ABSTRACT  The pharmaceutical industry is one of the largest and most profitable industries in the world, and in the United States, the industry has a particularly privileged economic position. Yet the cost of drugs in the United States is higher than anywhere else, due largely to the fact that the industry is focusing increasingly on marketing rather than on the development of meaningful new medications; available evidence does not support claims of great expense for the development of new drugs. Because of its vast resources, the pharmaceutical industry has assumed an increasing influence in medicine, which, given the differences in values and priorities between medicine and the drug companies, is a cause for concern. The pharmaceutical industry has acted to maximize its profits in ways that frequently conflict with medicine's need for truth and full disclosure; indeed, the industry has arguably worked to compromise physicians' judgments, as well as academic standards. As a result, despite government regulation there have been unnecessary adverse effects from drugs. The experience with bupropion (Wellbutrin®) exemplifies problems in the current system and the harm that can result. Changes are suggested to make the pharmaceutical industry more responsive to the needs of patients and physicians.

MEDICINE AND THE PHARMACEUTICAL INDUSTRY have a mutually dependent but uneasy relationship. There are many reasons for this uncase, and the concerns, though increasing, are not new (see, for example, May 1961). Physi-
Physicians and the pharmaceutical industry have fundamentally different priorities and goals. For physicians, the ideal of patient management is an unbiased analysis of what would be best for treatment of an individual patient. However much this ideal is or can actually be practiced, it forms the basis for physicians’ judgments of themselves and of others involved in patient care. By contrast, the primary obligation of drug companies is to make a profit for their shareholders. As appropriate as this goal may be for a business, it is inherently amoral, and in a medical environment, it may readily become immoral.

This article will explore the role of the pharmaceutical industry in the development, promotion, and regulation of drugs, as well as the industry’s influence on the medical profession, using the experience with butorphanol (Stadol®) to illustrate current problems. Much of the information in this review has been obtained through the Freedom of Information Act and would not be available without this legislation and the effort required to obtain information under this Act. Many of the events discussed in this article were not generally known at the time they occurred.

The Pharmaceutical Industry

Profits

Pharmaceutical companies are among the largest and most profitable in the world. Most are now multinational. At least 10 of these companies had revenues in 2000 greater than $9.8 billion—the largest had revenues of $40 billion (Wayne and Petersen 2001). Profits of the 11 drug companies in the Fortune 500 averaged 19 percent of revenue; the median for all other Fortune 500 companies was 5 percent (Fortune 2001). Since 1982, the pharmaceutical industry has topped Fortune’s ranking for return on revenue. This return relative to other Fortune 500 companies has been increasing, from twice that of the median for other Fortune 500 companies in the 1970s to about four times today (Public Citizen 2001).

Drug Development Costs

The pharmaceutical industry justifies its high profits by citing the high costs needed to develop new drugs. The figure commonly quoted by the industry, $500 million per new drug, stems from an analysis published in 1991 (DiMasi et al. 1991), with expenses extrapolated to current dollars. This study was performed by the Tufts Center for the Study of Drug Development (http://csdd.tufts.edu), whose sponsors include some of the largest drug companies, and was based on data supplied by the drug companies themselves. These data have never been independently verified, and the conclusions have been questioned by the Office of Technology Assessment (1993). Dr. Nelson Levy, a former head of research and development at Abbott Laboratories, has been quoted as saying that the $500 million cost to develop a drug “is a lot of bull” (Gerth and Stolberg 2000). DiMasi,
et al.’s, estimates of the costs of research and development (R&D) of new drugs is about four times higher than a previous pharmaceutical industry study (Wiggins 1987) and is not supported by figures from the Pharmaceutical Research and Manufacturers of America (PhRMA), the pharmaceutical trade association. Dividing the reported expenses for pharmaceutical R&D in the 1990s by the number of new drugs approved by the Food and Drug Administration (FDA) in the same period produces an estimate for the cost for developing a new drug on the order of $100 million (Public Citizen 2001). These figures do not include tax credits that would reduce the cost to the companies of every dollar spent on R&D by one-third. The pharmaceutical industry costs for R&D are also buffered by an unusually low effective tax rate—16 percent from 1993 to 1996, in comparison to an average effective tax rate of 27 percent for other major industries during the same period (Anderson 1999; Congressional Research Service 1999).

The pharmaceutical industry benefits from government largesse in other ways. The U.S. government or foreign academic institutions support much of the basic research involved in developing new medications. This was true for over 77 percent of the studies important for developing the five top-selling drugs in 1995 (NIH 2000). U.S. taxpayers are paying the highest prices in the world for drugs they have already paid to develop (Gerth and Solberg 2000). Americans now pay up to twice as much for the same drug as Canadians or Europeans, and those least able and most needy—the chronically ill elderly—are now usually paying the most (Angell 2000b). Companies in Europe or Japan have been as productive in developing new drugs as those in the United States, despite the price and profit controls on the pharmaceutical industry in both Europe and Japan (EFPIA 2000).

