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## The pharmaceutical industry: friend or foe?

Jennifer R. Niebyl, MD

**T**hank you for inviting me to be here today. It is a great honor to be president of the American Gynecological and Obstetrical Society.

First, I would like to thank my escorts, who have been my mentors and colleagues for many years. They are as follows: Richard Berkowitz, MD, Steven Gabbe, MD, Irwin Merkatz, MD, John Queenan, MD, Gloria Sarto, MD, PhD, and Joe Leigh Simpson, MD. I would also like to acknowledge the late Dr J. Donald Woodruff, who brought me to my very first meeting of this organization, and who was my mentor at Johns Hopkins Hospital.

In this address I intend to show you the degree to which the drug industry is profit motivated and ultimately responsible to shareholders. However, we, as physicians, have primary responsibility to our patients. I want to remind you that drug representatives are sales people, not educators. They live by quotas and they track the prescribing habits of physicians

to whom they market their drugs. Gifts, meals, samples, seminars, and advertising all influence our prescribing habits. In addition, I will briefly mention some issues about the Food and Drug Administration (FDA). It is paid by the pharmaceutical industry to approve drugs and has limited resources for postmarketing supervision of companies with regard to misleading advertising, or side effects of drugs discovered after FDA approval.

Drug representatives may find speakers, pay speakers, bring lunch, and bring gifts and samples. All of these behaviors influence physician prescribing and drive up the drug costs for hospitals and patients. That is, of course, why the drug companies pay for them.

Industry responds by pointing out that prescription drugs are expensive because they are valuable, and that they have large research and development costs. Indeed, drugs may enhance quality of life and lengthen life, and marketing may sometimes influence physicians to prescribe otherwise underprescribed drugs. However, the costs of drugs in this country are significantly increased because of the large marketing budget and profit margin of the drug industry.

Much of what I am going to say today came from the book by Dr Marcia Angell, *The Truth About the Drug Companies: How They Deceive Us and What to Do About It*.<sup>1</sup> She is the former editor-in-chief of the *New England Journal of Med-*

*icine*, a physician trained in both internal medicine and pathology.

In 2003 in the United States we spent \$250 billion on outpatient prescription drugs. That figure is growing 12% per year, and is the fastest growing part of health care costs. For example, the price of Claritin was raised 13 times over 5 years, a 50% increase, 4 times the rate of inflation.

I will use the term "Big Pharma" to refer to PhRMA, the Pharmaceutical Research and Manufacturers of America. This is the industry's trade association, an organization of all the drug companies around the world, including 5 giant European companies. In the United States, the pharmaceutical industry enjoys the rapid approval of drugs by the FDA and free pricing with no price controls. They also have long periods of exclusive marketing rights, and huge tax breaks.

Increased drug expenditures have come from 3 sources: 39% from increased numbers of prescriptions, 37% from the increased cost of drugs, and 24% from the shift to more expensive drugs.<sup>2</sup>

The average price per drug per year currently is approximately \$1500. Industry charges Medicare recipients without supplemental insurance more than HMOs or the Veterans' Administration, as the latter can buy in bulk. However, the Medicare Reform Bill of 2003 forbids Medicare to bargain for lower prices.

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In fact, research and development is actually a small part of the budget of drug companies. It is approximately 14% of sales, while profit is 18% of sales. The pharmaceutical industry makes vast expenditures for marketing and administration at 36% of sales. They have 1 sales person for every 4.7 physicians, and spend \$8000-\$15,000 per physician per year. Thus, prices could actually be cut significantly without threatening research and development. The major sources of innovation of new drugs are the National Institutes of Health (NIH), academic medical centers, and biotechnology companies. Many of the "new" drugs are actually just variations of older drugs, commonly referred to as "me-too" drugs. That is why we have 6 different statins that are very similar to each other, and 6 different selective serotonin reuptake inhibitors.<sup>3</sup>

Among drug company employees in the year 2000, the following was the distribution of tasks: marketing 39%, production and quality control 26%, research and development 22%, administration 11%, and distribution 2%.<sup>2</sup> Drug company jobs in marketing have significantly increased in recent years, whereas, drug company jobs in research have remained flat.

