Priority rated drugs are deemed by FDA to offer therapeutic advantages over existing remedies. As such, they may be expected to generate above-average profits, which could lead firms to target these drugs for first drug launch in the United States. However, because these drugs are novel, there may also

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70. 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.

71. Prior to 1992, priority-rated drugs includes those rated *A*, *AA*, or *B*. Drugs given a *C* rating (prior to 1992) indicate little to no therapeutic gain. K.I. Kaitin, *Pharmaceutical Innovation in an Era of Reform*, 2 Clinical J. Therapeutics 730–34 (1995). More information about the FDA's current review classifications can be found at U.S. Food & Drug Admin., What Do Chemical Type and Review Classification Code Stand For?, (Apr. 17, 2007), http://www.fda.gov/cder/drugsatfda/faq.htm#chemtype_reviewclass.

be greater uncertainty surrounding their approval prospects and use. Such uncertainty could reduce the probability of initial U.S. drug launch as firms seek to acquire more information in global markets prior to FDA approval.

The second variable, *orphan*, is defined as 1 for drugs that received an orphan designation from the FDA and 0 otherwise, and is included in order to test for the effect of orphan drug policies on the decision to first launch drugs in the United States. Orphan drug status is designated for diseases that affect fewer than 200,000 patients.[72] The 1983 Orphan Drug Act provided for added periods of exclusivity for orphan drug products in the U.S. market, which should increase expected profits for orphan drugs in the U.S. market.[73] The coefficient for this variable will reveal the extent to which the orphan drug policies have encouraged more initial U.S. launches of orphan drugs.

Ten drug class variables are included to represent the therapeutic categories of the drugs. They are *cardiovascular* for cardiovascular drugs, *analgesic* for analgesia drugs, *anesthetic* for anesthetic drugs, *cns* for central nervous system drugs, *infective* for anti-infective drugs, *AIDS* for AIDS drugs, *neoplastic* for anti-neoplastic (cancer) drugs, *endocrine* for endocrine drugs, *respiratory* for respiratory drugs, and *gastrointestinal* for gastrointestinal drugs. These variables broadly control for any drug class differences, such as the competitiveness of the therapeutic market in the United States, that may affect firms' decisions about whether to first launch drugs in the U.S. market. A positive sign of the coefficient for a drug class variable suggests that drugs in that class are associated with a higher likelihood of initial U.S. drug launch.

Firm characteristics include two variables. The first variable, *U.S. firm*, is a dummy variable equal to 1 for U.S.-owned drug firms and 0 otherwise. Prior research has found that the domestic status of a firm has been shown to influence drug launch strategies.[74] Here, the status of a firm is determined by the location of its parent company. A predicted positive coefficient for this variable will measure the extent to which U.S. firms are more likely to initially launch drugs in the United States. A second variable will measure the impact of past success with the FDA on the likelihood of initial U.S. drug launch. The variable *past approval* measures the number of prior NCE approvals obtained by the firm in the sample period. The coefficient for this variable will measure the extent to which the number of past FDA approvals influence the likelihood of initial U.S. drug launch.

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72.   Orphan Drug Act, Pub. L. No. 97-414, § 360bb(a)(2), 96 Stat. 2049 (1983).

73.   *Id. See also supra* notes 64–66 and accompanying text.

74.   *See* Kyle, *Role of Firm Characteristics*, *supra* note 60.

Finally, a time trend variable, *trend*, is included to control for general trends in initial U.S. drug launches over time. Like the PDUFA variables, the time trend is indexed to the year that a drug application is submitted to the FDA. The general trend will capture time-related effects separate from those associated with PDUFA.

A. *Data*

This study uses data for all new chemical entities (NCEs) approved by the FDA between 1990 and 2001. NCEs are new molecular compounds not previously approved in the United States, excluding biologics, vaccines, diagnostic agents, and new salts, esters, and dosage forms of previously approved compounds.[75] For each drug, the country and year of first drug launch were obtained from PharmaProjects,[76] a database maintained by the UK consulting firm PJB Publications. Using the year of first global drug launch from this source, lags between the year of first global launch and the year of FDA approval can be calculated.

Drug-specific characteristics, including, names, drug novelty ratings, the orphan drug status, NDA submission years, and the review times for all new chemical entities (NCEs) approved in 1990–1992, 1993–1995, 1996–1998, and 1999–2001 were obtained from published articles.[77] Therapeutic drug classes for each of the approved drugs was obtained from the authors of those published articles. Data from firm annual reports for the years used in the study were reviewed to determine whether the parent company of the firm was a U.S. firm. Past approvals were then constructed for each firm by parent company.