The pharmaceutical industry invests relatively little in new drugs, drugs that the FDA calls “new molecular entities.” Much drug development involves new dosage forms or combinations of existing drugs, which may offer little or no therapeutic gain. The latest government, non-industry, information about this is from 1991; subsequently, reportedly under pressure from the pharmaceutical industry, the FDA stopped reporting such data (Drake and Uhlman 1993). Non-governmental research, however, indicates that 65 percent of new drugs introduced between 1989 and 2000 used active ingredients already on the market, and 76 percent offered no significant benefit over already available products (National Institute for Health Care Management 2002).

It is impossible to be certain of pharmaceutical R&D costs, since the industry has not allowed any outside examination. The General Accounting Office attempted to obtain such information, in order to determine whether the expense of producing new drugs justified the costs paid for these drugs by government agencies such as the Department of Veterans Affairs. However, the pharmaceutical industry waged a successful nine-year legal battle, up to the Supreme Court, to prevent such disclosure (Office of Technology Assessment 1993, Appendix D). Obtaining information from the pharmaceutical industry about the
cost of R&D would require congressional action—and this has not been forthcoming. The pharmaceutical industry spends considerably more than any other industry for congressional lobbying; drug companies spent $177 million during the last election cycle for lobbying and $20 million on campaign contributions (Wayne and Petersen 2001). This is $50 million more than the industry with the next highest lobbying expenditures (the insurance industry), and four times that, for example, of automobile manufacturers.

Marketing

The pharmaceutical industry is increasingly focused on marketing rather than on creating new drugs (Harris 2000). In 2000, the eleven Fortune 500 drug companies spent 30 percent of their revenues for marketing and administrative costs, and only 12 percent on R&D (Public Citizen 2001). Moreover, the industry is increasingly interested in clinical trials designed to produce a marketing advantage rather than a clinically meaningful effect (Langreth 1998). Since regulations for TV advertising were relaxed in 1997, direct-to-consumer (DTC) advertising has increased from $791 million to $2.5 billion in 2000. This marketing strategy has been successful—the increase in advertising has fueled an increased spending on drugs (Petersen 2001). DTC advertisements are thought to bring a return of $5 to $6 for each dollar spent and have become a recognized tool for producing a high-selling drug (Hall 2001). Of the $20.8 billion increase in retail spending for prescription drugs from 1999 to 2000, 47.8 percent was due to sales of the 50 drugs most heavily advertised to consumers; the other 9,850 available drugs accounted for the remaining 52.2 percent (National Institute for Health Care Management 2001). In 1998, Schering-Plough spent more money advertising its allergy drug Claritin® than Coca-Cola spent advertising Coke. Claritin® was arguably marketed in a questionable fashion and is possibly less effective than older, less expensive medications used for the same indication, some of which are produced by the same company (Hall 2001). Nonetheless, the sales of the Claritin® line of drugs in 2000 was $2.6 billion—30 percent of Schering-Plough’s revenue.

Since the mid-1980s, federal laws have increased the availability of less expensive generic medications in return for allowing drug companies to extend the patent life of new products (Public Citizen 2001). Given the large profit from delaying generic medications, the pharmaceutical industry has expended considerable resources to undercut the purpose of these laws. Their efforts have included lobbying for legislation to extend the patent life of a specific drug, legal action related to patent infringement for aspects of a drug’s production not directly related to its therapeutic value, and payments to generic manufacturers for not producing a drug (Harris 2000; Stolberg and Gerth 2000). On 31 July 2002, the U.S. Senate passed legislation designed to reduce the ability of drug companies to delay the approval and marketing of generic products (Pear 2002).
Sales Promotions

The pharmaceutical industry now spends $13 billion a year on promotions, most of which is directed towards physicians. There is approximately one pharmaceutical sales representative for every 10 to 15 physicians in the United States, at a yearly cost of about $5 billion (Wolfe 1996); drug companies spend an estimated $8 to $13 thousand per year for each physician (Drake and Uhlman 1993). Such promotional activity has produced concern in the medical community as well as elsewhere.