Big Pharma has been the most profitable industry for 2 decades in the United States, more profitable than oil. The drug industry median profit as a percent of revenue was 18.7% in 2000, compared with the other industry median profit as a percent of revenue of 5%.<sup>4</sup>

The pharmaceutical industry uses its wealth and power to influence the US Congress, the FDA, academic medical centers, and physicians in practice. They have 2 lobbyists for every congressman and spent \$100 million on lobbying in 2006. They are the largest lobby of all industries in Washington, DC.

Companies may control the publication of data and may not allow publication if the data are not favorable to their drug. They also regularly lead physicians to believe that drugs are more effective and safer than reality. In 1 study of drug representative statements to doctors, 11% were inaccurate, always in favor of the drug being marketed.<sup>5</sup>

Few companies rely on their own research for new drugs. One-third of drugs are now licensed from universities, the NIH, or small biotechnology companies. Medical schools and faculty may enter into lucrative financial arrangements with drug companies. Another issue to be addressed is that brand name companies pay generic companies to delay release of generic drugs. Bristol-Myers Squibb paid \$40 million to delay the release of the generic Plavix.

An example is the zidovudine (AZT) story. In 1983 the NIH and the Pasteur Institute in Paris discovered that AIDS was caused by a retrovirus. In 1985 the NIH screened antiviral agents at the National Cancer Institute (NCI) and Duke University and AZT was shown to be effective in clinical trials. Burroughs Wellcome patented it for treatment of AIDS and charged \$10,000 per year. Thus, the drug company charged high prices for a drug that it neither developed nor discovered. Another example is Taxol (paclitaxel). Research on this drug was supported by or conducted at the NCI with \$183 million of tax dollars. In 1991 Bristol-Myers Squibb signed a cooperative research and development agreement with the NCI to supply paclitaxel. Then the Pacific yew tree became in short supply, and in 1994 Florida State University synthesized Taxol. It was subsequently licensed to Bristol-Myer Squibb for royalties, which generated \$1-\$2 billion per year for Bristol-Myers Squibb and tens of millions in annual royalties for Florida State University. Bristol-Myers Squibb charges high prices for a drug it neither discovered nor developed.<sup>1</sup> Thus, Big Pharma is not an engine of innovation, but a vast marketing machine. It is not a free market success story, but lives off government-funded research and monopoly rights. An 800-lb gorilla can do anything it wants to do.

Most of the "me-too" drugs are new versions of already marketed drugs. Of the 83 drugs per year approved from 1998-2002, only 32% were new molecular entities, and only 14% received priority review from the FDA.<sup>1</sup> Of the top 5 selling drugs in 1995, 16 of 17 key scientific papers leading to their discovery and development came from outside the in-

dustry. Fifteen percent of all relevant research came from the industry, 55% from NIH-funded laboratories, and 30% from foreign academic institutions.<sup>1</sup>

Seventy-seven percent of 415 new drugs approved by the FDA from 1998-2002 were "me-too" drugs. They do not have to be shown to be any better than drugs already on the market. The companies just have to show that the drugs are effective compared with placebo. They do not have to show that they are as effective as the old drug or more effective than the old drug. They can compare different doses or different clinical scenarios, such as an extended release formulation to make the new drug look different. The costs can be significantly different. Sarafem brand of fluoxetine costs \$167, compared with generic fluoxetine, which is \$25.<sup>6</sup> Interestingly, price is almost never mentioned in the advertising.

