Turning Medicine

Into Snake Oil

HOW PHARMACEUTICAL MARKETERS PUT PATIENTS AT RISK

MASSPIRG Education Fund

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The State PIRGs

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False and misleading prescription drug advertising is common and dangerous. Prescription drug marketers are inundating doctors, and to a lesser extent, the public, with marketing that misrepresents risks, promotes unproven uses, and makes unsubstantiated claims. The false and misleading messages are communicated through conventional advertising, sales representatives, doctors speaking on behalf of drug marketers, and through clinical trial suppression, manipulation and misrepresentation. Sadly, the Food and Drug Administration (FDA) is ineffective at addressing the problems. This report takes a comprehensive look at all of these facets of the prescription drug marketing problem and suggests effective solutions.

FINDINGS IN BRIEF

We looked at enforcement letters FDA sent to drug marketers from 2001-2005. Our research reveals:

Deceptive drug marketing is pervasive, dangerous, and primarily aimed at doctors.

- From 2001-2005, 85 companies received 170 notices from the FDA explaining that the marketing for 150 different drugs was false and/or misleading.
- 62% of the false or misleading messages targeted doctors, and those messages were expressed by 38 different types of advertising. By contrast, the public was exposed to 17 different types of false or misleading ads.
- The false messages were serious: 35% misrepresented risk; 22% promoted unproven uses; and 38% made unsupported or misleading claims. For deceptive messages targeting doctors, 37% misrepresented risk; 24% promoted unproven uses; and 36% made unsupported or misleading claims.

Recidivism is rampant.

- 28 companies—approximately 1/3 of the total—received more than one letter declaring their ads false or misleading in the five years we examined. In fact, these companies accounted for two-thirds of all the letters received.
- 26 companies received more than one letter relating to advertising for the same drug that was deemed false or misleading in the same way.

Deceptive marketing includes sales representatives.

- Sales representatives, as a group, form long and deep relationships with doctors, beginning in medical school. Research suggests those early relationships increase doctors' receptiveness to sales representatives once they are in practice.
- Perhaps reflecting those relationships, other research has shown that sales representatives have a profound influence on prescribing decisions.
- Sales representative statements accounted for 30 of the 869 deceptive messages in the FDA letters, an amount that is enormous given the very small percentage chance that the FDA will detect such statements. Other research suggests that as much as 11% of sales representative statements are false and favorable to the product they pitch.

Deceptive marketing includes clinical trials.

- In the letters identifying advertising as false or misleading because it contained unsupported claims, FDA highlighted at least 82 times that the advertising cited clinical trials for propositions they did not support. In some instances, the cited trials even contradicted the claims.
- Drug marketers turn clinical trials into marketing tools by suppressing some unfavorable data; by using PR firms to write favorable reports (the PR firm does not appear as an author of the report,

instead a doctor is retained to be the named author); by misrepresenting unfavorable data that is published; and, most subtly, by designing studies to get only the results they want.

Our numbers dramatically understate the problem.

The FDA letters we examined do not address anywhere near the full universe of prescription drug marketing.

- The FDA routinely reviews only "classic" advertising and does not comprehensively monitor sales representatives, doctors acting as pitchmen, or clinical trial data manipulation. Moreover, the FDA's review of classic advertising is not complete; not all ads are submitted to it, and of those that are, the FDA only reviews some.

- The FDA letters rarely identify how many times, or where, an ad was used. A deceptive print ad may have run in several newspapers and magazines. Each of those print runs would be another dissemination of the deceptive messages in the ads.

- The FDA reviews advertising after it has been disseminated and only requires corrective measures a quarter of the time.

- The best measure is how many people internalized the deceptive measure, an impossible figure to determine. The 869 disseminations of deceptive messages that we were able to count from 2001-2005 included TV ads, print ads, and other mass media. How many people are deceived by a single deceptive TV ad watched by a million viewers? Similarly, a single sales representative may convey deceptive messages to hundreds or thousands of doctors in a year.

RECOMMENDATIONS

States Can Solve the Problem

- To address the scientific misconduct that is the suppression, manipulation and misrepresentation of clinical trial data, states should establish a comprehensive, searchable database of clinical trials. Drug marketers would register every clinical trial done in humans for every drug they sell in the state. To be successful, the clinical trial registry must include all the clinically significant aspects of the trial design and trial results. Such a registry would be placed in the state's department of health, and could be financed with registration fees from the drug marketers.

- To address the problem of deceptive classic advertising, deceptive sales representative statements and deceptive doctor-to-doctor marketing, states can create a new type of citizen lawsuit. This would allow citizens to sue for injunctive relief—stopping the false advertising and conducting corrective advertising—reasonable attorney's fees, and, at the judge's discretion depending on the circumstances of the case, civil penalties payable only to the state. Suits could only be won if the deceptive advertising created a public health risk; deceptive advertising that misleadingly, but not dangerously, hypes a drug's properties would not qualify. Doctors, their patients, attorneys general, and in certain instances, the public, would have standing to sue, depending on the type of marketing.