Statements made by pharmaceutical representatives about drugs may contradict information readily available to these representatives (Ziegler, Lew, and Singer 1995). Pharmaceutical advertising is frequently misleading. One study designed to assess pharmaceutical advertising reported that 57 percent of the advertisements had no educational value; 44 percent could lead to improper prescribing; and 62 percent would not have been recommended for publication or would have required major revisions (Wilkes, Doblin, and Shapiro 1992). Such commercial, non-scientific material is the predominant source of drug information for physicians. As one study stated: "Drug advertisements are simply more visually arresting and conceptually accessible than are papers in the medical literature, and physicians appear to respond to this influence" (Avorn, Chen, and Hartley 1982). Physicians are now under additional coercion from drug advertisements due to pressure from patients related to the increase in DTC promotions.

Physician contact with drug representatives starts in medical school and continues frequently—about four times per month—during a physician's career (Wazana 2000). In one study, 54 percent of physicians reported being visited at least once a day by a pharmaceutical company representative (Guldal and Semin 2000). These contacts influence—at times strongly—drug prescription habits, as well as requests by physicians for formulary additions (Chren and Landefeld 1994; Lurie et al. 1991; Wazana 2000). The effects of these interactions are frequently reinforced by gifts, meals, travel, honoraria, and research support. Both medical faculties and residents appear to recognize that contact with drug sales representatives can influence their behavior. In one study, a majority of those surveyed felt that gifts worth more than $100 would likely compromise a physician's independence and objectivity, and a majority favored eliminating presentations by pharmaceutical representatives at their hospitals (McKinney et al. 1990). Policies restricting contacts with pharmaceutical company representatives during residency training have been shown to result in fewer contacts after training and a less positive attitude towards the information from such contacts (McCormick et al. 2001). Physicians feel that they have had inadequate training about dealing with drug representatives (McKinney et al. 1990), and even brief resident training appears to enhance residents' awareness of problems associated with the pharmaceutical industry's marketing practices (Hopper, Speece, and Musial 1997). Patients appear more concerned about the influence of pharmaceutical
gifts to physicians than physicians themselves (Gibbons et al. 1998), indicating that physician-pharmaceutical industry contacts may be causing a problem for physician-patient interactions and trust.

**Teaching, Research, and the Pharmaceutical Industry**

The relationship between the medical profession and the pharmaceutical industry is wide-reaching. Rapid changes in medicine have created an increasing need for continuing medical education (CME). With other sources of funding becoming less available, drug companies have assumed an increasingly prominent role. Such CME, however, tends to highlight the sponsor's drug(s) (Wazana 2000). Pharmaceutical advertising represents a meaningful percentage of the income of many medical organizations that own the journals (Glassman, Hunter-Hayes, and Nakamura 1999). However, of greatest concern has been the complex relation between the pharmaceutical industry and medical education and research. Martin and Kasper (2000) have clearly articulated this concern:

Academic principles of education without bias, of discovery driven by curiosity, and of the ownership of intellectual property by its inventor—whether writer, artist, or scientist—are deeply embedded in our institutions and culture. These principles stand in contrast to the industrial sector's missions of product development, marketing, and profitability.

A “strong” association has been found between authors' financial interest in a drug's manufacturer and favorable reports on the drug's safety (Stelfox et al. 1998). In 34 percent of 789 scientific journal articles in 1996, one or more of the authors had a financial interest in the subject studied (Stolberg 1998). The pharmaceutical industry now provides 70 percent of money for clinical drug trials; companies sponsoring these trials have forbidden publication of results without the company's consent, have suppressed unfavorable reports, and have threatened researchers with unfavorable results with loss of future funding (Bodenheimer 2000). In general, companies retain control over the data that allows them to then present the results in as favorable a light as possible. Furthermore, for-profit companies are increasingly managing drug trials. In 1991, 80 percent of money for industry-sponsored drug trials went to academic medical centers; by 1998, this figure had dropped to 40 percent (Getz 1999). Particularly where a drug is in a crowded therapeutic field ("me-too" drugs), some company-sponsored studies are actually for "seedling," namely, a means of promoting a drug by paying physicians to prescribe the drug under the guise of a clinical trial (Kessler et al. 1994).

The ties between clinical researchers and industry involve more than grant support. Researchers serve as consultants or on advisory boards, are paid as speakers to promote a company's products at symposia, are supplied with expensive gifts or trips, enter into patent and royalty agreements, and may have equity interest in a company (Angell 2000a). Researchers have also agreed to be listed
as authors for articles that were written by an interested company itself. A recent review indicated that about one-quarter of the articles in peer-reviewed medical journals have “honorary” authors who do not meet authorship criteria, or “ghost” authors who are not listed but who have contributed substantially to the work (Flanagan et al. 1998). These abuses have led to calls for generally applicable guidelines for conflict-of-interest rules between medical institutions and the pharmaceutical industry (Korn 2000; Martin and Kasper 2000). At the moment, however, these guidelines lack uniformity and specificity (Cho et al. 2000; Lo, Wold, and Berkeley 2000). The present situation has raised concerns about public confidence and trust in biomedical research. There is also concern about a changing relationship between researchers and their patients. Patients have traditionally volunteered for research largely for altruistic reasons. With money now such a prominent feature of the medical research environment, patients are asking why they should not be included in the financial return (Kolata 2000).

