

How Have User Fees Affected the FDA?

The 1992 FDA reform successfully reduced drug review times.

MARY K. OLSON

YALE UNIVERSITY

DELAY IN THE APPROVAL OF NEW drugs has been a policy problem in the United States since the mid-1970s. Scholars have argued that the delay historically has resulted in part from excessive caution on the part of the Food and Drug Administration, which did not want to risk approving a product that would later be responsible for drug-related tragedies. That caution contributed to longer FDA review times for new medicines and, hence, more delay in the approval of new drugs.

In 1992, Congress passed legislation to reduce delay in the review and approval process. The legislation introduced prescription drug “user fees” for FDA new-drug review. The program altered the agency’s financing arrangement with Congress by making the FDA dependent on industry for a portion of its funding. The result has been a 50-percent increase in the speed of review. That increase has enabled pharmaceutical firms to bring new drugs to market earlier in their patent lives and enabled U.S. patients to gain faster access to important new medicines.

The dramatic effects of the user fee program have led many to question how a change in the funding source could accomplish such change. Why has the reform had such an

Mary K. Olson is an associate professor of health policy and administration in the School of Public Health at Yale University. She can be contacted by e-mail at mary.olson@yale.edu.

effect on FDA behavior?

Some policy experts answer that question by arguing that budget constraints contributed to regulatory delays in the past. The reform simply relaxed those constraints by increasing the resources for new-drug review. However, there is little empirical evidence to suggest that changes in the FDA’s budget influenced regulatory delays and the speed of review prior to user fees. Other policy experts claim that the adoption of user fees altered bureaucratic motivations in the FDA by providing new economic rewards and creating new political pressures to accelerate review. Still others claim that politicians are using their control over agency financing to influence regulatory behavior.

Those claims will receive increased attention this year as the fall deadline approaches for Congress to renew the user fee program. With the fee set at about \$310,000 (in 2001) for each new-drug application and strong market demand for innovative new drugs, there is much at stake in the debate over the program’s reauthorization.

BACKGROUND

Between 1980 and 1992, the average time required to review and approve new-drug applications in the FDA was approximately 2.5 years. Increasing complaints from AIDS activists, pharmaceutical firms, and other patient groups about the delay led to new political efforts to combat the problem. The result was the 1992 Prescription Drug User Fee Act (PDUFA), which required pharmaceutical firms to pay fees to the FDA to help boost the agency’s resources for new-drug review. In return, the agency was expected to reduce regulatory delay and accelerate the approval of new drugs.

Review targets While proposed legislation was still pending in committee in 1992, the commissioner of the FDA, David Kessler, sent a letter to the chairmen of the House and Senate oversight committees in which he outlined new performance goals (review targets) that the FDA could meet if the legislation was enacted. The goals included a six-month review target for the most therapeutically novel drugs (given a priority rating by the FDA) and a 12-month review target for less novel drugs. The agency's promise to meet those targets led to bipartisan support for the legislation. Although the pharmaceutical industry had opposed user fees in the past, it supported the legislation primarily because of the new performance goals and the prospect of faster new-drug reviews.

The legislation contained a series of annual revenue targets for the agency to increase its resources for new-drug review. In addition, the legislation provided a schedule of user fees needed to meet the targets. Fees for new-drug appli-

cations were listed as \$100,000 in 1993, \$150,000 in 1994, \$208,000 in 1995, and \$233,000 in 1996. However, fees in any given year could be amended to meet the inflation-adjusted revenue targets. The agency collected fee revenues of \$36 million in 1993, \$56.7 million in 1994, \$77.7 million in 1995, \$89.5 million in 1996, and \$90.8 million in 1997.

The legislation required that all fee revenue be used to improve the efficiency and speed of review. To accomplish that objective, the agency devoted a majority of the revenue to hiring new-drug reviewers in the Center for Drug Evaluation and Research (CDER). As a result, CDER's staff increased from 1,408 fulltime-equivalent employees in 1992 to 1,780 in 2000. The legislation prohibited the use of fee revenues for other agency activities not related to new-drug review, such as generic-drug review, medical-device review, food regulation, or post-marketing drug safety surveillance. The legislation also required that the FDA's congressional budget appropriation

not be reduced in response to increasing user fee revenue over the duration of the program. Finally, the legislation established a five-year limit for the program. At the end of that time, Congress needed to pass new legislation reauthorizing the program or else it would expire. That feature effectively allowed politicians to link the agency's fee collection authority to its ability to meet the performance goals.