  Examples of sufficiently dangerous advertising might include promoting a drug for illnesses for which the company knows it's not effective, or denying or consistently minimizing serious risks. The advantage of this approach is it enables the recipients of deceptive advertising—the people who can most easily detect it—a way to address the problem but it avoids creating financial incentives that would distort enforcement.

Increasing Enforcement at FDA

To make the FDA a potent regulator able to prevent and correct deceptive advertising, it needs more power and financial resources to:

- Review all advertising submitted to it before it is disseminated, in a commercially relevant timeframe, so that deceptive classic advertising is not used;

- Review sales representative training materials and make unannounced inspections of training sessions;

- Review the presentation materials for talks given by doctors on behalf of drug marketers and make unannounced visits to the talks;

- Require and oversee corrective advertising in every situation where deceptive marketing occurs;

- Require drug marketers to get the FDA's approval before citing any study as support for any claim; and finally,

- Levy significant fines against drug marketers, fines that escalate to truly punitive levels, to serve as a deterrent and eliminate today's rampant recidivism.

The Medical Profession's Role: Improve Prescriber Education and Information Resources

The medical profession and the independent organizations and academic institutions that service it can help.

- Doctors need better access to independent, accurate, digested information about drugs. The information produced by the clinical trial registry should be packaged by an independent group or agency into a form easily useable by prescribers who want information about treatment options. The information provided should include not only the clinically important information about each drug, but also how the drug compares to other treatments in terms of safety, efficacy, and cost. The Drug Effectiveness Review Project (DERP) generates this information, but it is aimed more at policy makers than prescribers. Similarly, Consumers Union takes DERP's data and packages it for patients, as part of its BestBuyDrugs project. To the extent that the information is already accessible (for example, The Medical Letter), the profession must find a way to ensure that doctors use it. Only by breaking their reliance on sales representatives and other sources of promotional information can doctors ensure they are getting unbiased information.

- Medical schools and teaching hospitals should heavily invest in training students and residents to be skeptical of pharmaceutical sales representatives and to rely on independent sources of information.

REPORT ROADMAP

After introducing the problem and laying out the regulatory context, the report presents the results of our analysis of the most comprehensive database on false and misleading advertising available: FDA's enforcement letters to pharmaceutical companies engaging in deceptive marketing practices. We look at five years of letters to see what kinds of false messages pharmaceutical companies are directing toward whom and how. We also explain why those numbers are grotesque understatements of the problem. One reason they are understatements is that they mostly address conventional advertising, such as ads in professional journals or on TV; they rarely address sales representative statements or the presentations made by doctors consulting for the drug marketer. The latter activities are currently beyond the FDA's resources to monitor.

Then we look at the ways the FDA currently fails to address even the classic advertising slice of the false marketing problem, the one it monitors as closely as it can. As part of our evidence of the FDA's failure, we describe the high rates of "general recidivism," that is, drug marketers that have received multiple letters from the FDA about their false or misleading marketing, and "specific recidivism," that is, drug marketers who have received multiple letters about their advertisements for a single drug, advertisements that are all false or misleading in the same way.

We complete our analysis of the deceptive marketing problem by focusing on the marketing outside of the FDA's routine review. Specifically, we focus on prescription drug sales representatives and clinical trials. Sales representatives are powerful marketing forces because they have many opportunities to interact with physicians, and the evidence shows that they give false and misleading information far too often. As disturbing as our findings in this area are, they may be mitigated to some extent, given that

doctors may expect sales representatives to present misleading information. After all, their job is to sell drugs, not educate physicians. Clinical trials, however, are the cornerstone of prescription drug science, and few physicians let alone patients would anticipate the extent to which drug marketers shape and control them.

We conclude with concrete solutions that states can take now and offer recommendations for addressing FDA's problems. Fortunately, steps the states can take are powerful enough to rein in the drug marketers to the point where the public can again be confident that they and their doctors are consistently receiving accurate information. Best of all, the state steps are inexpensive.

THE APPENDIX—CASE STUDIES

To fill in the big picture of deceptive marketing we sketch, we present six case studies of deceptive marketing of prescription drugs in the appendix, located in the center spread. Four—Vioxx, OxyContin, Paxil, and Neurontin—are offered primarily to illustrate different features of the problem and to convey how deceptive messages can permeate drug marketing. Two other case studies, Accutane and Tindamax, are included to highlight the FDA's inability to police drug marketers.