The story of the purple pill, or Nexium, is eye opening. Prilosec was about to go off patent in 2001, a potential loss to AstraZeneca. Prilosec is a mixture of 2 isomers of omeprazole. The company patented the active isomer as Nexium, and launched a massive advertising campaign for "the purple pill." They spent half a billion dollars in 2001. Prilosec generic is over-the-counter at a fraction of the cost of Nexium, \$21 vs \$153.<sup>6</sup> In clinical trials, they compared 40 mg of Nexium with 20 mg of Prilosec, to make Nexium look better.<sup>1</sup> Thomas Scully, Administrative Head of Medicare and Medicaid told a group of doctors, "You should be embarrassed if you prescribe Nexium. It increases costs with no medical benefits."<sup>7</sup>

FDA-approved generic drugs contain the same active ingredients as the innovator drug. The inactive ingredients may vary, but the active ingredients need to be identical in strength, dosage form, and route of administration. They must have the same use indications, be bio-equivalent, and meet the same batch requirements for identity, strength, purity, and quality. They must be manufactured under the same standards of the FDA's good manufacturing practice regulations required for innovator products. In 2006, the University of Iowa implemented a health plan in which the em-

ployees have no co-pay if they use generic drugs. In the first year of the plan, generic use increased from 46% to 67% of prescriptions, and the health plan saved \$2.5 million (personal communication from Richard Saunders, Director, University of Iowa Benefits Office, Iowa City, IA, Oct. 4, 2007).

Another example of cost savings with generic drugs would be prevention of recurrent herpes in pregnancy. Giving 1000 mg of Valtrex a day for 30 days at the end of pregnancy would cost \$316. Giving 400 mg of Zovirax 3 times a day would cost \$363, but giving 400 mg of Acyclovir (generic) 3 times a day would cost \$43. Thus, a Valtrex prescription costs 7 times as much as generic acyclovir.<sup>6</sup>

Another example of marketing an isomer is Clarinex vs Claritin (desloratadine vs loratidine). Claritin went off patent at the end of 2002. Sales of \$2.7 billion in 2001 were one-third of Schering-Plough's revenues. Therefore, they had the FDA approve a Claritin metabolite, desloratadine, and they had it approved for year-round allergies, as well as seasonal allergies.<sup>1</sup> They marketed Clarinex at \$91 as an improvement, although it is identical to loratidine at \$22.<sup>6</sup>

Very few studies are funded by federal dollars. The NIH funded an antihypertensive and heart attacks trial involving 42,000 people over an 8-year period. Patients were randomly assigned to calcium channel blockers, alpha blockers, ACE inhibitors, and hydrochlorothiazide. The study concluded that there were fewer cases of heart failure and stroke with hydrochlorothiazide and increased heart failure with doxazosin (Cardura), and that diuretics were the best first choice to treat hypertension.<sup>8</sup>

Companies favor "me-too" drugs for chronic illness with a large market such as statins, antidepressants, and drugs for GERD. If a drug is not profitable, they can stop making it. There may be shortages of antivenoms and steroids, and they do not develop drugs for tropical diseases, because the countries are too poor to buy the drugs. "Me-too" drugs are heavily marketed.

Clinical trials are often funded at academic centers or physicians' offices. The companies may design the trials, keep the data, analyze the data, and decide on publication. For investigators participating in these trials it is critical to retain control of the data analysis and decision for publication. Companies also fund contract research organizations. In 1990, 80% of industry-funded studies were done at academic institutions, and this had dropped to 40% in 2000 because of lower costs at contract research organizations.<sup>9</sup> Industry-sponsored research is 4 times more likely to be favorable to a product as NIH-sponsored research.<sup>9</sup>

There may often be bias in comparative trials. The investigators may enroll young subjects who get fewer side effects. They may compare the new drug with an older drug at too low a dose. The study may be only short-term, when long-term use is recommended. The companies may present only the part of the data that looks good and withhold publication of negative results. The studies are often powered inadequately to assess safety.

Marketing has escalated in many areas, including direct-to-consumer advertising, sales pitches to doctors in offices with free lunches and free samples, advertising in medical journals, and promotion masquerading as educational activities. Companies have prepared manuscripts for publication, and then sought authors to sign them (and edit them some) for significant financial reward.

