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MORE ON DRUG COMPANY DECEPTIONS AND ABUSES

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Medical care costs have reached crisis proportions and are continuing to escalate, largely because of the exorbitant prices of certain drugs. Patients and insurers spent $22.6 billion more for prescriptions last year than in 2000 because of increased sales of just 50 drugs out of the 9,500 available. Revenues for these 50 ($71.56 average prescription price) jumped 34.3% compared to a 9.3% increase for all the others ($40.11 average prescription price). The most expensive and best selling drugs were Lipitor and other statins to lower cholesterol, Celebrex and Vioxx for arthritis and antidepressants.

This greater than 17% jump is the fourth consecutive year of double-digit hikes and 20% annual increases are now projected. Retail drug sales since 1997 have doubled to around $160 billion, forcing some senior citizens on fixed incomes to choose between buying food or purchasing the multiple medications they require. Increased drug costs have also resulted in higher health insurance rates.

The most successful pharmaceuticals were those that were also the most heavily promoted by direct consumer advertising. Drug companies spent much more on advertisements in newspapers and popular magazines in 1999 ($685 million) than in medical journals ($473 million), since a dollar spent on a print ad returned $2.51. TV spots are more costly and bring in only $1.69 for every dollar spent. However, they reach a captive audience of many millions on multiple occasions rather than a few million who tend to ignore or only glance over a magazine ad.

Direct consumer advertising is not permitted in any other country except New Zealand. It has been strongly opposed in Europe but this may change due to pressures from powerful pharmaceutical interests. At a meeting held in Brussels earlier this year, consumer and patient advocates, drug company representatives and government regulators debated proposed changes in legislation that would permit direct consumer advertising for European Union countries. Each group

ALSO INCLUDED IN THIS ISSUE

presented its own supportive statistics and predictions based on the U.S. experience, but these conflicted with one another, causing considerable confusion and controversy. Consumer advocates and public health experts expressed concerns about studies showing that direct advertising had been responsible for a rising spiral of drug costs and that patient pressures also resulted in an increase in inappropriate prescriptions.

Does Drug Advertising Help The Public?

Proponents pointed out that the proposed changes were necessary to allow the pharmaceutical industry to "provide information to the public". In addition, the proposed 5 year trial period would be limited to three disease areas (HIV/AIDS, diabetes and asthma) and "public advertising of treatments" for specific serious diseases. A subsequent summary of the meeting suggested that a translation error might have caused confusion over whether the proposal referred to "public advertising" or "information to the public". While this might seem like splitting hairs, the difference between providing "advertising" as opposed to "education" is really at the heart of the debate.

According to one official, "Whether the Commission uses the word 'information' or 'advertising' is beside the point. The real question is whether this legislative change will allow U.S. style prescription drug advertising. We believe it will." Everyone agrees it is important for the public to be knowledgeable by supplying them with information that is objective and comprehensive. While pharmaceutical promotions profess to adhere to these standards it seems quite clear that they are heavily biased and have a financial rather than educational goal that could prove harmful.

This was supported by a recent study in the British Medical Journal showing that the markedly increased sales of advertised drugs in the U.S. had raised serious questions about the appropriateness of many of these prescriptions. The pharmaceutical industry countered that drug advertising leads to improved patient health. This was disputed by one participant, who noted that, "In nearly 20 years of US drug advertising to consumers, there's no evidence that exposure to drug advertising improves health or prevents hospitalizations or deaths. We do know that advertising can lead to increases in use of new drugs - and that this happened even for drugs that were later withdrawn from the US market". For example, Rezulin, Propulsid and Baycol were all heavily promoted but pulled from the market fairly soon after they were approved because of deaths and other unacceptable risks.

Pharmaceutical interests emphasized the need to increase consumer awareness about disorders that are seriously underdiagnosed or undertreated, since without direct advertising that alerts patients to specific signs and symptoms, certain serious diseases might not be treated at all. Hypertension, "the silent killer" was cited as an example but the reality is that in many instances, doctors wind up prescribing costly new drugs that patients ask for instead of cheaper generics. Thiazide diuretics and beta-blockers are the first-line treatments for uncomplicated hypertension but such off-patent drugs are not advertised to consumers. Instead, the public is urged by celebrities like Jack Nicklaus to ask their physician for an angiotensin-converting-enzyme inhibitor or a calcium-channel blocker that is much more expensive.