Regulation

The FDA is responsible for ensuring that drugs are both safe and effective. The self-serving behavior of drug manufacturers when dealing with regulatory agencies has been well described (Abraham 1995). Since 1992, when the FDA was allowed to charge pharmaceutical companies a fee for reviewing New Drug Applications, the review process has been accelerated by about 50 percent. Whether causal or not, a disturbingly high number of drugs have had to be recalled for safety reasons. This was true for four of 39 drugs approved by the FDA in 1997, and an additional drug was withdrawn except for use in hospitals and nursing homes (Public Citizen 2000a).

There is serious concern about the effectiveness of the surveillance of drugs once they are approved by the FDA and made available to the public. Clinical trials often use surrogate endpoints that may not correlate with meaningful clinical improvement. For example, a drug that lowers blood glucose may be approved for treatment of diabetes mellitus even without demonstration that it improves the course of the disease. Most drugs are now approved for chronic illnesses and for long-term use, where the effectiveness or harm of the drug may not be apparent for a considerable period of time. Finally, the adverse effect of a drug may be difficult to separate from the effects of the condition the drug is designed to treat. As a result, drug companies are frequently asked to perform post-marketing studies as a condition of FDA approval. The pharmaceutical industry states that it views its responsibility to “ensure the safety of all approved medicines in the U.S. as a sacred trust” and lists post-marketing surveillance as part of this trust (Pharmaceutical Research and Manufacturers of America 2001). A recent survey, however, indicates that most of these commitments are not kept (Public Citizen 2000b). Between 1990 and 1994, the FDA approved 122 new drugs. Post-marketing research (Phase IV studies) was requested for 88, but as of 23 December 1999, only 11 studies (13 percent) had been completed. Since
1993, the FDA has maintained a voluntary system—MedWatch—for reporting adverse drug effects. However, report rates of 1 to 10 percent, as well as the restricted type of information that can be obtained from such a voluntary reporting system, limit the effectiveness of MedWatch (Brewer and Colditz 1999; Wood 2000).

The FDA has limited resources for monitoring drugs post-release and its effectiveness is less than desirable. This is striking, since adverse drug reactions are estimated to cause death of 100,000 people per year in the United States, and therefore represent a major public health problem (Lazarou, Pomeranz, and Corey 1998). In addition, large numbers of patients may now be exposed unnecessarily to potentially toxic drugs. About 20 million patients were recently exposed to five drugs withdrawn within a 12-month period (Wood 2000). These occurrences suggest that neither the companies that manufacture drugs nor the FDA that evaluates drugs prior to release may be the best groups to monitor the effects of drugs once they become available.

The FDA is charged with ensuring that drug advertisements are neither false nor misleading. In general, however, the FDA does not have the authority to require approval of promotional materials prior to their release (Kessler et al. 1994). Nor has this monitoring, as mentioned previously, necessarily been effective.

The problems in our current system of regulating and monitoring drugs, and the resultant tragic consequences, have recently been discussed in detail (Moore 1995). A class of cardiac antiarrhythmic drugs was found to cause cardiac arrests, resulting in an estimated 50,000 deaths. The drugs were first produced in 1972 and were approved by the FDA in 1985. Their use was markedly restricted in 1991, following controlled studies that decisively demonstrated their harmful effects. That the drugs caused these deaths in a patient population where such deaths may have occurred under any circumstances complicated recognition of their adverse effects. In addition, pressure from the manufacturers, as well as judgments by physicians who worked with the manufacturers and had a vested interest in the drugs, were major factors in causing negative information about the drugs to be ignored. This information would have limited the therapeutic indications for the drugs and therefore their potential profitability. Similar tragedies for similar reasons have occurred in drugs whose harmful effects were or should have been more obvious. This was true for butorphanol (Stadol®), which serves as a case study illustrating the problems with drug company influence, government regulation, and post-release surveillance.

**Butorphanol (Stadol®): A Paradigm of the Problem**

Butorphanol (Stadol®, Bristol-Meyers Squibb, Princeton, NJ) is a synthetically derived opioid. It is a part of a class of drugs that were developed as agonists at kappa-opioid receptors and as mixed agonists/antagonists at mu receptors. It was...
hoped that these drugs would be potent analgesics with few limiting adverse effects such as respiratory depression.