A total of 333 NCEs were approved between 1990 and 2001, but fifteen drugs had missing data.[78] Hence, the analysis is conducted on 318 NCEs for which both country of launch and firm characteristics were available.

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75.   *See* Kaitin et al., *The New Drug Approvals of 1990, 1991, and 1992*, *supra* note 22.

76.   I thank Margaret Kyle for making the foreign launch data that she obtained from Pharmaprojects available to me for this analysis. When data on the country or year of first drug launch from this source was missing, additional data on country of first launch from Tufts Center for the Study of Drug Development for the 1993–1998 approvals was used.

77.   Kaitin & Cairns, *supra* note 46; Kenneth I. Kaitin & Elaine M. Healy, *The New Drug Approvals of 1996, 1997, and 1998: Drug Development Trends in the User Free Era*, 34 DRUG INFO. J. 1 (2000); Kenneth I. Kaitin & Michael Manocchia, *The New Drug Approvals of 1993, 1994, and 1995: Trends in Drug Development*, 4 AM. J. THERAPEUTICS 46–54 (1997); Kaitin et al., *The New Drug Approvals of 1990, 1991, and 1992*, *supra* note 22.

78.   Eleven of these did not state the country of first drug launch.

B. *Summary Statistics*

Table 1 presents the summary statistics for the variables used in the analysis. Summary statistics were calculated for the 318 NCEs approved in 1990–2001. Forty percent of these drugs were first launched in the United States over the entire sample period. Table 2 shows how the percentage of first drug launches by submission year has changed over time. For drug submissions received prior to PDUFA I and approved during the sample period, 28 percent were initially launched in the United States. Among drug submissions received during PDUFA I, 40 percent were initially launched in the United States. For the drug submissions received during PDUFA II and approved by the end of the sample period, 58 percent of the drugs were initially launched in the United States.[79]

The mean FDA review time among these drugs was 21 months. Average review times declined in the PDUFA era. Among drug approvals in 1990–1992 prior to PDUFA, the mean review time was 31 months. For new drugs approved in 1993–1995, the first three years after PDUFA, the mean review time fell to 24 months. For new drugs approved in 1996–1998, the mean review time fell to 16.8 months. For new drugs approved in 1999–2001, the mean review time was 16.7 months. Thirty two percent of the drugs were pre-PDUFA submissions. Sixty-eight percent of these drugs were submitted after PDUFA was signed into law. Forty-one percent of the drugs represent therapeutically novel drugs. Nineteen percent of the drugs are classified as orphan drugs affecting small patient populations. U.S.-owned firms account for 54 percent of the drug approvals.

C. *Lags to FDA Approval*

Before moving to the regression results, it is interesting to examine the lag between the year of first global drug launch and the year of FDA approval to determine whether launch lags changed over time.[80] Figure 2 shows the percentage of drug submissions in pre-PDUFA, in PDUFA I, and in PDUFA II that have various lags between the year of first global launch and FDA approval. Lags are grouped into four intervals: 0, 1–2, 3–5, and greater than 6. A lag is coded as zero where the year of first global launch coincided with the year of FDA approval (i.e., first global launch occurred in 1990 and FDA approval occurred in 1990) or where first drug launch occurred in the United States. The second period includes drugs that have a 1–2 year lag between first global drug launch

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79.   This percentage reflects all the drugs approved by the end 2001, but does not include the submissions prior to 2001 that were approved in subsequent years.

80.   Seventeen drugs had missing data regarding the year of first drug launch and hence are excluded.

and FDA approval. All drugs in this interval were first launched abroad prior to FDA approval. The third interval includes drugs that have a 3–5 year lag between the year of first global drug launch and the year of FDA approval. The fourth interval includes all drugs that had a lag of six or more years between the year of first global drug launch and the year of FDA approval.