Promotional spending on prescription drugs started in 1996 at \$9 billion per year and increased to \$21 billion per year in 2002. This includes samples in physicians' offices, 56%; detailing to doctors, 25%; direct-to-consumer advertising, 13%; hospital detailing, 4%; and journal ads, 2%. Direct-to-consumer advertising on prescription drugs increased from \$0.8 billion in 1996 to \$2.5 billion in the year 2000. Direct-to-consumer advertising is prohibited in Europe and costs are lower. In 1997 the FDA loosened the rules for advertising so that the companies only have to mention major risks and give a website to address other risks. If the ads are misleading, the company may get a letter, but often after

the campaign has run its course. The FDA has very few staff to address misleading advertising.

However, the advertisements are effective. Doctors do respond to requests from patients to prescribe drugs they have seen advertised. Seventeen of 20 advertising campaigns were actually started within 1 year of FDA approval of the drug. The Institute of Medicine has recommended restriction of direct-to-consumer advertising until after more time on the market.<sup>10</sup>

Free samples are always of the newest, most expensive, patent-protected drugs. When a sample is exhausted, physicians often renew the drug, even if it is not their usual choice of therapy. Physicians will give samples as first-line therapy, even if it not their usual drug of choice. Of note, in 1 study, one-third of samples were used by physicians, families, and staff.<sup>11</sup>

Continuing medical education (CME) may be sponsored by private medical education companies, which are funded by the drug companies. They prepare teaching materials, including power point presentations, favoring the drug they are promoting. Doctors have been given lavish dinners and junkets to vacation spots to hear about drugs. Thought leaders are asked to be on speakers' bureaus. If the company can convince a physician to promote its drug, the return on investment is 2 times that of having a drug representative promote the drug.

A controversial topic is the role of lunches for faculty and residents. It is clear that gifts, even small, influence our prescribing behavior. The companies monitor our prescribing habits. There are electronic prescription tracking databases maintained by pharmacies. The representatives know what we are prescribing when they come and talk to us, and they know how to influence us to change our prescribing habits. After the lunches, the representatives collect data on the change in the numbers of prescriptions for the drug they have marketed. They receive bonuses based on sales quotas. The drug representatives are always attractive, friendly, and want to personalize the message to the physi-

cian. They offer food, flattery, and friendship.<sup>12</sup>

How common are physician-industry relationships? In 2001 physicians met with drug representatives on the average of four times per month. Ninety-two percent of physicians had received drug samples, 61% had received free meals, tickets, or travel, 13% had received financial benefits, and 12% had received incentives for participation in clinical trials.<sup>13</sup>

In 2002 the Pharmaceutical Research and Manufacturers of America published a new Code of Conduct. They emphasized that voluntary interactions between representatives and physicians should benefit patients, enhance the practice of medicine, and cost less than \$100. They discouraged tickets to entertainment, sports, and events, which were clearly for the personal benefit of the physician. They discouraged goods not for patients' benefit. They discouraged token consulting and advisory board relationships. The American Medical Association and the American College of Physicians adopted similar codes.<sup>14</sup> However, despite these guidelines, doctors are still regularly seeing drug sales representatives. From 2003-2004, 83% received food in the workplace, 78% received drug samples, 41% received travel, CME, or lodging, 18% had consulting relationships, 16% were speakers, and 9% were on an advisory board. In total, 94% of physicians had relationships with industry.<sup>14</sup>

One argument has been made that advertising is part of our society, so we should not be concerned about it. However, gifts are in some ways different from advertising. Gifts cost money and influence behavior, like other advertising. However, gifts create an obligation, a need to reciprocate, which is what creates a conflict of interest. Gifts create a sense of entitlement, unlike advertising, and may erode professional values, unlike advertising.

When internal medicine housestaff were asked about the influence of pharmaceutical promotions on their prescribing practices, 61% said that they were not influenced at all, 38% said they were influenced a little, and 1% a lot.