Introduction

Consumers and doctors are inundated with messages about which drug to use. Ubiquitous advertising is not necessarily bad; doctors need to learn the new treatments available, and consumers can be inspired to see their doctors for necessary treatment, as well as empowered to be active participants in their health care. But when drug marketers give false and misleading information about their products to doctors, patients are placed at risk.

On purely medical criteria, the decision to prescribe a certain drug for a certain person is very complex; each drug's effects are different, and each patient has unique issues that must be considered, including their age, gender, disease state, other medications they are taking, and other medical conditions they have. Moreover, non-medical factors also can influence prescribing decisions. Research reveals patient demand, driven by direct-to-consumer advertising, affects prescribing,[1] as does contact between doctors and sales representatives,[2] advice from other doctors,[3] gifts to doctors,[4] the availability of free samples,[5] and the insurance coverage the patient has.[6]

Nonetheless, our society has so far maintained bedrock faith in one idea: doctors can sort through all the issues and pressures and consistently make appropriate prescribing decisions. A 2003 survey showed broad trust in doctors' prescribing decisions, but also the corrosive effect of drug marketing.[7] Roughly two-thirds of the respondents "trust[ed] [their physician] to choose the drug that is best," while 23 percent worried their doctors' judgment might be impaired by drug marketing and another ten percent were undecided.

The public's trust in their doctors' prescribing decisions might plummet if the public understood just how often drug marketers conceal risks from doctors, urge doctors to prescribe drugs for uses that have not been shown to be safe or effective, and make misleading claims to doctors about the drugs they promote.

Deceptive Advertising Distorts the Crucial Risk/Benefit Analysis

The Food and Drug Administration (FDA) approves drugs for very particular uses, based on the data showing safety and efficacy and the balance between them. After negotiation with the drug's maker, the FDA codifies its risk-benefit judgment as the drug's indication in the drug's label. As Dr. Henry I. Miller, former head of the FDA's Office of Biotechnology recently explained in the *Wall Street Journal*:

> The 'safety' of a drug is a relative thing. Safety and efficacy, the two criteria required for marketing approval of a drug, are inextricably linked. The judgments of regulators (and practicing physicians) require a global and often difficult calculation of risk and benefit, including consideration of what alternative therapies are available. For a given drug, we are willing to tolerate greater uncertainty and more severe side effects for a potential cure for pancreatic cancer or AIDS, for example, than a new drug that treats heartburn. When FDA grants marketing approval, the drug is deemed safe and effected to be used for the conditions on the label.[8]

Thus, for the uses the FDA has said a drug maker can market a drug—and only for those uses—the public should have confidence a drug is effective enough to be worth the risk. FDA's critics, however, argue such confidence is misplaced.[9] If the critics are right, some drugs approved uses, however limited, are already broader than justifiable.

The delicate risk-benefit analysis that underlies prescription drug approvals is what makes ensuring doctors have full and accurate information about a drug so important. The marketing regulations are intended to ensure that is what doctors get.

Doctors are free to prescribe "off-label," meaning

for uses that the FDA has not approved. This practice makes sense as long as the underlying premise is true: motivated by their patients' needs and aware of their unique situations, doctors are making thoughtful, informed choices to use drugs experimentally. Doctors are capable of making the necessary judgments. Recognition of that capability justifies the right to prescribe off-label.

In contrast, in recognition of drug companies' desire to sell as many drugs as possible, the law does not allow drug companies to promote drugs for off-label uses. If drug marketers can promote drugs for off-label uses, the concept of "on-label" use is empty; the drug labeling is irrelevant.

Defining Deceptive Advertising

FDA regulations identify two different kinds of prescription drug advertising: product specific ads and reminder ads.[10] Product specific ads promote a certain drug and are subject to the most extensive disclosure requirements. Risks must be disclosed with equal prominence as benefits, the drug's approved uses must be clear, and every claim about the drug (such as "it's cheaper," "patients like it better," or "it improves patients' quality of life") must be supported by substantial evidence. Furthermore, the drug marketer can promote only approved uses and must disclose any limits on a drug's approved use—such as being appropriate only after other treatments have failed or only for the most severe forms of the illness.

Reminder ads build brand awareness by "reminding" people of the drug's name. The opposite extreme of product specific ads, these ads cannot include any information about the drug. These ads help build brand awareness and are generally aimed at doctors in the form of gifts emblazoned with a drug's logo.

Disease awareness ads are a third type of ad. The ads help consumers understand what the symptoms they experience might mean and inspire them to go to the doctor for diagnosis. Drug marketers generally run these ads about diseases that their drugs treat, so the increased diagnoses lead to increased sales. Disease awareness ads cannot have any drug related information at all.

The FDA deems any deviation from these requirements "false or misleading advertising."