Renewal The 1997 Food and Drug Administration Modernization Act (FDAMA) renewed the user fee program for another five years. The legislation included a new set of revenue targets, a new fee schedule, and a new set of performance goals. The goals maintained a six-month review target for therapeutically novel or priority drugs and set a new 10-month review target for other drugs. In addition, new performance goals were added in areas relating to agency-firm communications, meetings with industry, and dispute resolution. Under both PDUFA and FDAMA, fee revenues and fee rates would be adjusted annually for inflation. However, FDAMA included a new provision that total application fee revenues and fees would be adjusted annually to reflect increases or decreases in workload.

The FDA reports that fee rates have increased from \$256,846 in 1998 to \$272,282 in 1999, \$285,740 in 2000, and \$309,647 in 2001. Fee revenues collected totaled \$113.1 million in 1998, \$122 million in 1999, and \$137.7 million in 2000. Currently, user fee revenue represents approximately 13 percent of the agency's budget appropriation from Congress. However, fee revenues are approaching 50 percent of FDA spending on its drug review activities.

THE EFFECTS OF THE REFORM

Figure 1 shows the mean FDA review times for new molecular entities (NMEs) approved by the agency between 1981 and 2000. NMEs are new molecular compounds, excluding biologics, vaccines, and diagnostic agents, that have not been previously approved



in the United States. A drug's FDA review time is defined as 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. That period includes both FDA review time and the time that firms take to respond to regulator requests for additional information to support the application. The length of review is often highlighted as the key performance measure for the agency. Much of the political and media attention surrounding the user fee reform has focused on the speed of review.

Figure 1 shows that mean new-drug review times averaged 30 months prior to the 1992 reform. However, two years later, mean review times declined to less than 20 months. Six years after user fees were introduced, mean review times declined to less than 12 months. Those numbers represent a substantial reduction. Although mean review times have increased in 1999 and 2000, they remain at levels that are approximately 50 percent less than pre-PDUFA levels.

Approvals It is important to note that the increase in review speed did not come at the expense of the number of new-drug approvals. In addition to faster new-drug reviews, the agency has approved more applications over time. Figure 2 shows that new-drug approvals increased to a high of 53 NMEs in 1996. Although product approvals have declined since then, the total number of new drugs approved in the post-PDUFA period exceeds the total number of new drugs approved in the eight years prior to PDUFA. Between 1985 and 1992 the agency approved a total of 170 NMEs, while from 1993 to 2000 the agency approved 259 NMEs.

Given the trends described above, it is not surprising that the probability of gaining FDA approval has increased after the reform. The percentage of applications that are ultimately approved increased from approximately 66 percent in the pre-PDUFA years to roughly 80 percent for applications submitted between 1993 and 1995. Among NMEs there was a smaller increase in approval rates, from 76 percent for pre-PDUFA drugs (submitted during 1988-92) to 81 percent for post-PDUFA drugs.

The changes in FDA review times may have also eliminated lags between the approval of new drugs in the United States and

in other countries. In the early 1980s, only 2-3 percent of new drugs were first introduced in the U.S. market because pharmaceutical firms typically completed other countries' approval processes before they finished the FDA's. But by 1998, more than 60 percent of new drugs appeared first on the U.S. market. That change suggests that U.S. patients are gaining faster access to the most innovative pharmaceutical therapies. In addition, firms are enjoying the financial rewards associated with reduced regulatory delay and faster access to patient markets.

Responsiveness to firms To investigate how the reform may have altered FDA responsiveness to firms, I conducted an analysis that explored how the differences among firms influenced FDA review times for new drugs approved both before and after the reform. The analysis examined how the introduction of user fees changed the relative importance of firm characteristics on the length of new-drug review among all new drugs approved between 1990 and 1995.

Among the new drugs approved from 1990 to 1992 (before the reforms), several firm characteristics influenced the length of review. For instance, a firm's research intensity, specialization in pharmaceutical sales, size, and current experience with the FDA were all significantly related to the speed of review. The analysis showed that more research-intensive firms and more specialized pharmaceutical firms received faster reviews than less research-intensive firms and more diversified firms. The analysis also showed that firms that were larger and had more experience with the FDA received faster reviews than firms that were smaller or had less experience with the agency. New-drug applications from foreign-owned firms also received faster reviews than applications from U.S. firms. Those results indicate that the differences among firms systematically influenced the speed of new-drug review prior to the reform.