Drug Review

The Drug Abuse Advisory Committee (DAAC) of the FDA, the highest scientific review board for drugs with abuse potential, reviewed the safety of butorphanol for intramuscular injection on 1 June 1978. This review occurred in the context of unsatisfactory experiences with a similar drug, pentazocine (Talwin®). Talwin® had become a popular “street” drug and was frequently combined with an antihistamine that diminished its unpleasant side effects (Caplan, Thomas, and Banks 1982). Despite assurances from the manufacturer about the safety of the drug, serious problems had surfaced, including psychological disturbances, addictions, and deaths. The previous meeting of the DAAC had recommended that pentazocine be a federally scheduled drug. Scheduling a drug warns physicians of the need for caution in its use and enables its sales to be monitored. (There are five levels of scheduling, schedule I being the most restrictive, for the most dangerous drugs, and V the least restrictive.) Although states can also schedule drugs, scheduling at the federal level means that all prescriptions for that drug must have the prescribing physician’s Bureau of Narcotics and Dangerous Drugs identification number. In addition to reminding physicians of the potentially harmful properties of a drug, this also allows sales of the drug to be monitored nationwide.

Given the available evidence and the experience with pentazocine, the DAAC questioned the safety of butorphanol at its 1 June 1978 meeting (DAAC 1978). The primary spokesperson for the opposing view was an employee of butorphanol’s manufacturer, then Bristol Laboratories, who had invented and held patents on the drug. An investigator supported by Bristol Laboratories had been involved in most of the human studies quoted to support the release of butorphanol. The DAAC voted 12 to two, with two abstentions, to schedule butorphanol. As one panel member stated, “I was taught in pharmacology that if drugs look alike, and there are just subtle differences when it comes to certain pharmacological effects and certain abuse effects, then you can predict that the substance will be abused” (DAAC 1978).

However, the recommendation of the DAAC was not followed. Butorphanol was released as a federally non-scheduled potent intramuscular synthetic analgesic on 23 August 1978. Despite intensive investigation, the person or the reasons responsible for this unusual decision have never been determined. An argument presented forcefully for not scheduling the drug during the DAAC meeting was that a non-scheduled drug was required for commercial success. Unless this occurred, research funds for such drugs would not be available. “The carrot in front of the pharmaceutical industry is the hope that they’re going to wind up with a non-scheduled drug . . . The scientific dog is more and more wagged by the marketing tail” (DAAC 1978; my italics).
The FDA’s Medical Officer’s Review of New Drug Applications (NDA) recommended that butorphanol “should be reconsidered for control” (New Drug Application 1978). The state of Oklahoma scheduled the drug at its release, and a review discussing butorphanol published in 1980 concluded that there was not enough information “to allow judgment on the frequency and severity of adverse reactions or on the liability to dependence” (Vandam 1980).

**Intramuscular Butorphanol**

Possibly because of it was administered intramuscularly, butorphanol was mainly prescribed for acute pain management. Its use was therefore limited. Nevertheless, there were about 60 adverse drug reactions (ADRs) per year consistent with narcotic use associated with butorphanol, including six reports of addiction and one death per year. Given the low reporting rate for ADRs discussed above, estimates of the actual incidence of these adverse effects would require multiplying by 10 to 100. There were also scattered reports of illicit diversion as well as “recreational” use when combined with antihistamines—an experience reminiscent of that with pentazocine (Austin 1983; Smith and Davis 1984).

At a meeting on February 4, 1980, the DAAC recommended by a vote of nine to four that the FDA reconsider its position on butorphanol control (Drug Abuse Advisory Committee 1991). An argument raised against scheduling butorphanol was that pentazocine had been released as a non-scheduled drug, and that butorphanol should receive similar treatment until, as in the case of pentazocine, it was shown to be harmful. In retrospect, this represented a striking reversal of the usual medical argument that first one should do no harm. Even by 1991, there was no agreement in the DAAC about the controls needed for butorphanol, and the “disatisfaction on the issue went to such lengths that Committee members requested that the issues be taken up continually” (DAAC 1991).

An argument against scheduling butorphanol had been that it was a synthetic drug and therefore not subject to the Controlled Substances Act in the absence of proof of the drug’s harm. In 1983, however, butorphanol was synthesized from a naturally occurring opium derivative. As such, butorphanol should have been scheduled as a schedule II controlled drug (DAAC 1991). Again, such scheduling did not occur.