How the FDA Polices Deceptive Advertising

Under current regulations, drug marketers submit their promotional material to the FDA before using it, but are then free to use the material until the FDA tells them otherwise. Eventually, the FDA reviews some of the material submitted to it; if the FDA deems an ad false or misleading, it writes the drug marketer an "Untitled Letter" explaining its decision and telling the marketer to stop using the ads. If the FDA is very concerned about the false and misleading messages in the ad, it issues a "Warning Letter" instead of an Untitled Letter, and demands that not only the marketer stop the false advertising, but also that it send out corrective messages.

On occasion, the FDA attends medical conferences or lectures at which drugs are promoted and determines that statements made by sales representatives or doctors consulting for the drug marketers are false or misleading. The FDA also learns of these types of violations from upset doctors or competing drug marketers. The FDA responds in the same way: it writes Untitled and Warning Letters.

The FDA letters are clear and detailed, and most are posted on the FDA's website, along with the promotional material to which they refer. While these letters are not the same as a conclusive finding of falsity because the drug marketer has the right to respond and appeal, they are nonetheless the best available database to indicate what the scope of the deceptive advertising problem is.

Deceptive Advertising's Role in Maximizing Profits

In the face of strong pressure from Wall Street to produce "blockbuster" drugs, drug marketers have a significant incentive to engage in deceptive advertising. FDA limits on how drug marketers can promote a drug's uses and strict risk disclosure requirements pose a tremendous sales challenge to drug marketers. Approved uses define the size of the legitimate market for a drug, and full awareness of risks can deter some doctors and patients within that market.[11] In many cases, marketing solely within the FDA's prescribed limits caps a drug's potential sales at a relatively low number. Persuading doctors that a drug is safer than it is, or that it is useful beyond its indication, is a shortcut to blockbuster status.

Deceptive Advertising Findings

Table 1
Types of Deceptive Marketing Aimed at Doctors

Aimed at Doctors	No. of Ads	% of Ads
Detail aid/Sales aid	43	20%
Journal ads	36	17%
Brochure	19	9%
Oral statements by sales representatives	19	9%
Convention panel/Exhibit panel/Booth panel	15	7%
Audio conferences	11	5%
Direct mailers	10	5%
Case study	8	4%
Visual aid	8	4%
Posters	6	3%
Dear Doctor letter	3	1%
Abstract distributed at conference	2	1%
Flash card	2	1%
Medical information packs	2	1%
Reprint carrier	2	1%
Video	2	1%
Booklet	1	0.4%
Bottle holders	1	0.4%
Calendar	1	0.4%
Dear Director of Nursing letter	1	0.4%
Fact card	1	0.4%
File card	1	0.4%
Four sided card	1	0.4%
Handout	1	0.4%
Jar	1	0.4%
Material distributed at a conference	1	0.4%
Model	1	0.4%
Notepad	1	0.4%
Packers	1	0.4%
Physician starter packs	1	0.4%
Pill wall chart	1	0.4%
Professional formulary switch aid	1	0.4%
Professional promotional labeling	1	0.4%
Promotional banner	1	0.4%
Puzzle	1	0.4%
Sell sheet	1	0.4%
Wall chart	1	0.4%
Wholesaler fact sheet	1	0.4%

DECEPTIVE DRUG ADVERTISEMENTS ARE WIDESPREAD

To assess the scale of the deceptive advertising problem, we studied all 170[12] of the FDA Warning and Untitled Letters from 2001-2005 posted at http://www.fda.gov/cder/warn/warn2005.htm and tallied how many times drug marketers disseminated misleading or false messages to doctors and the public. We also reviewed the existing literature to contextualize the results. We found false advertising is common, varied, and targeted at doctors more than at the public. Many of the false messages minimized or omitted risks or promoted unproven uses for the drug.

From 2001-2005, 85 companies deceptively marketed 150 drugs.
From 2001-2005, the FDA wrote at least 170 letters to 85 different companies for false and misleading advertising.[13] The letters involved the promotion of 150 different drugs, drugs for conditions as mild as allergies to as serious as cancer.

False advertising aimed at doctors was more common and varied than false advertising aimed at consumers.
In the period we studied, drug marketers disseminated a total of 358 false or misleading ads, 210 (59%) to doctors and 148 (41%) to consumers. As Tables 1 and 2 show, the types of deceptive marketing are varied. In total, 38 different types of false and misleading marketing pieces targeted doctors, and no one kind dominated; in fact, seven different kinds of advertising occurred with double digit frequency, and combined, these accounted for only 73% of the deceptive ads aimed at doctors.

As Table 1 shows, doctors are bombarded with false messages in all areas of their professional life, whether when reading journals, attending conferences, meeting with sales representatives, reviewing materials given to them by sales representatives, listening to talks by other doctors or reading their mail. Focusing

misleading messages on doctors makes sense from a marketing perspective because doctors are the ones who produce sales by writing prescriptions.