However, among the new drugs approved in the first three years after the 1992 reform, the analysis showed that, with one exception, firm characteristics did not influence the speed of new-drug review. (Only foreign-owned pharmaceutical firms continued to receive faster reviews for their applications, but the magnitude of that effect became smaller after the reform.)

FIGURE 1

New Drugs, Faster

Mean review times; 1981-2000

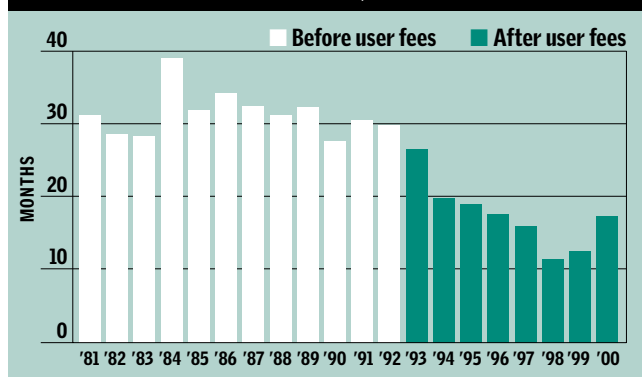
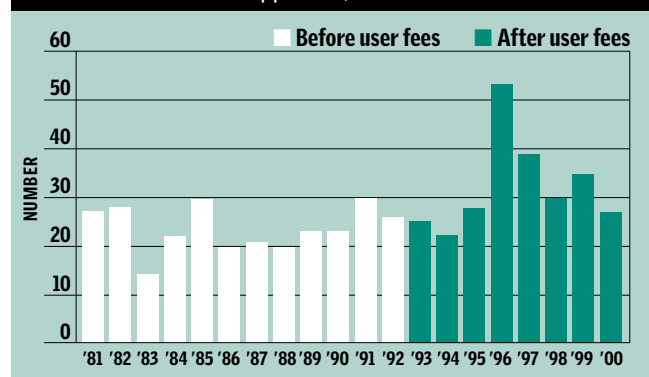


FIGURE 2

More New Drugs

NME approvals; 1981-2000



Those results suggest that FDA regulators have become less responsive to the differences among firms submitting applications following the introduction of user fees. They also suggest that the program reduced the relative advantages of larger, more research-intensive, specialized, or experienced firms in the review process. Because the differences among firms no longer influenced the speed of new-drug review, the results imply that regulators began treating firms with different characteristics more equally in the review process. Hence, user fees have created more equity in new-drug review.

Responsiveness to drugs I also examined how the reform affected the relative importance of drug characteristics, such as therapeutic novelty and class, on review times before and after the reform. Among the new drugs approved between 1990 and 1992, the analysis showed that applications in selected therapeutic classes, namely the cardiovascular, analgesic, and central nervous system categories, had significantly longer review times than drugs in other therapeutic classes, even after controlling for a drug's therapeutic novelty. One explanation for that result is that many of the drugs in those categories are intended for chronic conditions. For such drugs, the applications may often be longer, more complex, and more difficult to evaluate than applications in other therapeutic categories.

In contrast, among the new drugs approved between 1993 and 1995, the analysis showed that a drug's therapeutic class is no longer significantly related to the speed of review. That finding is not too surprising considering that the user fee performance goals are also independent of therapeutic drug classes. However, the result implies that the relative benefits of the reform, in terms of reduced review times, were greater for some classes of drugs than for others. That may suggest that the extra user-fee resources and administrative reforms accompanying the program have made it easier for the FDA to process longer, more complicated drug applications, particularly for cardiovascular, analgesic, and central nervous system drugs.

One drug characteristic that increased in importance was a drug's therapeutic novelty status. New-drug applications are given either a priority or a standard rating by the agency. A priority rating reflects the agency's estimate that the drug represents a significant therapeutic gain over existing remedies, while a standard rating reflects the agency's estimate that the drug offers little to no therapeutic gain. The analysis showed that drugs receiving a priority rating from the FDA received significantly faster reviews after the introduction of user fees. That suggests that the political pressures to meet the user fee performance goals strengthened FDA incentives to accelerate the review of therapeutically novel drugs. Those results further suggest that politicians were quite successful in designing a reform to realign regulatory incentives in the agency. In particular, the reform encouraged regulators to place more emphasis on accelerating patient access to the most innovative medicines.

