Center for American Progress

Prescriptions for Drug Safety

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Walter G. Bradley and Michael Halle

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Introduction

Protecting American consumers from the potentially fatal side effects of prescription drugs already behind pharmacy counters should be one of the top tasks of the U.S. Food and Drug Administration. Yet the FDA today has little authority and even less money to police prescription drugs after it has given final approval for a new drug to be prescribed by doctors across the country. Under current rules and regulations approved by Congress most recently five years ago, the presumption was that the FDA's rigorous testing of prescription drugs prior to approval for sale to the public offered enough protection to consumers. That presumption is wrong.

The Prescription Drug Use Fee Act of 1992, or PDUFA, which Congress renewed in 1997 and 2002 and which is up for renewal again this summer, authorized the FDA to establish a clear but streamlined new drug approval process alongside the means to pay for the necessary extra staff—user fees from the pharmaceutical industry. PDUFA worked wonders for its users: double-digit profit margins because Big Pharma can now get more new drugs approved more quickly. The average time it takes the FDA to approve a new drug has dropped by 40 percent since PDUFA was first implemented; 50 percent of the world's new drugs are now launched first in the United States, up from 8 percent in 1992.

The problem, as recent research has shown, is that FDA staff at its Center for Drug Evaluation and Research is trying too hard to meet the deadlines of PDUFA. The prestigious Institute of Medicine pointedly notes that the funding method and swift review guidelines of PDUFA are "excessively oriented toward supporting speed of approval and insufficiently attentive to safety." Indeed, a study published earlier this year by George Washington University's School of Public Health and Health Services found that the rate at which drugs already on the market registered unforeseen health safety problems was appreciably higher for those drugs approved by the FDA within PDUFA's expedited approval timelines.

Yet the headline news about the adverse effects of some of these drugs, such as the heightened risk of heart attacks from the painkiller Vioxx and of liver failures from the antibiotic Ketek, compete with the results of another reform implemented by the FDA since the introduction of PDUFA—direct-to-consumer advertising by the pharmaceutical industry. Even as drug industry executives face serious charges of not doing enough to ensure the safety of their own drugs once they are approved for sale by the FDA, these companies' marketing mavens are spending billions of dollars advertising their products to consumers directly through the media.

The high cost of those drugs to American consumers relates directly to the cost of the pharmaceutical industry's media marketing programs and user fees paid to the FDA to get drugs approved quickly. The price of prescription drugs increased 8.3 percent annually between 1994 and 2004, the last year for which complete data are available, compared to the average annual rate of total inflation of 2.5 percent. Spending on prescription drugs grew by 59 percent between 2000 and 2005, while all other health expenditures grew by 40 percent.

The upshot: higher profits for the drug industry but less safe drugs for consumers due to the unforeseen consequences of PDUFA and direct-to-consumer advertising. But what's worse is that there is still no regulatory system in place to review the safety of prescription drugs after the public is allowed to purchase them.

Congress has an obligation to fix what ails the FDA's drug review process as it works to reauthorize PDUFA in the coming months. And there are plenty of good ideas on how to do so: new proposals from the Institute of Medicine; a set of policy recommendations published recently by scholars in the Archives of Internal Medicine; and key bipartisan legislation already proposed in the Senate and House of Representatives.

Yet both chambers of Congress have recently passed bills that fall short of the mark.

That's why the Center for American Progress today offers five policy prescriptions for improved drug safety with the intention of influencing the final bill as key members of the House and Senate now in conference committee try to work out differences in legislation passed by the two chambers. Specifically, CAP proposes that Congress:

- Eliminate the almost automatic thirty-month patent exclusivity extension allowed under current law so that generic drugmakers can compete that much more quickly with pharmaceutical companies that have already enjoyed the full extent of patent protection.

- Restore the moratorium on direct-to-consumer advertising in effect prior to 1985 so that direct-to-consumer advertising follows the same guidelines as advertisements directed at health care professionals, including full disclosure of side effects and warnings.

- Create an independent Center for Post-Market Drug Evaluation and Research outside of the FDA to establish an effective system for post-marketing surveillance of drugs.

- Require pharmaceutical companies to undertake post-marketing phase IV safety studies and make the results available, along with Phase III safety trials, on a government website.

- Discourage the proliferation of "me too" drugs by requiring that new drugs go through extensive comparative clinical trials and are tested for safety and efficacy. Fully fund the FDA and the new Center for Post-Market Drug Evaluation and Research so that the agency and the new Center can do their jobs properly.

These five steps are easily proposed but not so easily implemented. The complexity involved in all five reforms means that Congress must pay special attention to how the safety of our drugs came to be compromised by previous legislation and subsequent regulatory action.

This paper will detail the legislative and regulatory history of drug safety efforts in the United States over the past 100 years, with particular attention paid to the past 20 years in which successive victories by the pharmaceutical industry came at the expense of consumers. Once we have underscored exactly how drug safety came to be compromised at the FDA, a more com-

plete analysis of our prescription drug policy proposals points the way, we believe, for Congress to act.

History of Prescription Drug Regulation

Prior to the establishment of the Food and Drug Administration in 1931 and its organizational precursors, drugs and drug makers were largely unregulated. Drug makers could market untested compounds as remedies for any number of conditions. In 1906, the Federal Food and Drugs Act added regulatory functions, such as oversight of drug labeling, to the Bureau of Chemistry, which had previously been a scientific agency within the Department of Agriculture. Then, following the creation of the Food and Drug Administration in 1931, the Food, Drug, and Cosmetic Act of 1938 broadened the regulatory jurisdiction of the FDA to include cosmetics and medical devices.