Statements made by sales representatives and audio conferences given by drug marketer-sponsored doctors to other doctors were the 4th and 6th most common sources of false and misleading messages identified by the FDA letters, respectively, accounting for 14% of the total combined. Both of these types of marketing occur largely outside the FDA's monitoring; that the FDA detected them frequently enough for them to rank as the 4th and 6th most common forms of false advertising targeting doctors suggests that the false advertising problem in those two settings could be enormous.

In contrast, only three types of ads account for 79% of the deceptive marketing aimed at consumers—print ads (36%), TV ads (26%) and websites (21%)—and drug marketers are required to submit these ads to FDA for review. Nonetheless, these advertisements, like all direct-to-consumer (DTC) ads, have the potential to mislead millions of people, far more than the marketing aimed solely at doctors. Moreover, doctors are members of the public, so these deceptive ads can reinforce the misleading messages doctors are already receiving.

FALSE ADVERTISEMENTS OFTEN CONTAINED MULTIPLE FALSE MESSAGES

The 358 ads addressed by the FDA letters often contained multiple false or misleading messages. A single ad might omit some critical risks, minimize others and promote for unproven uses. Nearly three-fourths of the letters involved five or fewer deceptive messages (72 %), while 20% had between 6 and 10 deceptive messages, and 8% had more than 10. Three of the FDA letters discussed the dissemination of more than 40 deceptive messages.[14] The letters that involved high numbers of deceptive messages either involved the most different pieces of marketing (e.g., multiple sales aids, journal ads, etc.) or had the most complete information on dissemination of the false ads, or both.

Table 2
Types of Deceptive Marketing Aimed at the Public

Types of Ads	No. of Ads	% of Ads
Print ads	48	32%
Tv ads	38	26%
Websites	31	21%
Radio ads	9	6%
Videos	5	3%
Billboards	3	2%
Press release	3	2%
Fulfillment letter	2	1%
Answers at toll free #	1	1%
Infomercial	1	1%
Brochure	1	1%
Puzzle	1	1%
Direct mail	1	1%
Starter kit	1	1%
Tear sheet	1	1%
Restroom poster	1	1%
Special magazine	1	1%

As Table 3 shows, the ads discussed by the FDA letters contained a total of 869 false or misleading messages.

Doctors received more false messages than the public.
Of the 869 deceptive messages, 535 (62%) were aimed at doctors, and 334 (38%) were aimed at the public. To some extent, Table 3 shows the explosion in direct-to-consumer advertising; in 2001, drug marketers targeted doctors with more than three times as many misleading messages as they did the public; in 2002, drug marketers targeted doctors with more than twice as many misleading messages; in 2003 and 2004, marketers targeted the public for more misleading messages, but the gap narrowed. In 2005, the trend reversed and doctors again were targeted for more misleading messages than the public, although the gap was again narrow.

Table 3
Number of Ways FDA Identified Ads as False or Misleading, 2001-2005

Year	Misrepresented risk and safety information			Promoted for Uses not proven safe and effective			Unsubstantiated or misleading claims			Other			Total		
	For Dr's	For Public	All	For Dr's	For Public	All	For Dr's	For Public	All	For Dr's	For Public	All	For Dr's	For Public	All
2001	93	28	121	80	23	103	79	27	106	11	8	19	263	86	349
2002	39	17	56	22	5	27	43	18	61	0	7	7	104	47	151
2003	27	22	49	14	21	35	24	37	61	0	2	2	65	82	147
2004	18	23	41	5	11	16	16	25	41	0	6	6	39	65	104
2005	20	15	35	9	5	14	31	30	61	4	4	8	64	54	118
2001-2005	197	105	302	130	65	195	193	137	330	15	27	42	535	334	869

Note that the 2001 numbers are significantly higher than the other years in most categories; that is because FDA issued nearly twice as many letters in 2001. Why is not clear. It may reflect a shift in enforcement emphasis; the FDA issued several letters relating to promotion at medical conferences in 2001, but very few in the other years. The change may reflect the change of administration in Washington D.C. and a resulting shift in resources and priorities. The sharp decrease between 2001 and 2002 may also reflect a decrease in false advertising by drug marketers, however, the year to year changes among 2002-2005 are nowhere near as great, so it is hard to imagine that a change in marketing practices represents the whole shift between those or any other years.