EXPLAINING THE CHANGES

Given politicians' previous failures to combat regulatory delay, the success of this reform in altering FDA behavior and accelerating new-drug review is really quite striking. The

reasons for its success deserve further attention.

The review targets of six months for priority drugs and 12 months for standard drugs provide very clear measures to gauge FDA performance after the reform. While the 1962 amendments to the Food, Drug, and Cosmetic Act did provide a single review target of 180 days for reviewing each new-drug application, it is interesting and relevant to note that the agency seldom, if ever, met that goal. One reason for that failure may be that there were no provisions in the 1962 legislation or accompanying incentives in the agency to encourage or force it to meet the goal. Another reason may be that the threat of drug-related tragedies (e.g., Thalidomide) encouraged regulators to place greater emphasis on safety over access in the approval of new drugs.

Resources or incentives? The revenue from user fees provides the FDA with more resources to help accelerate new-drug review. However, if resources alone explain the change, then Congress could have previously reduced delay by simply increasing the agency's budget. Furthermore, increases in agency resources should be associated with reductions in FDA review times prior to the reform. Data suggest that that has not been the case. Figure 3 shows the number of CDER staff and the annual mean FDA review times for new drugs approved from 1971 to 1998. There appears to be a positive correlation between staff and review times prior to the introduction of user fees—that is, the more staff the FDA had, the longer it took to review applications. However, after the implementation of the reform, there is a strong inverse association between the two—the larger the staff, the faster the review times. As shown in Figure 4, politicians had increased the FDA's budget several times prior to the reform, but those increases resulted in little decline in review times. That suggests that other reform-specific factors, such as changing regulatory motivations, may have played a role in reducing FDA review times.

In my previous paper "Managing Delegation with Agency Financing," I examined the impact of the user fee reform on the speed of new-drug review, controlling for changes in FDA resources and workload over time. The analysis estimates annual mean review times for new-drug approvals between 1971 and 1998 as a function of the agency's annual budget (and CDER's annual staff resources), the number of annual new-drug applications received by the agency, and a dummy variable for the user fee reform. Results show that, even after controlling for increased agency (and divisional) resources and increased agency workload, the reform has led to a 34- to 35-percent reduction in new-drug review times.

The evidence suggests that the FDA is placing greater emphasis on accelerating new-drug review than it had in the past. One reason for the change in behavior is that there are new economic rewards for reducing regulatory delay. Assuming that agency administrators prefer bigger budgets, the user fee reform creates new incentives to accelerate review and meet the user fee performance goals. CDER, in particular, will benefit from the continued legislative authority to collect user fee revenue because it receives the bulk of those revenues. By meeting the performance goals, CDER can

ensure that politicians will renew the program. Program renewal means that the agency, particularly CDER, will continue to receive fee revenues to supplement its budget. If CDER fails to meet the performance goals, the program will not be renewed and the agency will lose its user fee revenue. That feature of the program introduces new accountability for the new-drug review division.

Political pressure In addition, two features of the reform increase the political pressures on the agency to accelerate new-drug review. First, there are new provisions for monitoring FDA activities. The program requires the FDA to submit annual performance reports to Congress that document the agency's progress in meeting performance goals and outline how user fee revenues are being allocated and spent. The reporting requirements increase agency accountability and make it easier for firms and politicians to evaluate FDA performance.

Second, the program is designed so that its renewal may be conditioned on agency performance. At the time of renewal, stakeholders have an opportunity to revisit the program, provide feedback on the agency's performance, and garner public support for, or opposition to, its renewal. That gives the stakeholders an important voice in the political decision to renew the program. Both features improve the incentives of FDA administrators to care about meeting the user fee performance goals and accelerate new-drug review. Such incentives were not present in the agency prior to the 1992 reform.

REMAINING CONCERNS

Some stakeholders have raised two primary concerns about the user fee program. Specifically, consumer advocates and others have questioned whether there are potential conflicts of interest created by the user fee program, and whether tapping user fees for new-drug review has led Congress to underfund other FDA priorities. I will consider each of those concerns in turn.