The agency's early regulatory responsibility was limited to ensuring that producers met either governmental standards of purity, or that the manufacturers established and followed their own safety standards for their products, which were then included on the product label. Beginning in 1938, manufacturers were required to prove that a drug was safe before marketing the medication and then to label medications with adequate directions for safe use. Drug makers were also prohibited from making false therapeutic claims.

In subsequent years, Congress amended the underlying statute to expand FDA jurisdiction over drug approval, requiring manufacturers to prove the efficacy as well as the safety of new drugs. Congress also gave the agency regulatory oversight of pharmaceutical advertising and any adverse reactions to drugs and medical devices after drugs were introduced in the marketplace.

This strengthened set of oversight powers, however, still lacks certain tools, such as recall authority and civil money penalties, which could reinforce the agency's mission of assuring the safety, efficacy, and security of drugs. Unfortunately, more recent legislation related to the FDA and drug safety went in a different direction, seeking to speed up the pre-market drug approval process by the agency, extend some new patent protections drugs in the testing pipeline, and allow for the production of generic drugs after the expiration of a drug's patent protection. All of these changes had serious unforeseen consequences.

The Hatch-Waxman Act of 1984

The Drug Price Competition and Patent Term Act of 1984, known more commonly as the Hatch-Waxman Act because of its two key proponents, Sen. Orrin Hatch (R-UT) and Rep. Henry Waxman (D-CA) significantly shifted the focus of the FDA by changing patent law for newly-approved pharmaceuticals and by providing manufacturers with ex-

tended patents designed to ensure that the market value of new drugs did not expire during the wait for FDA approval.

In practice, manufacturers received a patent extension beyond the traditional 20-year limit equal to half the time between so called Phase III human clinical trials, which can last years, and FDA approval of manufacturers' New Drug Application, or NDA in pharmaceutical industry parlance. Under Hatch-Waxman, this patent extension cannot exceed five years or result in a total remaining market exclusivity of more than 14 years.

In addition, the Hatch-Waxman Act allowed for the manufacturing and marketing of generic versions of a drug after the patent has expired but with several key hurdles that first must be cleared by the generic drug makers. Specifically, any generic drug manufacturer applying for a so called abbreviated new drug application, or ANDA, must meet several criteria for approval, most important of which is a demonstration that the name-brand medication's patent is neither infringed nor invalid.

The patent owner in turn may file a patent infringement appeal, and receive an additional 30-month period of market exclusivity. The patent owner is then able to maintain this exclusivity until the FDA issues a decision on the infringement appeal, or (more typically) until the 30-month additional exclusivity period expires. At the end of this timeframe, the FDA can approve the ANDA and the generic manufacturer can begin production and marketing.

Hatch-Waxman, by implementing this new ANDA approval-and-appeal process, effectively created the U.S. generic drug industry, while providing protections for the original patent owner in the event of a dispute with the generic manufacturer. As it turned out, however, the subsequent implementation revealed some unforeseen consequences that sparked a new legislative effort to reform the FDA's drug approval process.

The Prescription Drug User Fee Act of 1992

A combination of the exponential growth in innovative pharmaceutical research in the 1970s and especially in the 1980s, alongside limited FDA staffing and other resources, led to a significant backlog of new drug applications at the FDA, resulting in a substantial waiting period between the manufacturer's submission of an NDA and FDA approval of a new drug. By 1993, on the eve of passage of the Prescription Drug User Fee Act of 1992, or PDUFA, standard new drugs endured a median review time of 27 months, while priority drugs targeted at serious and life-threatening diseases typically waited 21 months for approval.[1]

Critics at the time argued that the FDA's shortcomings adversely affected the entire U.S. drug market, which was unable to compete with other nations who had systems for drug approval that were efficient, predictable and punctual. These shortfalls also strained the agency. According to a 1991 report by the FDA's Advisory Committee, composed of several members including a consumer and industry or patient representative, "the FDA's grave resource limitations impose sometimes staggering burdens on the Agency."[2]

Congress responded by passing the Prescription Drug User Fee Act of 1992, which created application, product and establishment fees that support the FDA's drug approval staffing and activities. In addition to an FDA application fee for each new drug or biologic (drugs that are synthetically created while a biologic is prepared from animal tissue or another living source), drug manufacturers now had to pay new product and establishment fees that are annual charges for each drug a manufacturer has on the market. These fees fund a significant portion of the FDA's review costs. PDUFA also required the FDA to

dedicate a specified level of its overall appropriated budget to the drug review process.

This approach appeared to provide a successful remedy to the NDA backlogs, which prompted Congress to renew PDUFA in 1997 and 2002, extend the FDA's authority to collect user fees that support the agency's drug approval infrastructure, and adjust fees in accordance with inflation. The 1997 and 2002 reauthorizations of PDUFA (known as PDUFA II and PDUFA III) also included some notable changes to the statute—such as new incentives for pediatric drug research in 1997, and authority for the FDA to spend user fees on post-approval drug safety activities in 2002—but did not change the underlying philosophy of PDUFA.

Under current law, PDUFA establishes performance goals for the FDA, such as review of 90 percent of NDAs within 10 months of receipt of the application. PDUFA III will expire in September, 2007.

Effects of Hatch-Waxman and PDUFA

The combined effect of the policy changes made by Hatch-Waxman and the various incarnations of PDUFA has had a major impact on the U.S. pharmaceutical industry. In particular, the industry has expanded its global reach and achieved record profitability. Policy changes that have particularly contributed to these dynamics include extended market exclusivity available to expired patents upon the filing of an ANDA appeal and decreased waiting times for new drug approvals.