Figure 2 shows the percentage of drug submissions with a zero lag increased from pre-PDUFA to PDUFA I and PDUFA II. About 40 percent of submissions pre-PDUFA have a zero lag, while 58 percent of PDUFA I and 75 percent of PDUFA II submissions have a zero lag. The percentages reflect the increase in first U.S. drug launches. However, they also reflect an increase in drugs in which the year of first global launch is the same as the year of FDA approval (lag = year of first global drug–year of FDA approval). The percentage of drugs having the longest lags (greater than six years) declined under PDUFA I and PDUFA II, but did not fully disappear: 20 percent of pre-PDUFA submissions had a lag of six years or more while only 12 percent of PDUFA I submissions and 10 percent of PDUFA II submissions had lags of this length. Intermediate lags of 3–5 years also declined substantially over time: 18 percent of pre-PDUFA submissions had intermediate lags of 3–5 years, while only 12 percent of PDUFA I submissions and only 3 percent of PDUFA II submissions had such lags. An important effect of PDUFA appears to be the elimination of such lags. Finally, submissions with 1–2 year lags fell under PDUFA, but primarily under PDUFA II. About 20 percent of submissions pre-PDUFA had 1–2 year lags, while 18 percent of PDUFA I submissions and 12 percent of PDUFA II submissions had lags of this length. It is also surprising that as higher lags diminished, lags of this relatively short length also fell.

D. *Results*

Table 3 presents the results from the logistic regression with coefficients in column (1) and standard errors in column (2).[81] Results show that faster FDA review times are associated with an increase in the probability of initially launching new drugs in the United States. The coefficient for review time is negative and significant at the 0.01 level. To examine the magnitude of this effect and better interpret the results, the average marginal effect is calculated using the partial derivative

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81.   One limitation of the results is that they are right-censored, which means that a data point is above a certain value, but it is unknown by how much. Drugs that were submitted to the FDA prior to 2001, but yet not approved by the end of 2001 are not observed or included in the analysis. This could lead to an overestimate of the effect of PDUFA, particularly in later years in the sample.

method, where marginal effects are estimated for each observation and then averaged over all observations. This method yields an average marginal effect of -0.01, which suggests that a one month reduction in review time is associated with a 1-percent increase in the likelihood of initial U.S. launch. Since review times fell from an average of 31 months in 1990–1992 to about 17 months in 1999–2001, the decline in review times over this period translates into a 14 percent increase in the probability of an initial U.S. launch.

In addition to the effects of review speed, PDUFA submissions are associated with an increased probability of initial U.S. drug launch. The coefficients on both *PDUFA I* and *PDUFA II* are positive and significant at the 0.1 and 0.05 levels, respectively. To better interpret the results, the predicted probabilities of initial U.S. launch are estimated for the different years of PDUFA I and II. This probability $P(Y = 1) = e^{\beta'x} / (1+e^{\beta'x})$ is calculated for each observation, assuming a given value for *PDUFA I* or *PDUFA II*. Then, the probabilities associated with each observation are averaged. For instance, the average probability of initial U.S. launch, assuming *PDUFA I* = 0 and *PDUFA II* = 0, is 0.20, which implies a 20 percent probability of initial U.S. launch prior to PDUFA. This probability increases to 25 percent in the first year of the program (*PDUFA I* = 1), 31 percent in the second year of the program (*PDUFA I* = 2), 37.5 percent in the third year of the program (*PDUFA I* = 3), 44 percent in the fourth year of the program (*PDUFA I* = 4) and 51 percent in the fifth year of the program (*PDUFA I* = 5). Hence, the change in probability of initial U.S. drug launch increased by 31 percent from year 0 to year 5 of PDUFA I. Using this same approach to interpret the impact of PDUFA II, the probability of initial U.S. launch increased 27 percent from the first year of PDUFA II (*PDUFA II* = 6) to the fifth year of PDUFA II (*PDUFA II* = 10). These results indicate that other PDUFA-related changes, such as those leading to increases in the probability of approval or reduced drug development times (primarily under PDUFA II), also increased the probability of initial U.S. drug launches. In fact, the marginal effects suggest that the impact of these other PDUFA-related factors exceed the impact of the changes in review speed.

Two other variables have also influenced the probability of initial U.S. drug launch over time. The coefficient for *orphan* is positive and significant at the 0.01 level, which suggests that orphan drugs are more likely to be initially launched in the United States. Since this is a dummy variable, the marginal effect is determined by looking at its effect on the event probability as above. It is calculated by taking the difference in the predicted probabilities when the variable is 0 and then changes to 1, holding other factors constant. Using this approach, the marginal effect

of moving from a non-orphan to an orphan drug is a 19 percent increase in the predicted probability of initial U.S. launch. The result may further suggest that the Orphan Drug Act has also been effective in terms of improving patient access to orphan drugs by encouraging more initial U.S. launches of these products.