New drugs are not necessarily superior or safer, especially when taken with others that may be contraindicated. Posicor, a calcium channel blocker, was recalled after little more than a year due to 24 deaths and 400 potentially fatal reactions with 25 medications it had not been tested with. It was approved over the objections of FDA reviewers who noted that an unpublished study showed 143 sudden deaths and that the vast majority were in patients given Posicor rather than a placebo.

Advertising Distortions And Deceptions

The first direct-to-consumer advertisement for a prescription drug was published in a 1981 issue of Reader's Digest. Others subsequently appeared and the FDA became concerned about their potential effects on consumers. A moratorium on direct public advertising was initiated in

order to consider what regulatory options would be most appropriate. The FDA concluded that "direct to the public prescription advertising was not in the public interest" but had to lift the ban in 1985 because of freedom of speech issues raised by pharmaceutical interests who argued that existing regulations were sufficient to protect the public. **Direct-to-consumer advertisements were permitted with the provision that they presented true and balanced information about any side effects and contraindication of the drugs as well as efficacy.** Prior approval of drug advertisements was not required but the FDA was mandated to monitor strict compliance with these criteria.

Spending on advertising directly to consumers increased almost ten-fold from $266 million in 1994 to over $2.5 billion in 2001. This was largely due to television advertising, which accounted for 13% of direct-to-consumer expenditures in 1994 but skyrocketed to 64% in 2000 and is now higher because it has proven so profitable. A recent survey found that nearly one in three adults had talked to a doctor in response to a pharmaceutical television commercial and **80% of patients who requested an advertised drug received a prescription for it.**

This helps to explain why the most profitable industry in the U.S. is manufacturing pharmaceuticals and why this group spends more on direct consumer advertising than anyone else does. Merck invested $161 million for Vioxx ads in 2000, compared to $124 million spent for promoting Pepsi Cola and $146 million for Budweiser. Advertising is mostly for new drugs similar to those already available. **Only 15 percent of drugs approved in the past decade were deemed to provide significant improvements, largely because name brand drug companies now focus much more on marketing than research and development.**

The vast majority of direct drug to consumer promotions violate established guidelines in ads carefully crafted to appeal to various emotions rather than provide an educational message. Most describe medication benefits in vague, qualitative terms rather than supportive data, ("Help your child out of the jungle of allergies" and "If your diabetes is uncontrolled Glucophage can help".) Others appeal to widespread use, ("More than 100,000 people have begun using Rezulin to help manage diabetes") or testimonials from ordinary people rather than experts, ("taking Premarin is something I do for myself every day" and "John wanted to tell you about Accolate for asthma but he's off to the park"). Some other examples include:

- Viagra - Let the dance begin.
- Detrol - Overactive bladder is a treatable medical condition.
- Claritin - Take clear control. Take Claritin.
- Premarin - Everyday they are learning more about estrogen loss. That's why I'm glad I take my Premarin.
- Aricept - Is it just forgetfulness ….. or Alzheimer's disease?
- Humalog - Why cheat? When now, it's OK to dose and eat!
- Crixivan - if you are HIV+, Crixivan may help you live a longer, healthier life.
- Zithromax - Your son has another ear infection. He may need an antibiotic, and remember, he has to take all of it.
- Lipitor - If you're trying to lower your cholesterol, but your numbers still come up high ask your doctor about Lipitor.
- Cardizem CD - Cardizem CD may help you live well.
- Lymerix - I got Lyme disease last spring and I'm being treated for serious health problems. I couldn't prevent it then, but now you could.
- Zyban - On to the nicotine-free pill.
- Prilosec - If your heartburn medicine works so well, why do you keep getting heartburn?