METHODOLOGY FOR FALSE MESSAGES: WHAT WE COUNTED

To the extent possible, we counted how many false and misleading messages were being disseminated to doctors and/or the public. Thus, a print ad that the FDA said omitted some serious risk information and minimized other risk information counted as two violations; if the letter indicated the ad ran in both the New York Times and the Washington Post, that was counted as disseminating four false or misleading messages. In one case, a letter criticized five print ads aimed at the public and mentioned 11 different publications the ads ran in, and indicated that the ads ran in other outlets too. The letter did not clarify which ran where, however, so we conservatively counted 11 disseminations of each violation in the ads, rather than assuming all five ads ran in all 11 publications, which would have produced 55 disseminations of each violation. However, most of the time the FDA letter did not indicate where an ad was used, so we primarily counted how many times drug marketers created false or misleading messages for dissemination.

We counted only what the FDA characterized as the violation of the drug marketing regulations, rather than each example of the violation the FDA included in the letter. Thus when the FDA stated that an ad made misleading claims about the drug's impact on a patient's quality of life and gave four examples from the ad, we counted it as one violation. But if the FDA indicated the ad made several types of misleading claims, each type of misleading claim was counted separately.

Some letters addressed ads that the drug marketer had designed as either a disease state ad or as a "reminder ad", but which made product-specific claims and so were really product-specific ads in disguise. These ads violated the rules in a number of ways, always including the omission of risk information and what the drug's approved uses are. However, the FDA was not consistent in describing these violations, so rather than create our own method of counting violations or simply add them to our totals relating to risk or promotion of unapproved uses, we placed them as single violations in the "other" category. In the five years we reviewed, the FDA identified 15 such ads, ten aimed at the public and five aimed at doctors. Placing these ads in the "other" category reduced the other totals.

The category "Misrepresented Risk and Safety Information" includes these FDA-identified violations: omitting risks; minimizing risks; inadequately communicating risk; misrepresenting safety profile; misleading safety claim; omitting safety information; using outdated labeling (new version included more risk information); and lack of "fair balance." Fair balance is the FDA's requirement that risk information be displayed as prominently as a drug's benefits and is a type of minimizing or omitting risk information.

The category "Promoted for uses not proven safe or effective" includes the FDA-identified violations of: promotion of unapproved use; promotion of an investigational drug (i.e. one not yet approved for sale in the U.S.); broadening a drug's indication; inadequate communication of a drug's indication; omission of material facts relating to a drug's indication or use; promotion of an unapproved dosing regimen; and inadequate communication of contextual information, in one case regarding the appropriate population for a drug, and in the other, regarding health risks.

The category "Unsubstantiated or misleading claims" includes the FDA-identified violations of: unsubstantiated claims; unsubstantiated superiority claims; unsubstantiated efficacy claims; misleading superiority claims; misleading comparative claims; misleading claims; misleading efficacy claims; overstatements of efficacy; and failure to disclose a material fact (unrelated to safety or type of use).

The category "Other" includes the 15 ads that were identified as product-specific ads in disguise and violations such as failing to make adequate provision for consumers to get full information about the drug, failing to disclose the drug's prescription status or minimizing the role of the prescriber, failing to include a brief summary of a drug's prescribing information, and failing to disclose the drug's generic name.

To some extent, that change in distribution may also reflect FDA reducing its investigation of sales representatives' statements at conferences—certainly there were far fewer letters for those in the later years—and a change in how FDA enforcement resources are allocated. According to the Government Accountability Office, the FDA cannot review all advertising submitted to it and prioritizes reviewing broadcast advertisements.[15] Thus as direct-to-consumer advertising grew, the FDA had less resources to review other forms of advertising, and the relative decrease in detecting false ads aimed at doctors may only reflect a reduction in detection, not in occurrence.

DECEPTIVE ADVERTISING IS DANGEROUS

Deceptive advertising puts patients at risk. The FDA's May 29, 2003 Warning Letter to Hoffman-LaRoche explains the stakes:

> You have disseminated a professional sales aid and a patient video that omit or minimize material facts regarding the safety profile of Xeloda, make misleading efficacy claims for Xeloda, make unsubstantiated superiority claims over other cancer therapies and omit material facts about the approved indications for Xeloda. ***These claims have the potential to misguide physicians in making prescribing and treatment decisions, and, therefore, jeopardize patient safety.*** (Emphasis added; at p. 8)

Sometimes the FDA was even more explicit:

> "Aventis' false or misleading promotion in the sales aid **may compromise patient survival and safety.**" (Emphasis added; 12-15-02 Untitled Letter to Aventis at p.2)

Or

> "Your **failure to disclose the serious, sometimes fatal, risks associated with treatment with these agents and the appropriate conditions for their use** raises significant public health and safety concerns." (11-14-02 Untitled Letter to Xanodyne)

Our review of the deceptive messages identified by the FDA found that many of them, particularly those targeting doctors, either misrepresented drugs' risks or promoted drugs for unproven uses. Both of those types of deceptive messages are particularly dangerous for patients because they can directly result in inappropriate prescriptions.