Conflicts of interest According to the first concern, the

arrangement of having regulated firms pay for the activities of the FDA increases the risk of conflicts of interest inside the agency and creates opportunities for industry to exert inordinate influence over agency decisions. Such influence may occur in the agency-industry negotiations over user fee performance goals and the FDA's decisions about which drug applications to grant a priority rating. While the concern about conflicts of interest has led to some opposition to program renewal, it has also led some consumer advocates to seek a greater voice in setting the agency's performance goals and in the designation of priority status of new-drug applications.

That concern reflects a fundamental objection to user fee financing for FDA regulatory activities. Economists have argued that user fees are a legitimate way to recover regulatory costs. The rationale is provided by the benefit principle of taxation, which suggests that those who benefit from a government service or product should be required to pay for it. In accordance with that rationale, user fees have been imposed on both individuals and businesses at all levels of government for an array of purposes and programs. While patients may benefit from a reduction in regulatory delay in the review process, a firm receives the direct financial benefits associated with being able to market drugs earlier in their patent lives. Those benefits (profits) are concentrated among firms that submit new-drug applications, while the benefits to consumers are more dispersed and spread out over time. Hence, firms possess a strong rationale to pay the fee to ensure a timely review.

While user fee financing may create more opportunities for conflicts of interest among regulators, it has also been an incredibly effective policy for reducing regulatory delay and accelerating patient access to innovative new medicines. The features of the program that are responsible for the change in FDA behavior are the same ones that create a potential for conflict of interest among regulators. Without the features of the reform that increase agency accountability and encourage regulators to place more emphasis on accelerating new-drug review, we would not have seen such changes in FDA behavior.

It is important to preserve the agency's new accountabil-

FIGURE 3

Better Use of Staff

CDER staff vs. review times: 1971-1998

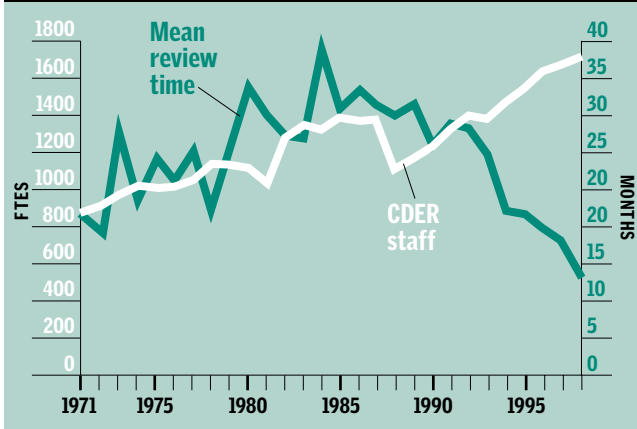
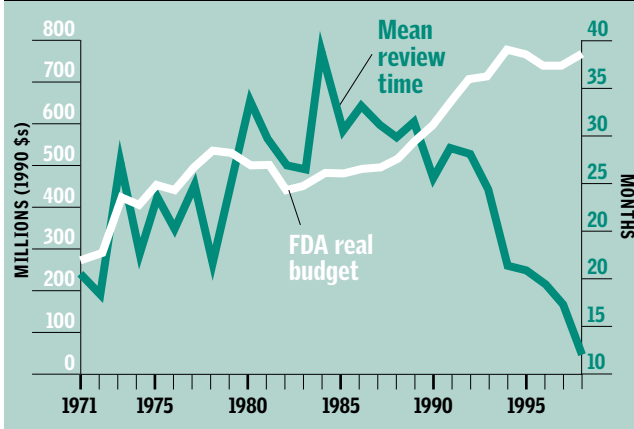


FIGURE 4

Better Use of Money

Budget vs. review times: 1971-1998



ity arising from the linking of performance goals to program renewal and future user fee revenue. That link will ensure that agency incentives continue to be aligned with the preferences of political overseers. The potential for conflicts of interest should be investigated and, if needed, addressed with new provisions designed to limit such influences.

Underfunding The second concern is that increased user fee revenues may have undercut congressional support for FDA appropriations used to pay for other non-PDUFA activities, most notably post-marketing safety programs. All stakeholders agree that Congress was not providing sufficient increases in the agency's budget to cover all of the agency's non-PDUFA activities and regulatory responsibilities. Consumer protection advocates, patient advocates, and health professionals share an interest in increasing funding for the post-marketing safety surveillance of new drugs. The removal of several new drugs from the market for safety reasons in the last few years and an increase in adverse drug reactions since the early 1990s have raised public awareness about the issue of post-marketing surveillance and new-drug safety.