Effects on Industry

Analysts have concluded that PDUFA has had a significant impact on the pharmaceutical industry's profitability. In comparison to other U.S. industries, the pharmaceutical industry enjoys generous profit margins. Right before the passage of PDUFA III in 2002, Fortune 500 pharmaceutical companies in fiscal year 2002 generated an average profit margin of 18.5 percent compared to 2.2 percent for all other industries.[3] By fiscal year 2006 this percentage had grown to 21.1 percent for the 10 largest U.S. pharmaceutical companies compared to the 7.9 percent profit margin generated by the Fortune 500 companies as a group.[4]

Over this same period the United States became the worldwide leader in new drug development. Before 1992, only 8 percent of new drugs were first launched in the United States. Today, 50 percent of new drugs are first launched in this country.

The growth of the pharmaceutical industry's profitability is in part attributable to the policy changes enshrined in Hatch-Waxman and PDUFA I, II and III. For example, the companies routinely file infringement appeals on ANDA applications by generic drug manufacturers to produce and sell generic versions of previous patented drugs, thus triggering a thirty-month extension of patent rights. This practice enables pharmaceutical companies to prolong their patent exclusivity and control over supply to the detriment of consumers and their health insurance providers.

A 30 month extension within the Medicaid program alone would have saved state governments $1.5 billion between 2000 and 2004 if generics for just three drugs—Augmentin, Glucophage, and Prilosec—had been available and substituted when patent protection first expired.[5]

What's more, the initiation of user fees and the subsequent greater investment in the FDA's approval infrastructure accelerated the drug approval process and decreased waiting times for NDA approvals. From 1993 to 2003 the average approval time for standard drugs fell by nearly

36 percent.[6] The median approval time for priority drugs (typically innovative or pediatric medications) decreased to six months in fiscal year 2004 from 13.2 months in FY 1993. Since implementation of the original PDUFA legislation, the FDA has approved 1,010 new drugs and 100 new biologics.[7]

Effects on the FDA

User fees have increased exponentially since the passage of PDUFA. As NDA application fees have grown and the total number of NDA applications has increased, the FDA's user fee revenue has grown to $304 million at the end of FY 2006 from $87.5 million in FY 1997.[8] Today, user fees provide more than half of the funding for the review of human drugs.

The FDA has used these funds to improve their information technology systems and, most significantly, to hire additional review personnel. FDA staff devoted to the NDA review process has more than doubled, from 1,277 full-time equivalents in FY 1992 to 2,503 in FY 2004.[9]And some experts believe that PDUFA, in particular, has significantly changed the culture at the FDA, particularly at the agency's Center for Drug Evaluation and Research.

A recent Institute of Medicine study noted that drug safety is impaired by multiple factors, including resource constraints that affect the quality of science brought to bear on approval decisions, and unclear and insufficient regulatory authority. But the IOM pointedly noted that the PDUFA funding mechanism and PDUFA-related reporting requirements are "excessively oriented toward supporting speed of approval and insufficiently attentive to safety," and thus throw the agency's priorities out of balance.

The IOM report also argued that the extent to which the FDA relies on user fee revenue to fund its basic function of drug approval may cause the FDA to concern itself with maintaining a productive relationship with fee-paying manufacturers at the expense of the public interest in drug safety.[10] In addition, some studies indicate that the review deadlines imposed by PDUFA may have led to overly hasty approvals, with the subsequent need for post-approval regulatory actions, including warnings and withdrawals.

Research has found that the rate at which FDA-approved drugs experience post-marketing regulatory problems is appreciably higher for drugs approved in the months before the PDUFA clock deadlines, compared to other drugs, especially those approved in the months just following the elapsing of the deadline.[11]

In response, the Institute of Medicine has called for the inclusion of safety-specific performance goals in PDUFA IV, the implementing legislation of which is now on conference committee as House and Senate committee members try to reconcile the versions passed by the two chambers. Others, including former FDA commissioners and groups such as Public Citizen, have called for the abolition of user fees altogether, which would require congressional appropriations for the FDA to increase significantly to provide the resources needed for drug review.[12]

In fact, the FDA has received decreasing funding from Congress since FY 2003, even though the payroll costs have risen at 4 percent to 5 percent per year over the same period.[13] As a result, the FDA has been unable to hire all the additional staff envisioned in PDUFA III and now must devote some of its industry-generated user fee revenue to non-payroll items. In FY 2005 $169 million (59.7 percent of user fees) was expended on personnel, according to the FDA.[14]

The Cost of Hatch-Waxman and PDUFA to Consumers

The cost of prescription medications in the U.S. has increased disproportionately over the lifetime of PDUFA. Prescription drug prices increased by 8.3 percent annually between 1994 and 2004, compared with a 2.5 percent annual rate of inflation over the same period. Spending on prescription drugs also increased at a higher rate than health expenditures as a whole. Between 2000 and 2005, prescription drug spending grew by 59 percent, while all other health expenditures grew by 40 percent.

The several reasons why this has happened—primarily changes in patent law related to the drug approval process—have already been detailed, but there is another piece of regulatory history that is often overlooked as the cause of skyrocketing drug costs in the United States—changes to FDA's policy of policing pharmaceutical advertising in the wake of passage of the Hatch-Waxman Act in 1994.

Direct-to-Consumer Advertising

Direct-to-consumer drug advertising—television spots, print advertisements, and other media content with messages aimed at potential patients rather than medical professionals—increased dramatically over the past two decades. Prior to 1985, virtually all drug marketing was aimed only at physicians in an effort to influence physician prescribing patterns. In 1985 the FDA lifted the moratorium on direct-to-consumer advertising, referred to as DTCA in advertising circles, for prescription drugs and formalized DTCA requirements.

DTCA drug advertising was required to provide information regarding side effects, known complications, and effectiveness of advertised drugs. Nonetheless, spending on DTCA grew exponentially in subsequent years. Then, in a further relaxation of DTCA regulations in 1997, the FDA allowed manufacturers to disclose only the most common and dangerous side-effects.