**Butorphanol Nasal Spray**

In 1989, Bristol-Meyers Squibb applied to the FDA for butorphanol to be released as a nasal spray (Stadol® Nasal Spray [NS]) (New Drug Application 1991). The nasal spray was approved for marketing in a non-scheduled fashion on 12 December 1991. However, doubts remained butorphanol’s safety. At the meeting of the DAAC prior to release of the nasal spray, one participant stated: “Clearly, at some point we need to address the inconsistencies in scheduling among the mixed agonist-antagonists. We from a clinical point of view need to know are these safer drugs than the pure mu agonists” (Drug Abuse Advisory
Committee 1991). The drug’s manufacturer insisted that the abuse potential was low. There was, however, clinical as well as experimental evidence in animals for drug dependence. In addition, no studies had examined the abuse potential of butorphanol if used for more than one month. There was concern about the effect of the nasal spray delivery system, both because of increased accessibility and the possible delivery of a higher concentration, and because the clinical trials conducted with the nasal spray had been relatively insensitive for detecting possible abuse. Based partially on the fact that butorphanol had not been scheduled previously, the DAAC voted not to schedule the nasal spray. Post–marketing surveillance, however, was considered critical. Even the primary spokesperson for the company conceded that many of the questions could only be answered by such surveillance. The manufacturer stated that butorphanol would only be used intermittently for severe pain and would not be used in a chronic fashion. A “cautious” marketing strategy was urged.

Yet once butorphanol was approved as a nasal spray, Bristol-Meyers Squibb began a major advertising campaign. This campaign focused on the use of butorphanol in the treatment of migraine headaches—a common condition—that might then result in frequent use and high profits. The company argued that migraine is episodic. Repeated use over an extended period of time—chronic use—could be expected for a drug that ameliorates migraine headaches. The promotional literature emphasized that butorphanol was not a federally controlled drug. The main side effect was said to be somnolence (43 percent), the possibility of drug dependence was either not mentioned or said to be minimal, and only 3 percent of users were said to have symptoms “suggestive” of abuse. Bristol-Meyers Squibb provided a diary (My Personal Profile) for the use of migraine patients. This diary encouraged repeated use of the drug, as well as its use for headaches of “moderate” severity. Drowsiness, dizziness, and nausea and vomiting were reported as side effects; a potential for addiction was not mentioned. The author personally attended a promotional session for butorphanol in which side effects were minimized and abuse potential not discussed.

The Drug Abuse and Dependence section of the Prescribing Information for butorphanol provides at best limited warning of the drug’s potential for abuse. There is a warning that all mixed agonist/antagonist analgesics have been reported to be abused, that butorphanol has been reported to produce mild withdrawal symptoms, and that there have been reports of overuse and “self-reported addiction.” For the nasal spray, it is noted that behavioral symptoms “suggestive” of opioid withdrawal had been reported in two patients who stopped the drug abruptly after using an unusually large amount—more than a bottle per day for three months—and behavioral symptoms “suggestive” of possible abuse had been found in 3 percent. Butorphanol is not recommended for those who are emotionally stable or for those with a history of drug abuse.

Soon after release of butorphanol nasal spray, patients called their physicians
about the “new treatment for migraine,” and severe reactions were reported (Robbins 1993). The number of ADRs reported to the FDA increased from about 60 to 400 per year. Reports of dependence/addiction increased from 6.5 to 24 percent of the ADRs, such that dependence/addiction was now reported at a rate of about 100 per year in contrast to the previous six. These reports included about three deaths per year that might be attributed to the use of butorphanol. Given the reporting rates of ADRs, these figures would represent 1,000 to 10,000 addictions and 30 to 300 deaths per year. A high percentage of the remaining reports were for major psychological disturbances—hallucinations, depression, psychosis, and paranoid reactions—that can be seen with opiate use. Given the large number of patients with dependence/addiction due to butorphanol, the cost of the drug (about $70 per bottle for 10 sprays), and the high cost of dependence/addiction (at least three bottles per week, or $10,000 per year), those abusing the drug must have accounted for a considerable portion of the sales of butorphanol.

Concerned about the large number of ADRs it was receiving, the FDA sent a memorandum on 24 June 1994, to State Drug Program Directors, Boards of Pharmacy, and Drug Enforcement Officials, requesting information about the experience with butorphanol (Wilms 1994). The response to this survey, which was released on 28 November 1995, indicated major problems with butorphanol (Barnes 1995). Thirty-nine of 47 responding states were aware of non-medical use, diversion, or abuse in their states. The response from Georgia was typical: “With introduction of Stadol NS, abuse has dramatically increased on the street. Stadol is in the top five of drugs being abused.”