When they were asked if other physicians were influenced, 16% thought that other physicians were not influenced at all, 51% thought they were influenced a little, and 32% a lot.<sup>15</sup>

Gifts impose a sense of indebtedness. They create an obligation to reciprocate, conscious or not, and that influences behavior. The feelings of obligation are not related to the size of the gift.<sup>16</sup> In a randomized trial, in a restaurant in Ithaca, NY, when the waiters and waitresses presented the bill alone, compared with a bill with a chocolate on it, tips increased from 15%-18% when the chocolate was included with the bill.<sup>17</sup>

Do we really need the gifts? Meetings with pharmaceutical representatives are associated with requests by physicians to add drugs to the formulary. They also lead to nonrational and costly prescribing. Even small gifts influence prescribing and the profit potential for the company significantly outweighs the value of the gifts. Many physicians will claim that that they are not influenced by the trinkets and pens. A survey of 117 first- and second-year residents at a university-based internal medicine training program assessed attitudes toward 9 types of promotion. Most thought that conference lunches, dinner lectures, articles, and pens were appropriate, but fewer thought that social events, textbooks, or luggage were appropriate.<sup>15</sup> However, among respondents who considered an activity inappropriate, a significant percentage did participate or would have participated. Of note, our patients are more likely to consider a gift influential than are other physicians. Approximately 50% of patients thought that dinners and trips for physicians were influential on physicians' prescribing habits.<sup>18</sup> Wouldn't you be embarrassed if a patient asked you, "Are you prescribing drug X for me because that is what is written on your pen?"

The American Association of Medical Colleges (AAMC)<sup>19</sup> has published a policy on conflicts of interest and asked academic medical centers to take the lead. They want to dispel the myth that small gifts have no influence. They want to inform us that drug prescriptions increase after physicians attend company-spon-

sored symposia, accept free samples, or see sales representatives. Just disclosing a conflict does not eliminate a conflict of interest.<sup>19</sup>

The recommendations of the AAMC are as follows:

1. Ban all gifts. Ban free meals, travel to meetings, and payment for CME.
2. Ban free samples to physicians. Provide vouchers for low-income patients.
3. Exclude professionals with financial relationships with drug manufacturers from Pharmacy and Therapeutic Committees and the FDA Advisory Committees.
4. Faculty should not serve as members of speakers' bureaus.

I congratulate the institutions that have already implemented these measures: Yale University, University of Michigan, University of Pennsylvania, Stanford, and University of California-Davis, and others perhaps of which I am not aware.

Currently, there are wide differences between institutions in terms of educational policies and interactions with drug representatives. Some have allowed no contact with faculty or residents. Some have highly structured and limited contact, but comprehensive policies are rare and most policies are limited and offer little guidance. Therefore, we have a significant educational opportunity to inform our residents and medical students about the potential influence of industry on physician prescribing.

Finally, I want to say a few words about the FDA. In the 1980s the pharmaceutical companies complained that it took a long time to have their proposed drugs approved. The FDA Prescription Drug User Fee Act was passed in 1993, and so the industry started paying salaries at the FDA to review drug company submissions, so-called "user fees." They now comprise 40% of the budget of the FDA,<sup>20</sup> increasing from 9 million dollars in 1993 to 205 million dollars in 2004. Initially, only a small portion of the fees was used to evaluate post marketing side effects (5%), but with the renewal of this

bill in September 2007 more money is allocated for this because of the Vioxx postmarketing problems. A recent review of postapproval drug studies revealed that 71% were not yet started, 15% were in progress, 3% were behind schedule, and only 11% were completed.<sup>20</sup> So, most follow-up studies of safety are currently not performed in a timely fashion.

Who is the client of the FDA? Is it the pharmaceutical industry or the people of the United States? The drug companies are still major funders of the agency meant to regulate them.

The following is a partial summary of the recommendations for reform by Dr Marcia Angell<sup>1</sup>:

Reform no. 1: Shift emphasis from “me-too” to innovative drugs. Require new drugs to be compared with old ones, not just with placebos.

Reform no. 2: Strengthen the FDA to regulate drugs. Remove FDA from the industry payroll. Shift drug resources from drug approval to monitoring drug safety, inspecting plants, and ensuring truthful advertising. Eliminate experts on advisory committees with financial ties to industry. Increase FDA funding from government.

Reform no. 3: Create an NIH Institute to oversee clinical testing of drugs, before FDA approval. Stop biased research by companies. The NIH should administer trials of prescription drugs. Research should be performed by independent investigators.