These changes sparked a sharp jump in spending by the pharmaceutical industry on adver-

TABLE 1: SPENDING ON DIRECT-TO-CONSUMER ADVERTISING, 1997-2005

FISCAL YEAR	SPENDING ON DTC ADVERTISING ($ BILLIONS)	PERCENTAGE INCREASE FROM PREVIOUS FY
1997	1.1	—
1998	1.3	18%
1999	1.8	38%
2000	2.5	39%
2001	2.7	8%
2002	2.6	-4%
2003	3.3	27%
2004	4.0	2.1%
2005	4.2	5%
Average Annual Percentage Increase		19.6
Total Percentage Increase (1997-2005)		281.2

Source: U.S. Government Accountability Office, "Prescription Drugs: Improvements Needed in FDA's Oversight of Direct-to-Consumer Advertising" (2006).

The FDA does not require pharmaceutical manufacturers to submit advertisements for approval before running DTCA. However, the Pharmaceutical Research and Manufacturers of America in 2005 asked that all of its members submit their direct-to-consumer TV advertisements to the FDA before being broadcast.[16] Yet the FDA typically does not review or approve these advertisements before they are disseminated to the public, and manufacturers often submit an advertisement to the FDA at the same time as they begin running it.

The FDA acknowledges that it is unable to monitor the increasingly wide range of DTCA. From 1997 to 2002, the FDA's Division of Drug Marketing, Advertising, and Communications issued 88 regulatory letters, only four of which were warning letters indicating advertisements that exaggerate a drug's efficacy or otherwise egregiously violated FDA's advertising rules. The agency also admitted that it was unable to review all newly disseminated advertisements.[17]

DTCA is one of the important elements that have changed the decision-making balance between patients and physicians. Patients play an increasingly decisive role in determining their drug regimens as a result of what they learn from advertisements in the media. A Henry J. Kaiser Family Foundation study in 2001 found that 30 percent of those interviewed were prompted to inquire about a drug they learned about through advertising.[18] Of the 30 percent who made an inquiry to their physician, 44 percent received a prescription for the drug.[19]

The same study found that only 16 percent of physicians interpreted DTCA as educational and 39 percent viewed the effect of DTCA on patients as negative. Indeed, physician-patient relationships are jeopardized by DTCA because patients perceive as negligence the unwillingness of a physician to prescribe a drug learned about through DTCA.[20]

DTCA is also responsible, in part, for escalating prescription drug spending. Among the top-selling classes of drugs, DTCA is accountable for an increase of 12 percent, or $2.6 billion, in consumer drug spending.[21] For every dollar pharmaceutical companies invest in DTCA, drug sales increase by $4.20 as a result.[22]

Safety Concerns

FDA time and funding dedicated to post-marketing safety is not sufficient to protect consumers. Manufacturers are required to submit a so-called adverse-event report within 15 days of receiving notification that such an event has occurred. Adverse-event reports are the FDA's primary method of monitoring post-marketed drugs, yet these reports represent a small minority of drug-related complications experience by patients. The reason: adverse-event reports are voluntarily generated, usually by a health care provider, yet there is no system in place at the FDA for receiving these reports or for other post-marketing drug surveillance.

Nevertheless, reports of adverse events increased by about 900 percent in the time between 1992 and 2004. The FDA has told Congress that it does not currently have the resources to receive, respond to, or analyze adverse event report data once it is received. The FDA currently receives about three-fifths of its adverse event reports on paper, which must be manually entered into the FDA database.

"Me Too" Drugs

One result of the Hatch-Waxman Act is the proliferation of so-called "me too" drugs, drugs that essentially mimic existing drugs but are different enough in chemical formulation to warrant a new patent. These drugs provide manufacturers with the means to extend the life of a patent or a way to dip into an already profitable drug

market. Efforts to research and market "me too" drugs are counterintuitive to the principle behind patents because they hinder innovation while increasing drug industry profits.

Manufacturers, however, have significant incentives to enter the "me too" drug market because these drugs are more likely to be approved and are more easily advertised to consumers who are already familiar with similar drugs. The flip side of this incentive is that the Big pharma are spending less on innovative drug research.

Only one-third of pharmaceutical industry research and development spending, about $802 million per so-called "new molecular entity" in 2000 is devoted to creating these innovative drugs that do not contain molecules already approved by the FDA.[23] Only one half of those drugs are first-in-class breakthroughs. New and innovative breakthrough drugs are receiving a limited amount of focus from the pharmaceutical industry due to clearly misplaced incentives introduced by certain aspects of the Hatch-Waxman Act and PDUFA.

Recent Policy and Legislative Initiatives

These changes in prescription drug approvals, oversight, spending trends, and safety—all of which have occurred as a direct or indirect result of Hatch-Waxman and PDUFA—are now the focus of a congressional conference committee, which hopes to iron out differences in legislation the House and Senate passed separately earlier this year. As Congress considers the reauthorization of PDUFA for the fourth time it has developed a range of proposals designed to address these issues. These proposals have been informed by expert panels and independent analysts who have examined the current drug approval system.

The recent Institute of Medicine study, for example, identified a number of shortcomings in drug safety. While noting that other parts of the health care industry also bear responsibility for drug safety, the report highlights drug safety concerns specific to the FDA's culture, funding streams, organization, and regulatory authority. The IOM's recommendations range from creating a six-year term for FDA commissioners to improving the agency's implementation of statistical surveillance methods for enhancing post-approval monitoring, and from improving the scientific information available to the agency when considering NDAs to building the FDA's capacity for scientific research, particularly in the fields of epidemiology and informatics.