Over 50 percent of the of the states had found it necessary to institute special controls to limit access to butorphanol beyond that usually used for prescription drugs, and seven states (six in addition to Oklahoma) had made it a scheduled drug. These problems had surfaced within two years of release of the nasal spray, and the nasal spray was the form of butorphanol predominantly abused. The FDA recognized the abuse problem but felt it was best handled by the states. Interestingly, if requested, the FDA would “provide scientific and medical support for a state considering control under the State Controlled Substances Act” (Barnes 1995).

In hearings held before the New Mexico Board of Pharmacy in August 1994, several months after the FDA sent out its memorandum about butorphanol, Bristol-Meyers Squibb argued for reversing the scheduling decision in that state (New Mexico Board of Pharmacy 1994). As before, the company argued there was no convincing evidence that butorphanol was causing problems. The company recognized that butorphanol could be addicting, but they attributed this mainly to problems in those receiving the drug—in other words, “given to the wrong people, bad things will happen.” Bristol-Meyers Squibb claimed it had not been able to find evidence for multiple-drug or street use. The company
gave this testimony about a drug for which careful post-release monitoring had been a condition of its release, and in an industry that claims to view post-marketing surveillance as a "sacred trust."

The New Mexico Board of Pharmacy rejected the arguments by Bristol-Meyers Squibb, and by six to one voted to maintain butorphanol as a controlled substance. All of the testimony for not scheduling butorphanol had come from those salaried by the company. As one Board member stated: "if it walks, talks, and quacks like a duck, then it's probably a duck... It [Stadol] is obviously addictive and ought to be a controlled substance" (New Mexico Board of Pharmacy 1994).

Butorphanol is addicting, possibly highly addicting, and is anecdotally a drug from which withdrawal is difficult and frequently unsuccessful. Nonetheless, Bristol-Meyers Squibb continued to promote butorphanol NS as a safe analgesic for migraine and other uses. Material sent to state regulatory boards included reviews by health agencies that did not recommend control. All of these reviews, however, were carried out before 1991—before release of the nasal spray. The company also emphasized the low citations of butorphanol in the Drug Abuse Warning Network (DAWN). DAWN reflects drug abuse reports from emergency rooms and is considered an unreliable tool: it was described by the DAAC as "lousy" and "useless" (Drug Abuse Advisory Committee 1978). And DAWN is especially poor for identifying butorphanol, since it is not detected by standard drug screens.

On 11 April 1996, the FDA sent a letter to Bristol-Meyers Squibb requesting changes in its advertising material for butorphanol (Shnitizler 1996). In particular, the claim "low potential for abuse" was thought to be misleading and the patient brochure "My Personal Profile" needed to indicate that butorphanol was an opioid product. This letter was sent four years after this type of promotional material was introduced, and almost two years after the FDA was aware of serious problems with butorphanol. On 27 June 1996, in a reply to the FDA's letter, Bristol-Meyers Squibb agreed to abide by the requests as of 1 September 1996.

For the responsible physician, little additional information was available. In 1993, butorphanol was reviewed in the Medical Letter on Drugs and Therapeutics, a respected newsletter about drugs. This review commented that "adverse effects may be troublesome" and that "possible" abuse could occur, but that few studies had been published and the only information about abuse came from the manufacturer (Butorphanol 1993). In a supplement to a prominent neurological journal dealing with management of severe headaches, three of four articles supported the use of butorphanol and gave no warnings of serious side effects (Rapoport 1994); this supplement was supported by an "educational" grant from Bristol-Meyers Squibb. A 1995 article based on a study funded by Bristol-Meyers Squibb noted frequent side effects but emphasized the low potential for abuse (Hoffert et. al. 1995). And a 1995 article published in a pain newsletter indicated the need for careful monitoring of butorphanol (Saper 1995). Al-

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though the newsletter was published under the auspices of Bristol-Meyers Squibb, the company had not informed the author of the evidence for abuse or of the controls instituted by many states.

Butorphanol Nasal Spray: Scheduling

Following publication of a review in 1997 (Fisher and Glass 1997), the problems with butorphanol were reported in the national press and were aired on the ABC “Nightline” show on 11 July 1997. Perhaps because of the national publicity and shortly prior to the “Nightline” presentation, the FDA recommended to the Drug Enforcement Administration that butorphanol should be a Schedule IV controlled substance. Scheduling became effective on 31 October. Bristol-Meyers Squibb had actually written the FDA on 24 February 1995, asking that the “necessary steps” be taken to have “Stadol NS Nasal Spray” scheduled (Gunter 1995). Injectable butorphanol was not mentioned in the letter. This was an unusual request, as those responsible at Bristol-Meyers Squibb must or should have known that the FDA regulates drugs, not specific delivery systems; the basis for this request can only be surmised. In a subsequent letter dated 24 May 1996, Bristol-Meyers Squibb indicated that, if only scheduling the nasal spray was slowing the process, they would not “resist” the scheduling of all dosage forms (Gunter 1996). Bristol-Meyers Squibb was still promoting butorphanol at these times without meaningful warnings of its risk.