Prilosec, the "Purple Pill", provides a prime example of distorted direct advertising and other deceptive drug company practices.

Promoting & Preserving The Purple Pill

Prilosec is the second most heavily direct-to-consumer advertised drug, which explains why Astra Zeneca's phenomenal purple pill has

been the world's biggest-selling prescription drug for the last five years. U.S. sales alone in 2000 were over $4.2 billion. Prilosec also illustrates how a company can utilize legislative loopholes to preserve an unfair advantage that prevents Americans from gaining access to prescription medications at fair market prices. We pay $4.00/pill, the highest price in the world and patients in Niagara Falls, NY pay 236% more for Prilosec than those in Niagara Falls, Ontario, with whom they share a common border.

Prices were supposed to plummet on October 5, when Prilosec's patent expired and generic versions would be available. Andrx anticipated marketing its generic on or shortly after this date but AstraZeneca successfully blocked it with a series of legal challenges. Generic versions have now been delayed indefinitely while the FDA reviews the situation as well as the outcome of law suits by generic drug makers. The 1984 US Competition and Patent Term Restoration Act ("Hatch-Waxman Act") can allow up to 30 months of market exclusivity for companies that apply for additional patents pending a final determination. Andrx's President complained that, "AstraZeneca has raised delay tactics beyond an art form — what they have done is unparalleled. By innuendo they have tried to imply that there should be a problem with generic Prilosec." Until the suits are settled, Andrx would be taking a gamble in launching a generic because it faces triple damages if the courts find against it.

AstraZeneca claims patent infringement over inactive ingredients that provide no health benefits and has demanded that one competitor resubmit its application for FDA approval because it changed the description of its pill from "tan" to "off white." It is fighting 70 similar cases in Canada, Israel, Australia and in Germany, where it is attempting to get a "supplementary protection certificate" for further patent protection in Europe.

AstraZeneca has applied for 11 additional US patents on Prilosec over the past decade or so and contends it will still have exclusivity in the U.S. via formulation patents valid to 2007. **It is already facing generic versions of the same drug sold as Losec in much of Europe but continues to make $77 million here for every week it is able to keep less expensive generic versions away from consumers by exploiting Hatch-Waxman loopholes.**

Historically, big sellers like Prilosec could anticipate losses following patent expiration at a steady rate, but after Prozac's patent expired last August sales dropped over 70% in two months because of generics almost one third less expensive. Surveys show that the vast majority of physicians also see little difference between Prilosec and similar drugs and that three out of four patients could be switched to generic omeprazole within a year if it were 50-75% cheaper as proposed. AstraZeneca has tried to protect its position with an advertising blitz for Nexium, (esomeprazole) introduced in March 2001 as "The new purple pill". They also hired 1300 representatives to specifically shower doctors with samples that have already encouraged over a third of Prilosec patients to switch to Nexium in the hope that most will retain brand loyalty. At a special Awards Dinner a few months ago for direct drug to consumer advertising, Nexium took the bronze medal for best integrated campaign (after Lipitor and Celebrex) and the silver medal for best branded web site (after Zyrtec).

Various public interest groups are urging changes in existing regulations arguing that any victory for a branded manufacturer against a generic competitor is "a huge victory at the expense of consumers". One patient who takes Prilosec for symptoms due to a pre-cancerous condition told a Senate Committee in April that her yearly costs jumped to over $1,100 after her insurance carrier decided to limit the amount they would reimburse for this expensive medication. General Motors reported that they had spent $55 million last year on Prilosec and that 90% of their employees had never tried less expensive competitive products that were not heavily advertised

More Drug Company Chicanery

The patent on Bristol-Myers Squibb's anti-anxiety drug BuSpar was due to expire on Nov. 21, 2000 and a cheaper FDA

approved generic version should have been available to consumers the next day. Large amounts of generics had been manufactured and were ready for shipping, but Bristol-Myers got a new patent hours before the expiration to prevent this. The additional patent was not based on anything new but rather how the drug is metabolized after it is ingested. The present legislation's wording allowed the company to claim that a generic would violate their new patent. **The generic companies sued but it took four months for courts to decide in their favor, during which Bristol-Myers made over $200 million because it retained exclusivity.**