The Institute of Medicine also made recommendations for mandatory registration of the results of pre-approval drug trials and public access to those trial results. The IOM also called for strengthened FDA regulatory authority, particularly related to enforcement tools, including fines, injunctions, and withdrawal of drug approvals.

Other analysts also recommend significant changes to the FDA's regulatory authority. A recent report published in *Archives on Internal Medicine* proposes five ways to improve safety through FDA regulation:

- Give the FDA more direct legal authority to pursue companies that violate regulations and ignore post-marketing safety study obligations
- Authorize the adoption of a conditional drug approval policy
- Provide the FDA with additional financial resources to ensure that safety operations are funded
- Mandate FDA restructuring with an emphasis on evaluating and proactively monitoring post-marketing drug safety
- Enhance FDA advisory committees by expanding representation of safety experts

After discussions with the pharmaceutical industry, the FDA submitted a set of recommendations for PDUFA reauthorization to Congress in March 2007.[24] These included increased spending on safety initiatives that would be funded out of increased user fee revenues, new performance goals that would reduce timeframes for NDA reviews to two and a half months, and new fees for advertised products, which would fund FDA staff to screen DTCA television spots.

Taking all of these recommendations into consideration, both chambers of Congress passed new PDUFA legislation earlier this year. Senate bill S1082 was passed on May 9, 2007, reauthorizing the Prescription Drug User Fee Act through 2012.The bill requires that pharmaceutical companies pay the FDA about $443 million in user fees in fiscal year 2008, compared with $305 million in fiscal year 2007. The legislation also includes a number of prescription drug safety provisions, including the establishment of a computerized network to scan public and private health insurance and pharmacy records for indications of safety issues with new medications.

The Senate bill would also increase the minimum civil fine that the FDA could impose on pharmaceutical companies for failure to comply with agency requests for label revisions or additional studies of medications. The minimum fine would rise to $250,000 from $10,000, with the maximum fine rising to $2 million from $1 million. The bill also would allow the agency to fine companies for false or misleading advertisements—$150,000 for a first offense and $300,000 for additional offenses

On July 11 the House of Representatives passed H.R. 2900, which would also authorize PDUFA through 2012. Both bills increase user fees and make attempts at addressing post-market surveillance as well as DTCA, but fail to do so effectively.[25] The House bill creates a new FDA program subjecting new drugs to increased surveillance and safety requirements. Additionally, the House bill increases penalties placed on companies that fail to comply with safety standards.

While both pieces of legislation emphasize the need for more efficient and faster approval of drugs through increased user fees, they do not establish an outside agency to address drug safety post-marketing. An outside agency would ensure that the approval for drugs was not influenced by special interests or political pressures. Instead, the Senate bill establishes post-marketing safety provisions within the FDA, including a computerized network for monitoring insurance companies and pharmacies for safety issues with new drugs. The House bill creates a new FDA program subjecting new drugs to increased surveillance and safety requirements. These measures may improve post-marketing surveillance, but do not attend to the need for neutrality and oversight.[26]

Both bills establish a fee-for-advisory review of DTCA and impose fines on pharmaceutical companies that issue false or misleading advertisements. The fine structures differ slightly between the two bills, with the Senate version setting $150,000 for the first offense and $300,000 for subsequent offenses. The House version sets a maximum of $250,000 for the first offense and $500,000 per day for subsequent offenses within a three-year period. Still, neither bill goes as far as to revert to the pre-1985 moratorium on DTCA.

Some additional aspects of the Senate bill include the implementation of systems that transmit safety information to the public and increased fines for companies that fail to comply with FDA requests for label revisions or additional studies on drugs. The House bill includes measures to ensure that the FDA will not act based on the personal financial interests of advisory panel members.

Unfortunately, neither bill addresses the 30-month patent extension, which slows the entrance of generic drugs into the marketplace. Nor do the two bills address the control of "me too" drugs.

CAP Policy Recommendations

PDUFA reauthorization provides an opportunity to address some of the widely-acknowledged problems associated with the U.S. drug approval, marketing, and surveillance systems. As Congress continues to consider its policy options related to extending PDUFA in conference committee, it should pay particular attention to patent exclusivity, DTCA, and drug safety concerns, including post-marketing surveillance and enforcement. Specifically, the Center recommends:

Congress should remove from the Hatch-Waxman Act the 30-month exclusivity provision for patented drugs facing a generic drug ANDA. This would allow the FDA to approve the manufacture of a generic immediately following expiration of a drug's patent term. Repeal of the 30-month exclusivity provision would decrease drug spending since generic drugs are sold at a fraction, usually 60 percent, of what patented drugs cost. The provision boosts pharmaceutical profits but hurts consumers, who pay artificially high prices for drugs that, if generic, would be far less expensive.

Congress should require that the FDA revert back to its pre-1985 moratorium on direct-to-consumer advertising. Before 1985, the FDA allowed DTCA provided it follow the same guidelines as advertisements directed to health care professionals, including full disclosure of side effects and warnings. Additionally, this provision would ensure that pharmaceutical companies spend funds more efficiently, toward new drug development rather than advertisements.

Congress should create a Center for Post-Marketing Drug Evaluation and Research independent of the FDA to maintain neutrality and oversight in the review of drugs after they are approved for use by the general public. This new center would evaluate adverse-event reports and react appropriately, and would have regulatory authority to withdraw approved drugs that prove to be unsafe.

Congress should ensure that pharmaceutical companies are also accountable for ensuring greater post-market drug safety. Pharmaceutical companies should be required to undertake post marketing, or Phase IV, safety studies and make the results available, along with Phase III safety trials, on a government website. In addition to mandating the structural and policy changes, Congress must adequately fund the FDA.