The coefficient for *U.S. firm* is positive and significant at the 0.01 level, which indicates that drug submissions from U.S.-owned firms are more likely to be first launched in the United States. The average marginal effect calculated by the method above for dummy variables indicates that being a U.S. firm increases the probability of initial U.S. launch by 21 percent. This result is consistent with other studies that have found that domestic status influences global drug launch strategies. There are different reasons for why such an effect might exist, including more knowledge of local markets and lower fixed costs of entry in the U.S. market relative to foreign-owned firms.

Two results differ from prior findings. After controlling for the effects of *U.S. firm*, the coefficient for past FDA approvals is negative and weakly significant at the 0.1 level. This suggests that prior FDA approvals do not increase the likelihood of initial U.S. drug launch. After controlling for review speed, the coefficient for *novel* is not significantly associated with the likelihood of first U.S. drug launch. This contrasts with the findings of Professor Kyle, who found that drug importance (measured independently of the regulator) increases the hazard of drug launch in a market and increases the number of markets entered by firms.[82] Her study did not include a variable for the regulatory treatment of such drugs.[83]

U.S. regulators have tried to accelerate the approval of novel drugs over time. However, the decision about where to target a drug for first launch may reflect additional considerations. Although novel drugs are likely to be associated with increased profitability, they may also be associated with more risks, which lowers expected profitability in the U.S. market. A study of new drug approvals from 1990 to 1995 shows that novel drugs are associated with an increased number of serious adverse drug reactions compared to non-novel drugs in their two years after FDA approval.[84] These competing effects may offset after controlling for the speed of review.

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82.   *See* Kyle, *Pharmaceutical Price Controls*, *supra* note 60, at 96, 98.
83.   *Id.* at 95.
84.   *See* Mary K. Olson, *Are Novel Drugs More Risky for Patients than Less Novel Drugs?,* 23 J. HEALTH ECON. 1135–58 (2004).

V. Concluding Remarks

Patients in the United States have historically faced delays in accessing important new medicines. One reason is that many drugs were first launched abroad prior to U.S. approval. The Prescription Drug User Fee Act was introduced with the goal of improving drug access for U.S. patients by speeding up the FDA review process. Less attention has focused on how PDUFA may have affected firms' initial drug launch strategies, an important indicator of U.S. patient access to new drugs relative to other countries. This Article's hypothesis is that the changes occurring under PDUFA lowered U.S. regulatory barriers to entry and hence, led to more drugs being targeted for first launch in the United States. To investigate this hypothesis, the analysis examines the impact of PDUFA and subsequent increases in FDA review speed on the likelihood of initial U.S. drug launches in the 1990 to 2001 period.

Results indicate that both increased review speed and other PDUFA-related changes have led firms to target more drugs for first launch in the United States. Faster FDA review times from 1990 to 2001 were found to increase the probability of initial U.S. drug launch by 14 percent. Other PDUFA-related changes (beyond review speed), such as increased probability of approval and shorter drug development times, increased the probability of initial U.S. drug launch 31 percent by the end of PDUFA I and 27 percent by the end of PDUFA II. Overall, the results show that the regulatory changes associated with PDUFA improved drug access for U.S. patients by encouraging more first U.S. drug launches.

What are the implications of these results for consumers? The answer depends on how these changes have affected consumer health. Improving patient access to innovative new drugs, especially those for life threatening illnesses, can certainly improve patient health.[85] Such health gains represent an important benefit associated with more first U.S. drug launches and improved drug access. However, more first U.S. drug launches may also pose some new risks for U.S. patients as the first users of such innovative new products. The reason is that less is known about new drugs when they are first marketed. Typically, regulators and firms learn more about the actual risks and benefits of new drugs only after those drugs have been used more widely in the population under conditions of actual use. With more first drug launches abroad prior to FDA approval, U.S. regulators may have benefited from the spillovers of safety information that come from other countries. As launch lags fall and more drugs are first launched in the United States, this potential source of drug safety information is eliminated. Research has shown that

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85.   *See* Lichtenberg, *supra* note 6.

drugs having shorter periods between first launch abroad and subsequent U.S. launch are associated with increased adverse drug reactions following FDA approval.[86] The health consequences of more initial U.S. drug launches on U.S. patients remains an important topic for future research.

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86.   *See* Mary K. Olson, *The Risk We Bear: the Effects of Review Speed and Industry User Fees on Drug Safety*, 27 J. Health Econ. 175–200 (2008).