Schering-Plough's antihistamine Claritin had sales of $3.2 billion in 2001 that accounted for 37% of its total revenue. Some of its patents are due to expire this year and although others could keep it protected for another decade, Americans can easily purchase it over the Internet from Canada, where it is already available without a prescription, as is Prozac. Schering expects approval in a few months for it to be sold in the U.S. over-the-counter, but it would not be covered by insurance plans. It has therefore launched an advertising campaign with tons of free samples and rebates to encourage patients to switch to its Clarinex, thus giving them control over both the prescription and non-prescription markets.

There is no compelling evidence that Clarinex is superior to Claritin, which highlights another flaw in the present system that pharmaceutical companies take advantage of. **Patients assume that newer drugs are better than their predecessors but the FDA only requires proof that they are safe and better than nothing for the indication specified.** When a drug company files an application for approval the agency tries to determine how important the medication is by placing it into one of two categories: "priority" drugs, which are believed to be a "significant improvement" over existing medications, and "standard" drugs similar to those already available.

Of all the pharmaceuticals approved over the past decade, 85% were deemed by the FDA as showing "no significant improvement" over existing medications. However, the vast majority of profits from prescription sales come from these copycat drugs, especially those that are heavily advertised, like Vioxx and Celebrex. **Americans spend over $4 billion a year on Vioxx and Celebrex although there is no evidence that they are more effective in relieving symptoms of joint pain and inflammation than medications that have been available for many years and are much cheaper.** Claims of greater safety because of less stomach ulcers are disputed and **studies showing an association with a higher incidence of heart attacks and delayed bone healing may require adding these to their warning labels**.

Calcium channel blockers (Cardizem, Procardia, Adalat, Calan, Isoptin, Plendil, Norvasc) for hypertension are also among the most profitable drugs because of aggressive advertising. Although they lower blood pressure, unlike diuretics and beta-blockers, which can be up to 12 times less costly, they do not reduce the risk of heart disease associated with hypertension. **A review of nine clinical trials that included more than 27,000 patients showed that those treated with calcium channel blockers had a 27% increased risk of heart attacks, and 26% increased risk for heart failure compared to patients who received other blood pressure medications.** Other studies suggest that calcium channel blockers increase risk of breast cancer, GI bleeding and suicide.

Similar problems will likely surface increasingly as drug companies pressure the FDA for speedier approval. It is estimated that an average manufacturer loses $1.3 million every day that FDA approval is delayed. This means that there will be fewer trials to detect adverse reactions with popular medications and other long-term safety problems. A 1998 study in the *Journal of the American Medical Association* estimated that **adverse reactions to medications already kill 106,000 Americans each year, making prescription drugs the fourth leading cause of death in the U.S., after heart disease, cancer and stroke.**

Conflicts Of Interest And Control

The phenomenal power of drug companies permeates not only physicians who establish treatment guidelines, but prestigious medical publications, academic institutions, the FDA and other regulatory authorities, including Congress itself. **The pharmaceutical industry has more lobbyists in Washington than all senators and representatives combined!** House members and their families own tens of millions of dollars in stock in drug companies whose profits could rise or plummet depending on the outcome of legislation designed to curb soaring drug prices. A recent review revealed that Rep. Robin Hayes owned over $11 million in drug stocks. Rep. Jim Sensenbrenner, the ranking Republican on a subcommittee that can deliver bonanzas to specific companies, owned shares worth up to $7.1 million in five drug firms. Sen. John Kerry sits on the Senate Commerce Committee that will have a role in approving any Medicare coverage for certain drugs. His wife owned shares in eight drug companies worth up to $4.2 million. At least 36 Congressmen, many of whom serve on committees with control over pharmaceuticals, had large drug stock holdings personally or through immediate family members.