Congress should require the FDA to discourage the proliferation of "me too" drugs by requiring all non-innovative drug NDAs to undergo extensive comparative clinical trials, during which the new drug will be compared with other medications with a similar therapeutic effect already on the market. The medications should be tested for safety, efficacy, and pharmacoeconomics in comparison to competing drugs and the results of these comparisons should be posted on a public website.

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Bibliography

Institute of Medicine of the National Academy of Sciences Committee on the Assessment of the U.S. Drug Safety System. 2006. "The Future of Drug Safety: Promoting and Protecting the Health of the Public." A. Baciu, K. Stratton K, and S.P. Burke, eds. Washington D.C. (Report Brief accessed on Jan. 1, 2007 at www.iom.edu/Object.File/Master/37/331/11750_report_brief_congress.pdf)

Berndt ER, Gottschalk AH, Philipson TJ and Strobeck MW. 2005. "Industry Funding of the FDA: Effects of PDUFA on Approval Times and Withdrawal Rates." Nature Reviews Drug Discovery 4(7)(2005):545-54.

Brown D. 2007. "Congress Seeks to Balance Drug Safety, Quick Approval." *The Washington Post*. July 5, p. A4.

Calfee, JE. 2006. "Innovative Drug Development in the Context of FDA Regulation." Washington: American Enterprise Institute for Public Policy Research. (Accessed Dec. 26, 2006 at http://www.aei.org/publications/filter.all,pubID.23845/pub_detail.asp)

Carpenter, D, Chernew M, Smith DG, and Fendrick AM. 2003. "Approval times for new drugs: Does the source of funding for FDA staff matter?" *Health Affairs* W3- 618-624.

Carpenter, D. 2007. "Deadline Effects in Regulatory Drug Review: A Methodological and Empirical Analysis." DefendingScience.org. (Accessed on July 5, 2007 at http://www.defendingscience.org/newsroom/upload/Carpenter_FDA_Deadlines-2.pdf)

Center for Medicare and Medicaid Services. 2006. "National Health Care Expenditures Projections 2005-2015." Washington. (Accessed Dec. 28, 2006 at http://www.cms.hhs.gov/NationalHealthExpendData/downloads/proj2005.pdf)

Congressional Budget Office 2006. "Research and Development in the Pharmaceutical Industry." Washington. (Accessed on Jan. 1, 2007 at http://www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf)

Danzon, PM, and Furukawa MF. 2003. "Prices and Availability of Pharmaceuticals: Evidence from Nine Countries." *Health Affairs* (10):1377. (Accessed Jan. 1, 2007 at http://content.healthaffairs.org/cgi/gca?ck=nck&allch=&SEARCHID=1&AUTHOR1=danzon&FIRSTINDEX=0&hits=10&RESULTFORMAT=&gca=healthaff%3Bhlthaff.w3.521v1#hlthaff.w3.521v1)

Food and Drug Administration. 2006a. "2005 Performance Report to the President and the Congress for the Prescription Drug User Fee Act." Washington. (Accessed December 20, 2006 at http://www.fda.gov/oc/pdufa/finreport2005/PDUFA05finrpt.html)

Food and Drug Administration. 2006b. "2005 Financial Report to the President and the Congress for the Prescription Drug User Fee Act." Washington. (Accessed Dec. 20, 2006 at http://www.fda.gov/oc/pdufa/finreport2005/PDUFA05finrpt.html)

Food and Drug Administration. 2006c. White "Paper: Prescription Drug User Fee Act (PDUFA): Adding Resources and Improving Performance in FDA Review of New Drug Applications." Washington. (Accessed December 20, 2006 at http://www.fda.gov/oc/pdufa/PDUFAWhitePaper.pdf)

Food and Drug Adminstration. 2007. "Prescription Drug User Fees. The Act; PDUFA IV." Washington. (Accessed on July 11, 2007 at http://www.fda.gov/cder/pdufa/PDUFA_IV.pdf).

"Fortune 500, Pharmaceutical industry ranking of revenues and profits." *CNN Money*, April 30, 2007 (Accessed on July 10, 2007 at http://money.cnn.com/magazines/fortune/fortune500/2007/industries/Pharmaceuticals/1.html).

Furberg CD, Levin AA, Gross PA, and Strom BL. 2006. "The FDA and Drug Safety: a Proposal for Sweeping Changes." *Arch Intern Med* 166:1938-42.

George Washington University School of Public Health and Health Services. 2007. "Reauthorizing the Prescription Drug User Fee Act: How are PDUFA, the FDA Budget and Drug Safety Related?" Washington.

Government Accountability Office. 2002. "Prescription Drugs: FDA Oversight of Direct-to-Consumer Advertising Has Limitations." Washington. (Accessed on January 1, 2007 at http://www.gao.gov/new.items/d03177.pdf)

Government Accountability Office. 2006. "Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process." Washington. (Accessed on Jan. 1, 2007 at http://www.gao.gov/new.items/d06402.pdf)

Grabowski HG and Wang YR. 2006. "The Quantity and Quality of Worldwide New Drug Introductions, 1982–2003." *Health Affairs* 25(2): 452-460.

Henry J. Kaiser Family Foundation. 2001. "Understanding the Effects of Direct-to-Consumer Prescription Drug Advertising." (Accessed Dec. 21, 2006 at http://www.kff.org/rxdrugs/upload/Understanding-the-Effects-of-Direct-to-Consumer-Prescription-Drug-Advertising-Report.pdf)

Henry J. Kaiser Family Foundation. 2005. "Prescription Drug Trends." (Accessed Dec. 28, 2006 at http://www.kff.org/insurance/upload/3057-04.pdf)

"H.R.2900: Food and Drug Administration Amendments Act of 2007." 110th Congress. Introduced in House June 28, 2007. (Accessed July 18, 2007 at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:h2900rh.txt.pdf)

Bibliography

Institute of Medicine. 2007. "The Future of Drug Safety: Promoting and Protecting the Health of the Public."