37% of the deceptive messages targeting doctors endangered patients by omitting, minimizing, or misrepresenting drugs' risks. While any false and misleading advertisement is bad, those teaching doctors that a drug is safer than it really is are particularly troubling. Doctors relying on that information will unintentionally endanger their patients.

Screening patients appropriately and closely following warnings, precautions and contra-indications ensures that each prescribing decision is as accurate a risk-benefit analysis as possible, which is what the public wants. When drug marketers misrepresent risks, this calculation is off and patients are unjustifiably endangered.

In the period we studied, 37% of the false or misleading messages targeting doctors involved omitting, minimizing, or otherwise misrepresenting drugs' risks. (Table 3, first set of columns, 197/535.) The public fared only slightly better: 31% (105/334) of the false or misleading messages aimed at the public omitted or minimized risks.

Again, if we had treated the 15 ads that pretended not to be product-specific ads differently, the proportion of risk violations would be even higher for both groups, because none of those ads contained any risk information for the drugs they promoted.

Examples of Marketing That Dangerously Misrepresents Risks:

- **Pharmacia promoted Celebrex for use in patients at risk of serious bleeding.** Pharmacia promoted Celebrex as safe for patients taking the drug Coumadin, although the prescribing materials state that patients taking both may experience serious bleeding. The FDA explained: "minimization of this risk raises significant public health and safety concerns." (FDA Warning Letter to Pharmacia 2-1-01)

- **A sales representative denied Sporonox's serious cardiac and liver risks.** A sales representative for the Janssen Research Foundation told visitors to Janssen's booth in the commercial exhibit hall of the American Society of Health-System Pharmacists' Annual Meeting that Sporonox does not affect the liver, that liver monitoring is not necessary when using it, and further, that he did not know of any cardiac risks associated with it. Despite the sales representative's assurances, Sporonox's prescribing information has a Black Box Warning about cardiac risks and also warns of rare but fatal liver risks, even in people who had no previous liver problems. Black Box Warnings are risks considered so serious and important that the FDA visually isolates them and puts them in bold text in a black box on the label. (FDA Untitled Letter 6-27-01)

- **Sales representatives denied warnings that Avandia could cause congestive heart failure.** Two sales representatives for GlaxoSmithKline (GSK) told visitors to the GSK exhibit booth at the 10th Annual American Association of Clinical Endocrinologists meeting that no new warnings had been added to the prescribing information for Avandia and that Avandia could be used safely with insulin. In fact, the Avandia information had been revised to warn that Avandia could cause congestive heart failure when used with insulin, even in patients without a history of congestive heart failure or pre-existing cardiac failure. The FDA had previously asked GSK to stop misrepresenting the congestive heart failure risk. (FDA Warning Letter 7-17-01)

To get a fuller understanding of how drug marketers can misrepresent the risks of their drugs, please see the case studies in Appendix A, particularly Vioxx, OxyContin, and Accutane.

24% of the Deceptive Messages Targeting Doctors Endangered Patients by Promoting Unproven and/or Unjustified ("Off-Label") Uses. As the data in the second set of columns in Table 3 shows, 24% (130/535) of the deceptive messages targeting doctors promoted drugs for uses for which FDA had not approved them as safe and effective. The public fared somewhat better; 19% (65/334) of the deceptive messages targeting them promoted drugs this way. Again, if we had treated the 15 ads that pretended not to be product-specific ads differently, the proportion of unproven use violations would be even higher for both groups, because none of those ads contained any information about the approved indication of the drugs they promoted.

Promoting off-label can be more dangerous than misrepresenting risks. Our analysis incorporates two basic types of off-label promotion; promoting unproven uses and promoting unjustifiably risky uses.

By definition, when drug marketers are promoting uses that are not in a drug's label because the drug marketer has not proven safety or efficacy, the drug marketer does not know the drug will work nor if such use will harm the patient. Thus the patient gets all the drug's risks and quite possibly no benefit. Worse, if effective treatments exist, the patient's condition may continue to worsen needlessly. An example of this type of off-label promotion is Neurontin, discussed in Appendix A.

When drug marketers promote off-label by broadening the drug's indication—meaning they urge doctors to ignore the safety-based limitations the FDA imposed on a drug's use—they are promoting the drug for uses it is effective for, but which the FDA decided are not justified, given the drug's risks. Patients given these prescriptions are by definition exposed to unnecessary, excessive risks. An example of this type of off-label promotion is OxyContin, discussed in Appendix A.