Butorphanol is now a federally scheduled drug, allowing for better monitoring of its use, and the drug is no longer heavily promoted for treatment of migraine. In that sense, it might be argued that the system has worked. At the same time, there was never any substantial evidence that butorphanol was safe. Given what had been a recent disastrous experience with pentazocine, it is striking that the drug was approved without controls. Thousands, possibly tens of thousands, experienced misery and many had their lives ruined because of butorphanol. Many, possibly hundreds, died. This arguably occurred because of the influence of a drug company, a federal agency only partly able to resist this influence, and researchers with a decided interest, even financial interest, in the drug. Even when it was clear that there were major problems with the drug, regulation was delayed, allowing for additional harm to patients as well as profit for the manufacturer. Change occurred only at a time when the problems were so flagrant that they received national exposure and threatened to become an embarrassment for both Bristol-Meyers Squibb and the FDA.

Conclusions and Recommendations

Most of the pharmaceutical information physicians now receive is self-serving and of questionable accuracy. Such information, as well as commercialization in medicine, is not new, but the present scale makes for a difference in quality. One consequence is skepticism within the medical community itself that undercuts
its self-confidence and makes it less able to resist the blandishments of those approaching medicine with a narrowly focused financial concern.

For reasons that have nothing to do with therapeutic benefit, patients in the United States now pay the highest costs for drugs in the world. If the high costs of drugs cannot be supported in third world countries because of the unnecessary suffering and deaths, can this be sustained in the United States? The current environment is now adversely affecting the previously unassailable level of drug company pricing and profits in the United States (Freudenein and Petersen 2001).

Physicians will never be totally disinterested and will always to some degree be subject to blandishments; as with any business, drug companies will always be driven by profit; and government agencies will always be subject to pressure from those they are charged with regulating. The harmful affects of these realities, however, can be modulated.

Recently, there have been efforts by individual drug companies (Petersen 2002a), the pharmaceutical industry itself, and states to limit and regulate acceptable promotional activities to physicians as well to other health professionals and hospitals (Petersen 2002b; Robeznieks 2002). These activities need to be encouraged and expanded. There is also a need for increased physician training and discussion about the relation between medicine and the pharmaceutical industry. Physicians appear to sense the need for such training and it can alter physician behavior.

Furthermore, we need to establish a healthier balance between the needs of academic science, industry, and the public. A national policy defining conflict-of-interest rules could be important. Martin and Kasper (2000) have proposed that such a conflict-of-interest policy should include at least three elements: (1) regular disclosure by faculty to academic institutions of potential conflicts with appropriate scrutiny of financial interests; (2) monitoring by an oversight committee; and, (3) a mechanism for granting exceptions when they are warranted by extraordinary circumstances. Although possibly desirable, it is probably unrealistic to expect universal, specific guidelines for all concerned parties. Nevertheless, even general guidelines could help create a framework acceptable for faculty-industry interactions. It is encouraging that, after considerable discussion, Harvard Medical School has decided to retain its rather stringent limits on consulting fees and equity holdings of its faculty. At the same time, institutions closely affiliated with Harvard Medical School have negotiated contracts with commercial partners—possibly establishing a model as to how this can occur within an environment of strong conflict-of-interest regulations.

For a nation that accepts the concept of checks and balances, the present situation concerning oversight of the pharmaceutical industry is anomalous. Because of inadequate oversight, there are possibly twice as many deaths each year due to drugs as to automobile accidents. At the moment, those monitoring the effects of a drug are either paid by those who approved its release it or by those
who directly profit from this decision. For this reason, there have been calls for a drug safety board independent of both the FDA and the drug manufacturers (Wood 2000; Wood, Stein, and Woosley 1998). Given the need, this seems only common sense. At a minimum, increased federal resources should be devoted to post-marketing surveillance, and the ADR system should be enhanced. Databases comparing information from drug users and non-users could enhance the ability to detect adverse drug effects. This information should also be readily available in a comprehensible fashion. Although ADRs are unfiltered, these data would provide some counterbalance to the not-necessarily-objective information from the drug companies. Finally, there is a need for congressional review of legislation regulating drug companies, including review of their finances. The goal should not be to diminish entrepreneurial zeal but rather to encourage the industry to concentrate on development of meaningful new products rather than on marketing.

The benefit of such changes for patients and physicians is apparent. The pharmaceutical industry itself may be receptive to change as drug costs assume an increasingly larger portion of health care expenses and the justification for these expenses is increasingly being scrutinized.

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