FDA advisory committees are required by law to disclose when members have any financial interest in the subject of the meeting, but a September 2000 review revealed the FDA had waived the restriction more than 800 times in the past two years. Some 300 experts are hired by the agency to sit on various committees that determine such things as which medicines should be approved or withdrawn, what the warning labels should say or how drug studies should be designed. **In 92% of meetings, one or more members had a financial conflict in the form of stock, consulting fees, research grants, a spouse's employment or lavish rewards for speeches and travel. In 55% of meetings at least half of the FDA advisers had such financial conflicts of interest or others that were not disclosed.** So did a third of the experts at advisory committee meetings convened to decide the fate of a specific drug.

Although the FDA must reveal any conflicts, the details are kept secret so it is impossible to determine which firm or how much money is involved. Committee members can also receive up to $50,000 a year from a drug company if it is allegedly for something other than what is being evaluated and own $5,000 in its stock without disclosing any financial conflict. In October 1999, a FDA committee of "independent experts" was asked to rule on whether Johnson & Johnson's Levaquin should be approved to treat penicillin-resistant pneumonia. Two of the committee members, including the Chairman, were paid consultants who had developed Levaquin and were excused from voting but four of the ten remaining members were given conflict-of-interest waivers. The drug was unanimously approved and this was ratified by the FDA a few months later. **Levaquin had been available since 1997 but the company was now able to market it as the first antibiotic approved for the more than 25% of pneumonia cases that are resistant to penicillin, at $8.00/pill**.

Companies also spend billions to persuade physicians to prescribe their products in unethical ways. Warner-Lambert's Neurontin was approved in 1994 to control certain types of seizures, but only if taken with other antiepileptic drugs. However, their sales reps encouraged doctors to prescribe Neurontin for pain, obsessive-compulsive disorder, psychoses and other conditions. Physicians were paid $350 or more to let sales reps sit in while examining patients to suggest dosages. Doctors can prescribe Neurontin for such "off label" uses but it is illegal for a drug company to promote a medication for any unapproved indication and there was never any approval for the drug to be used alone.

Pfizer, who bought Warner-Lambert in 2000, said that Neurontin sales had been increasing at an annual rate of 50%, were expected to exceed $2 billion this year and that almost 80% of prescriptions were for unapproved conditions. Although faced with criminal and civil suits, Pfizer plans to seek FDA approval for pain, which brings up other widespread unethical practices.

Just How Tainted Has Medicine Become?

That was the title of an April editorial in the *British Medical Journal* pointing out that a recent study of interactions between authors of clinical practice guidelines and the pharmaceutical industry found serious omissions in declarations of conflicts of interest. "Almost 90% of authors received research funding from or acted as consultants for a drug company. Over half of those who responded to the survey had connections with companies whose drugs were being reviewed in the guideline and the same proportion indicated that there was no formal procedure for reporting these interactions." The situation is probably much worse since 48% of the authors contacted declined to participate because the survey did not guarantee anonymity and most believe this was because they did not want to disclose their industry relationships. **One analysis of heart drug studies showed that 96% of investigators who had received company funding found the tested drug to be safe, compared with only 37% of those with no ties.**

Publication in peer-reviewed journals is the coin of the realm for academic researchers but for pharmaceutical firms, it is approval of a drug application. Prestigious journal articles are important to persuade physicians to prescribe products but are worth little without convincing clinical trials, and drug companies use devious methods to achieve both goals. According to court documents, Warner-Lambert tracked whether doctors prescribed Neurontin and rewarded those who were considered high-volume prescribers by paying them as speakers and consultants and for entering patients in clinical trials. Doctors who wrote articles about Neurontin were also paid, sometimes secretly, and a marketing company was hired to write first drafts.

Such ghostwriting is especially rampant in specialties like psychiatry, cardiology and arthritis where competitive drugs play the major role in treatment and rake in big bucks. **Researchers are accepting huge sums for allowing their names and academic affiliations to be appended to articles they have not written that endorse a particular product.**

"Is Academic Medicine for Sale?" was a similar editorial in the *New England Journal of Medicine* by Marcia Angell, who wrote, "Researchers serve as consultants to companies whose products they are studying, join advisory boards and speakers' bureaus, enter into patent and royalty arrangements, agree to be the listed authors of articles ghostwritten by interested companies, promote drugs and devices at company-sponsored symposiums, and allow themselves to be plied with expensive gifts and trips to luxurious settings. Many also have equity interest in the companies." She was quickly replaced as editor by a prominent asthma researcher with strong industry ties.