Jarvis, LM. 2006. "Life after Zocor." *Chemical and Engineering News* 84(34):32-33. (Accessed on Dec. 26, 2006 at http://pubs.acs.org/cen/business/84/8434bus2.html)

Kaufman, M. 2005. "Drug Safety Panel is Criticized." *The Washington Post*. June 8, p. A5. (Accessed on December 26, 2006 at http://www.washingtonpost.com/wp-dyn/content/article/2005/06/07/AR2005060701739.html)

Kesselhelm, AS, Fischer, MA, and Avorn, J. 2006. "Extensions of Intellectual Property Rights and Delayed Adoption of Generic Drugs: Effects on Medicaid Spending." *Health Affairs* 25(6):1637-1647.

Light, D. W., and J. Lexchin. 2004. "Will Lower Drug Prices Jeopardize Drug Research? A Policy Fact Sheet." *The American Journal of Bioethics* 4(1):W1-W4. (Accessed on Dec. 31, 2006 at http://www.bioethics.net/journal/pdf/4_1_IF_w01_Light. pdf)

Mossinghoff, GJ. 1999. "Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process." *Food Drug Law* J 54:187-194.

National Institute for Health Care Management. 2002. Changing Patterns of Pharmaceutical Innovation. (Accessed January 1, 2007 at http://www.nihcm.org/finalweb/innovations.pdf)

National Institute for Health Care Management. 2000. "Prescription Drugs and Mass Media Advertising." (Accessed Dec. 21, 2006 at http://www.nihcm.org/DTCbrief2001.pdf)

National Science Foundation. 2006. "U.S. Industrial R&D Performers Report Increased Expenditures for 2004." (Accessed December 28, 2006 at http://www.nsf.gov/statistics/infbrief/nsf07304/)

Department of Health and Human Services Office of Inspector General. 2006. "FDA's Monitoring of Postmarketing Study Commitments." Washington. (Accessed on January 1, 2007 at http://oig.hhs.gov/oei/reports/oei-01-04-00390.pdf)

Palumbo, FB and Mullins, CD. 2002. "The Development of Direct-to-Consumer Prescription Drug Advertising Regulation." *Food Drug Law* J 57:423-443.

PBS Frontline. Interview with John Kelly, spokesman for the Pharmaceutical Research and Manufacturers of America (PhRMA). Feb. 12, 2003. (Accessed Dec. 26, 2006 at http://www.pbs.org/wgbh/pages/frontline/shows/prescription/interviews/kelly.html)

Pharmaceutical Research and Manufacturers of America. 2005. Press release. Feb. 18. (Accessed Dec. 28, 2006 at http://www.phrma.org/news_room/press_releases/_r&d_investment_by_pharmaceutical_companies_tops_$38_billion_in_2004/)

Pharmaceutical Research and Manufacturers of America. 2005. "PhRMA Guiding Principles Direct to Consumer Advertisements About Prescription Medicines." (Accessed Dec. 26, 2006 at http://www.phrma.org/publications/policy_papers/phrma_dtc_guiding_principles/)

Philipson, TJ, Berndt, ER, Gottschalk, AHB, and Strobeck, MW. 2005. "Assessing the Safety and Efficacy of the FDA. The Case of the Prescription Drug User Fee Acts." Working Paper 11724. National Bureau of Economic Research. (Accessed Dec. 20, 2006 at http://www.nber.org/papers/w11724)

Public Citizen. 2002. "Pharmaceutical Industry Ranks as Most Profitable Industry -- Again." (Accessed January 1, 2007 at http://www.citizen.org/documents/fortune500_2002erport.PDF)

Ray, WA, and Stein, CM. 2006. "Reform of Drug Regulation – Beyond an Independent Drug-Safety Board." *New Engl J Med* 354:194-202.

Rosenthal, MB, Berndt, ER, Donohue, JM, Epstein, AM and Frank, RG. 2003. "Demand Effects of Recent Changes in Prescription Drug Promotion." Henry J. Kaiser Family Foundation. (Accessed Dec. 21, 2006 at http://www.kff.org/rxdrugs/upload/Demand-Effects-of-Recent-Changes-in-Prescription-Drug-Promotion-Report.pdf)

Steinman, MA, Bero, LA, Chren, MM, and Landefeld, CS. 2006. "The Promotion of Gabapentin: An Analysis of Internal Industry Documents." *Ann Int Med* 145:284-293.

Source Watch. 2006. "Direct-to-Consumer Advertising in the United States -- Drug Companies Pay for Ad Approvals." Center for Media and Democracy. (Accessed Dec. 26, 2006 at http://www.sourcewatch.org/index.php?title=Direct-to-consumer_advertising_in_the_United_States/Drug_Companies_Pay_for_Ad_Approvals)

"S930: Food and Drug Administration Act of 2005." 109th U.S. Congress. Introduced in Senate April 27, 2005. (Accessed Dec. 26, 2006 at http://thomas.loc.gov/cgi-bin/query/z?c109:S.930.IS:)

"S1082: Prescription Drug User Fee Amendments of 2007." 110th Congress. Introduced in Senate April 10, 2007. (Accessed July 18, 2007 at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:s1082es.txt.pdf)

Bibliography

"S3807: Enhancing Drug Safety and Innovation Act of 2006." 109th Congress. Introduced in Senate Aug. 3, 2006. (Accessed Dec. 26, 2006 at http://thomas.loc.gov/cgi-bin/thomas)

Tully, S. 2007. "A Profit Gusher of Epic Proportions." *CNN Money*. April 15. (Accessed July 10, 2007 at http://money.cnn.com/magazines/fortune/fortune_archive/2007/04/30/8405391/index.htm).