APPENDIX

TABLE 1
SUMMARY STATISTICS: NCE APPROVALS FROM 1990–2001
(N=318)

VARIABLE	DEFINITION	MEAN	SD
U.S. Launch	Equals 1 if initial U.S. launch, else 0	0.40	0.49
Review time	Review time (in months)	21	19
PDUFA I	1 for submissions in 1st fiscal year, 2 for submissions in 2nd year . . . 5 for submissions in 5th year of PDUFA I	1.52	1.90
PDUFA II	6 for submissions in 1st fiscal year, 7 for submissions in the 2nd year . . . 10 for submissions in the 5th year of PDUFA II, else 0	1.63	3.03
Novel	Equals 1 for priority-rated drug submission	0.41	0.49
Orphan	Equals 1 for orphan drug submission	0.19	0.40
U.S. firm	Equals 1 for U.S.-owned firm	0.54	0.50
Past Approval	# of prior drug approvals (since 1990)	2.95	3.30
Cardiovascular	Equals 1 for cardiovascular drug	0.21	0.41
Neoplastic	Equals 2 for neoplastic drug	0.12	0.32
Infective	Equals 1 for anti-infective drug (non AIDS)	0.13	0.33
AIDS	Equals 1 for AIDS drug	0.07	0.25
CNS	Equals 1 for central nervous system drug	0.13	0.34
Analgesic	Equals 1 for analgesia drug	0.08	0.27
Anesthetic	Equals 1 for anesthetic	0.03	0.16
Endocrine	Equals 1 for endocrine drug	0.09	0.29
Respiratory	Equals 1 for respiratory drug	0.05	0.22
Gastrointestinal	Equals 1 for gastrointestinal drug	0.03	0.16

TABLE 2
FIRST U.S. DRUG LAUNCHES OVER TIME:
NCE APPROVALS IN 1990–2001

SUBMISSION PERIOD	FIRST U.S. LAUNCHES	TOTAL U.S. LAUNCHES	% FIRST U.S. LAUNCH
Pre-PDUFA	28	103	27%
PDUFA I	57	142	40%
PDUFA II*	42	73	58%

*does not include NCE approvals beyond 2001

TABLE 3:
LOGISTIC REGRESSION RESULTS FOR INITIAL U.S. DRUG LAUNCH

Variable	Coefficient	(Standard error)
Review time	-0.06***	(0.02)
PDUFA I	0.38*	(0.22)
PDUFA II	0.40**	(0.19)
Novel	0.32	(0.34)
Orphan	1.05***	(0.40)
U.S. Firm	1.22***	(0.29)
Past Approval	-0.09*	(0.05)
Cardiovascular	0.33	(0.59)
Analgesic	0.14	(0.68)
Anesthetic	1.00	(0.91)
CNS	-0.28	(0.62)
Infective	-0.95	(0.65)
AIDS	0.75	(0.78)
Neoplastic	-1.17*	(0.67)
Endocrine	-0.29	(0.63)
Respiratory	-0.62	(0.83)
Gastrointestinal	-1.89	(1.33)
Trend	-0.19	(0.15)
Constant	1.54	(1.73)
Observations	318	
Log Likelihood	-161	

*statistically significance at the 0.1 level; **statistically significance at the
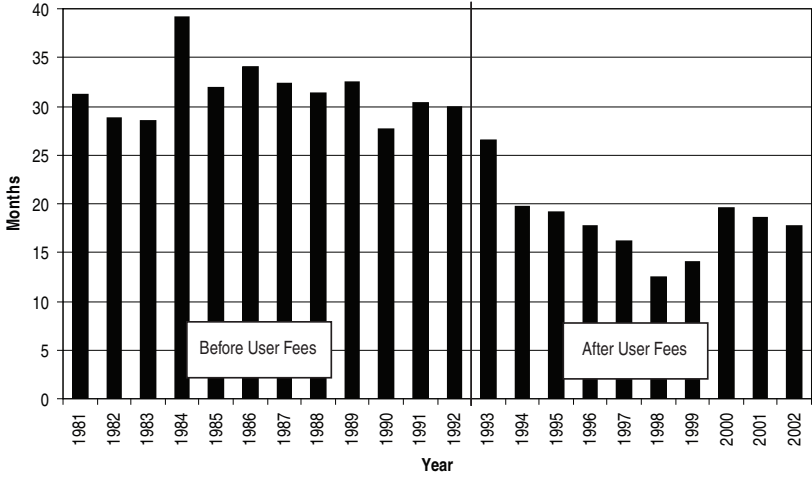0.05 level; *** statistically significance at the 0.01 level

FIGURE 1
MEAN NME REVIEW TIMES: 1981–2002

FIGURE 2
LAUNCH LAG FREQUENCY