Academic institutions are increasingly involved in deals with the same companies whose products their faculty members are studying. A recent *Wall Street Journal* article reported that Targeted Genetics Corporation will acquire Genovo, Inc. As part of the deal, James Wilson, a University of Pennsylvania scientist will receive 13.5 million dollars worth of Targeted stock in exchange for his 30 percent equity interest in Genovo. The University permitted Wilson to own a piece of Genovo even while he was doing research on its products, which is not surprising, given that Penn itself will receive 1.4 million dollars worth of stock for its 3.2 percent stake in Genovo.

Many institutions receive megabucks for allowing companies to set up research outposts in their hospitals and giving them access to students and house officers, as well as to large numbers of patients. As Angell noted in her critical editorial, "When the boundaries between industry and academic medicine become as blurred as they are now, the business goals of industry influence the mission of medical schools in multiple ways. **Medical schools have struck a 'Faustian bargain' with companies as their representatives lavish gifts and trips on doctors that subtly sway researchers to more favorable findings on their products with fees for speaking, consulting and other compensation."** This is mostly for trivial differences between existing drugs that can be hyped to bring in huge returns rather than for new pharmaceuticals with risky futures.

How Drug Companies Continue To Deceive Us And Why Things Will Only Get Worse

Pharmaceutical company profits were more than four times greater than the average for all Fortune 500 firms in 2000. Prescription drug spending increased 20% during the first quarter of 2002 and earnings are projected to continue to rise. The cost of an average prescription is more than double compared to ten years ago and close to four times greater for top selling brands. Drug companies claim this is because it costs so much to develop breakthrough drugs that are far superior to those currently available. The fact is that four out of five "new" drugs are simply copycat versions to replace existing cash cows whose patents are due to expire or can be hyped for marketing purposes. Despite their rhetoric, the primary goal of drug companies is not to help patients but to increase the bottom line so the stock will rise for investors. Why spend millions on research and development that might not pan out if you have a successful product that can easily be promoted to be even more profitable even though its advantages are dubious? **Over the last six years, as direct consumer advertising has risen, the number of R&D drug company employees has fallen while marketing staffs increased 60% and are now twice as large**.

Many ads are deceptive, such as a study showing that Fosamax would cut an osteoporosis patient's risk of a broken hip in half, which is a relative comparison. The actual reduction was from 2% to 1% for any given patient. Similar tactics are used for many other drugs but you are not likely to see an ad claiming that a product reduces your risk for heart attack by 1% rather than by half. Studies showing that a drug is not effective or has safety problems are routinely suppressed since contracts forbid disclosure of any results for three years without the sponsoring company's consent. Profits are so huge that generic companies are paid not to provide their products, such as Taxol. This popular cancer drug with billions in international sales was developed by Bristol-Myers (with government funding) but patent protection expired in Sept. 2000. **The company's price is $6.70/mg., about 95 times more than the 7 cents/mg. for a generic equivalent!**

Six companies are being sued by 29 states and the AARP for collusion with generic competition to suppress other generics. Many insurers have a co-pay of $5.00 for a generic and $10.00 - $25.00 for a preferred brand depending on its price but these costs are likely to more than double next year. AARP joined the suit because soaring prices have particularly affected its 35 million members and it also strongly supports the Administration's plan to provide Medicare payments for certain drugs. Bush's senior health care adviser, Gail Wilensky, holds $10.5 million in shares and options in companies that could benefit from this. **Legislation privately negotiated between the FDA and industry that is certain to pass, mandates much faster approval that will save manufacturers billions but further reduce safety studies.** Seven recently approved drugs were withdrawn because of being implicated in over 1,000 deaths. Stay tuned to see what happens.

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