Reform no. 4: Get Big Pharma out of medical education. The drug companies are in the business to sell drugs for profit. Industry information comes with bias and misinformation. The message is always that new drugs are better than the old ones. There should be no private medical education industry hired by

drug companies. We as physicians need to take control of education about drugs. Marketing is often masquerading as education. We need to regulate direct-to-consumer advertising.

Reform no. 5: Establish reasonable and uniform pricing. Profits could be adequate with lower prices if marketing was reduced. The Medicare Reform Bill of 2003 should be replaced by a guarantee to all Medicare beneficiaries of appropriate coverage of drug costs, a medical formulary, and government negotiated payments to industry.

Reform no. 6: Disallow gifts to physicians. Ban free lunches, drug samples, food, pens, and notepads. We need to remove real or perceived conflict of interest.

In conclusion, industry is responsible to shareholders, but we have primary responsibility to our patients. Gifts, meals, and samples influence our prescribing. The FDA has limited resources to regulate industry, and we as physicians need to take control of medical education about drugs. ■

#### REFERENCES

1. Angell M (2004) The truth about the drug companies, how they deceive us and what to do about it. New York: Random House; p. 58, 59, 65, 75, 78, 79.
2. Available at <http://www.nofreelunch.org>. Accessed on November 21, 2007.
3. Darves B. Too close for comfort? How some physicians are re-examining their dealings with drug detailers. Philadelphia: American College of Physicians Observer; 2003: 1.
4. Competition and pricing issues in the pharmaceutical market, PRIME Institute, University of Minnesota. Fortune Magazine, April 2000, Fortune 500. Available at <http://www.fortune.com>. Accessed on November 21, 2007.
5. Ziegler MG, Lew P, Singer BC. The accuracy of drug information from pharmaceutical sales representatives. *JAMA* 1995; 273: 1296-1298.
6. [www.drugstore.com](http://www.drugstore.com). Accessed on November 21, 2007.
7. Two new fronts in heartburn market battle. *NY Times* 2003 Aug 20: C12.
8. Furberg C. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97.
9. Bodenheimer T. Uneasy alliance—clinical investigators and the pharmaceutical industry. *N Engl J Med* 2000;342:1539-44.
10. Donohue JM, Cevalco M, Rosenthal MB. A decade of direct-to-consumer advertising of prescription drugs. *N Engl J Med* 2007;357: 673-81.
11. Coyle SL. Physician-industry relations: part 1, individual physicians. *Ann Intern Med* 2002;136:398.
12. Wazana A. Physicians and the pharmaceutical industry. Is a gift ever just a gift? *JAMA* 2000;283:373-80.
13. Wazana A. National survey of physicians: part II, doctors and prescription drugs. Washington, DC: Kaiser Family Foundation; 2002.
14. Campbell EG, Gruen RL, Mountford J, Miller LG, Cleary PD, Blumenthal D. A national survey of physician-industry relationships. *N Engl J Med* 2007;356:1742-50.
15. Steinman MA, Shlipak MG, McPhee SJ. Of principles and pens: attitudes and practices of medicine housestaff toward pharmaceutical industry promotions. *Am J Med* 2001;110:551-7.
16. Katz D, Caplan AL, Merz JF. All gifts large and small. *Am J Bioethics* 2003;3(3):39-46.
17. Strohmetz DB, Rind B, Fisher R, Lynn M. Sweetening the till: the use of candy to increase restaurant tipping. *J Appl Soc Psychol* 2002;32:300-9.
18. Gibbons RV, Landry FJ, Blouch DL, Jones DL, Williams FK, Lucey CR, et al. A comparison of physicians' and patients' attitudes toward pharmaceutical industry gifts. *J Gen Int Med* 1998;13:151-4.
19. Brennan TA, Rothman DJ, Blank L, Blumenthal D, Chimonas SC, Cohen JJ, et al. Health industry practices that create conflicts of interest: a policy proposal for academic medical centers. *JAMA* 2006;295:429-33.
20. Avorn J. Paying for drug approvals—whom's using whom? *N Engl J Med* 2007;356: 1697-700.