U.S. House of Representatives, Committee on Government Reform and Oversight. "Prescription Drug Pricing in the 7th Congressional District of Maryland: An International Price Comparison." 1999. Washington. (Accessed on January 1, 2007 at http://www.house.gov/cummings/pdf/intl.pdf)

End Notes

1 George Washington University School of Public Health and Health Services, "Reauthorizing the Prescription Drug User Fee Act: How are PDUFA, the FDA Budget and Drug Safety Related?" (2007).

2 Ibid.

3 Public Citizen. "Pharmaceutical Industry Ranks as Most Profitable Industry – Again." (2002). Available at http://www.citizen.org/pressroom/release.cfm?ID=1088 (last accessed July 10, 2007).

4 S. Tully, "A Profit Gusher of Epic Proportions." CNN Money, April 15, 2007. Available at http://money.cnn.com/magazines/fortune/fortune_archive/2007/04/30/8405391/index.htm (last accessed July 10, 2007); "Fortune 500 Pharmaceutical Industry Ranking of Revenues and Profits." CNN Money April 30, 2007. Available at http://money.cnn.com/magazines/fortune/fortune500/2007/industries/Pharmaceuticals/1.html (last accessed July 10, 2007).

5 A. Kesselhelm et al., "Extensions of Intellectual Property Rights and Delayed Adoption of Generic Drugs; Effects on Medicaid Spending," *Health Affairs* 25 (6) (2006).

6 D. Brown, "Congress Seeks to Balance Drug Safety, Quick Approval," *The Washington Post*, July 5, 2007, A04.

7 Food and Drug Administration, "White Paper: Prescription Drug User Fee Act (PDUFA): Adding Resources and Improving Performance in FDA Review of New Drug Applications." (2006). (Last accessed Dec. 20, 2006 at http://www.fda.gov/oc/pdufa/PDUFAWhitePaper.pdf)

8 Food and Drug Administration, "2005 Financial Report to the President and the Congress for the Prescription Drug User Fee Act." (2006). (Last accessed Dec. 20, 2006 at www.fda.gov/oc/pdufa/finreport2005/PDUFA05finrpt.html) and D. Brown, "Congress Seeks to Balance Drug Safety, Quick Approval," *The Washington Post*, July 5, 2007, p. A4.

9 Food and Drug Administration, "White Paper: Prescription Drug User Fee Act (PDUFA): Adding Resources and Improving Performance in FDA Review of New Drug Applications." (2006). (Last accessed December 20, 2006 at http://www.fda.gov/oc/pdufa/PDUFAWhitePaper.pdf)

10 Institute of Medicine, "The Future of Drug Safety: Promoting and Protecting the Health of the Public." (2007).

11 D. Carpenter et al., "Deadline Effects in Regulatory Drug Review: A Methodological and Empirical Analysis." DefendingScience.org, March 2007. (Last accessed on July 5, 2007 at http://www.defendingscience.org/newsroom/upload/Carpenter_FDA_Deadlines-2.pdf)

12 Institute of Medicine, "The Future of Drug Safety: Promoting and Protecting the Health of the Public" (2007).

13 Food and Drug Administration, "White Paper: Prescription Drug User Fee Act (PDUFA)."

14 Food and Drug Administration. "2005 Financial Report to the President and the Congress for the Prescription Drug User Fee Act."

15 U.S. Government Accountability Office, "Prescription Drugs: Improvements Needed in FDA's Oversight of Direct-to-Consumer Advertising." (2006). Available at http://www.gao.gov/htext/d0754.html.

16 Pharmaceutical Research and Manufacturers of America, "PhRMA Guiding Principles: Direct to Consumer Advertisements About Prescription Drugs." (Last accessed at http://www.phrma.org/files/2005-11-29.1194.pdf on July 25, 2007).

17 Government Accountability Office, "Prescription Drugs. FDA Oversight of Direct-to-Consumer Advertising has limitations." (2002). (Last accessed at http://www.gao.gov/new.items/d03177.pdf on July 11, 2007).

18 Kaiser Family Foundation, "Understanding the Effects of Direct-to-Consumer Prescription Drug Advertising." (2001).

19 Ibid.

20 National Institute for Health Care Management, "Prescription Drugs and Mass Media Advertising." (2000). (Last accessed December 21, 2006 at www.nihcm.org/DTCbrief2001.pdf).

21 M. Rosenthal et al., "Demand Effects of Recent Changes in Prescription Drug Promotion." Henry J. Kaiser Family Foundation. (Last accessed December 21, 2006 at http://www.kff.org/rxdrugs/upload/Demand-Effects-of-Recent-Changes-in-Prescription-Drug-Promotion-Report.pdf).

22 Ibid.

23 Congressional Budget Office, "Research and Development in the Pharmaceutical Industry." (2006).

24 FDA, "Prescription Drug User Fees. The Act; PDUFA IV. Recommendations transmitted to Congress March 16, 2007." (2007). (Last accessed at http://www.fda.gov/cder/pdufa/PDUFA_IV.pdf on July 11, 2007).

End Notes

25 "S.1082: Prescription Drug User Fee Amendments of 2007." 110 Cong. 1 Sess. Introduced in Senate April 10, 2007. (Last accessed July 18, 2007 at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:s1082es.txt.pdf) and "H.R. 2900: Food and Drug Administration Amendments Act of 2007," 110 Cong. 1 Sess. Introduced in House June 28, 2007. (Last accessed July 18, 2007 at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:h2900rh.txt.pdf).

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