One simple solution to the second concern is to allow some portion of user fee revenue to be directed toward improving the post-marketing surveillance of newly approved drugs. However, industry lobbyists have objected to such a change, arguing that post-marketing surveillance is a public health function that should be supported by government funding. They also argue that user fees are appropriate for product review because it is not a public health function and hence need not be supported by tax revenue.

That logic is faulty; the review of new drugs for their safety and efficacy is just as much a public health regulatory function as is the post-marketing surveillance of new drugs after they are approved. The FDA's statutory delegation of regulatory authority to ensure and protect the public health has a legislative origin in the Food, Drug, and Cosmetic Act of 1938 and the Harris-Kefauver amendments to the act in 1962. If fees are appropriate for new-drug review, then it would seem that they are equally appropriate for post-marketing surveillance to ensure the safety of newly approved drugs.

CONCLUSION

The prescription drug user fee reform has led to a substantial reduction in new-drug review times. User fee revenues have played a role in improving information technology and staff resources in the FDA's new-drug review division. However, the reform has also had an important effect on regulatory motivations in the agency. In particular, the reform has encouraged a greater regulatory emphasis on accelerating the review of new drugs. By meeting the review targets outlined in the legislation, FDA managers could help ensure the program's renewal and future user fee revenues. A desire to maintain user fee revenue has increased FDA accountability in a way that traditional budget appropriations and other political interventions have been unable to do over time.

There are many benefits for the stakeholders in this program. Firms are able to market drugs earlier in their patent

lives. Patients are gaining faster access to innovative, new medicines. In addition, there is more equity among firms in the new-drug review process. After considering those effects, it seems apparent that the program should be renewed. More than a simple resource transfer from firms to the FDA, the program and the political pressures surrounding it have improved agency accountability and strengthened agency incentives for caring about the speed of new-drug review. Although the program does create new regulatory costs for firms, the firms benefit financially from reduced regulatory delay because drugs can be marketed earlier in their patent lives. With such market rewards, the benefits to firms from faster reviews are likely to exceed the cost of the user fee.

Public concerns about conflicts of interest and new-drug safety are creating some opposition for program renewal. It is hard to imagine that any stakeholder truly wants to return to the kinds of delays in the review process that existed prior to the reform. For that reason, it is important for politicians and the agency to investigate and address the concerns. Of particular relevance are the concerns about new-drug safety. More evidence is needed to determine the effect of faster reviews on pharmaceutical risks and safety. Adequate funding must be provided for the post-marketing safety surveillance of the growing number of approvals. Because all pharmaceutical risks (such as drug interactions) are not revealed in clinical trials, it is important to have a surveillance program that can monitor and detect those risks. It is also important to have effective risk communication strategies for patients and physicians. Failure to address those important concerns may lead to an unraveling of the progress made in accelerating new-drug review. Because firms, in particular, want to preserve those benefits, they should allow fee revenues to support improvements in the FDA's post-marketing safety surveillance of new drugs. **R**

READINGS

- *Bureaucracy and Representative Government* by William Niskanen. Chicago Ill.: Aldine-Atherton, 1971.
- "Drugmakers Back User Fee Bill to Speed FDA Drug Approval," by Julie Rovner. *Congressional Quarterly*, September 19, 2000.
- "Firm Characteristics and the Speed of FDA Approval," by Mary K. Olson. *Journal of Economics and Management Strategy*, Vol. 6, No.2 (1997).
- "Managing Delegation with Agency Financing: User Fees and the Speed of New-Drug Review," by Mary K. Olson. Yale University, May 2001.
- "Regulatory Reform and Bureaucratic Responsiveness to Firms: The Impact of User Fees in the FDA," by Mary K. Olson. *Journal of Economics and Management Strategy*, Vol. 9, No. 3 (2000).
- "The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There Is a Problem?" by M.A. Friedman, J. Woodcock, M. Lumpkin, J.E. Shuren, A.E. Hass, and L.J. Thompson. *Journal of the American Medical Association*, Vol. 281 (1999)