Despite the risks, indirect evidence suggests that off-label promotion by drug companies is common and successful. In 2002, 115 million off-label prescriptions were written.[16] In 2003 *Knight-Ridder* did an investigative report on the dangers of off-label prescribing and explained the scope of the problem:

> Doctors are giving their patients epilepsy drugs for depression and hot flashes and to help them lose weight. They use antidepressants to treat premature ejaculation and pain, and powerful antipsychotics for insomnia and attention deficit disorder. High blood-pressure pills are prescribed for headaches and anxiety; antibiotics are used to treat viruses.
>
> Some drugs, in fact, are sold mostly for unapproved purposes. Eight out of 10 prescriptions for the epilepsy drug Topamax aren't for epilepsy.
>
> Thalidomide, the notorious morning-sickness drug that caused horrible birth defects and ushered in today's FDA drug-safety rules, even is on the market, and 99 percent of its prescriptions are off-label.
>
> [Of the]15 top-selling classes of drugs… some, such as cholesterol medicines, rarely are given as unapproved treatments. But three-quarters of anti-seizure medications are prescribed off-label, as are nearly two-thirds of antipsychotics and about one-quarter of antidepressants[.][17]

While off-label uses, by definition, lack sufficient evidence to demonstrate safety and efficacy, not all off-label uses are equally risky. Some have some support while others have none, and in some instances, patients are benefiting from off-label uses. Acknowledging that off-label use can benefit some and sometimes has some justification, however, does not change the imperative against off-label promotion. Off-label use, at doctors' discretion, is allowed precisely because of the potential benefits; off-label promotion is forbidden because drug marketers have a strong incentive—the need to sell as many pills as possible—to urge prescriptions for as many 'uses' as possible.

The widespread off-label prescribing identified by Knight-Ridder and quoted above is hard to understand absent a concerted off-label promotion effort. Interestingly, one drug class that Knight-Ridder found to be rarely given off-label are cholesterol medicines, a type of medicine that has an enormous on-label market, and one of the drug types most commonly prescribed off-label, anti-seizure medicine, has a limited on-label market. Could drug marketers' 'need' for a blockbuster-sized market for their drugs—and therefore off-label promotion—explain that difference in off-label usage?

Examples of Promoting Off-Label Use

- **Cubist Pharmaceuticals promoted Cubicin for off-label use as a pneumonia treatment despite data showing it is ineffective.**
  Cubist Pharmaceuticals used a website to promote its antibiotic Cubicin for use against the bacteria that causes community-acquired pneumonia. In fact, the prescribing information specifically says Cubicin should not be used for pneumonia because clinical trial results showed that Cubicin was not effective, leading to patient deaths. The letter noted the promotion for pneumonia "is misleading and poses a significant public health risk because such practice could lead to therapeutic failure and death." (FDA Warning Letter 8-17-04)

- **A sales representative promoted Tracleer for off-label congestive heart failure treatment, despite the data showing no benefit and increased risks to patients.**
  A territory manager for Actilion promoted Tracleer as useful for congestive heart failure to members of a congestive heart failure unit. The manager claimed that studies had shown that Tracleer had shown neither a positive or negative effect on congestive heart failure and suggested that the doctors might have a use for it. However, data that Actilion itself helped create showed no benefit and in fact some worsening of congestive heart failure patients. Furthermore, even if Tracleer posed no risk of worsening the patients' congestive

heart failure—even though ineffective treatment intrinsically poses such a risk—Tracleer is an intrinsically dangerous drug. It poses serious risks to patients' livers and to fetuses, risks high enough that it is not supposed to be used except through a specific risk minimization program. The territory manager mentioned neither the risks nor the risk program. (FDA Untitled Letter 10-30-02)

- **Berlex promoted Climara for off-label uses that are likely to endanger patients.** Berlex Laboratories promoted its estrogen patch Climara for the treatment of patients with gallstones and hypertrigliceridemia [elevated triglicerides] in a journal ad and a panel for an exhibit booth at conventions. Climara is not only not approved for those uses, but may endanger patients if used that way; Climara's prescribing information warns that Climara use can cause gallbladder disease and elevate triglicerides leading to pancreitis and other complications. (FDA Untitled Letter 1-6-03)

To get a fuller understanding of how drug marketers promote their drugs off-label, please see the case studies in Appendix A, particularly Neurontin, Tindamax, and Vioxx.

THE FDA LETTER DATA GROSSLY UNDERSTATE THE FALSE ADVERTISING PROBLEM

While the data from the FDA letters demonstrate that the deceptive advertising problem is pervasive and severe, we must emphasize that the data and case studies dramatically understate the problem.

Drug Marketers Help Shape Drugs' Labels—the Baseline for Judging Ads

The most subtle reason the numbers are an understatement is the fact that the baseline against which ads are judged is not as strict as the public and doctors might imagine.

Drug marketers have profound influence on the content of a drug's label, particularly after the drug is on the market and new evidence of serious risks has developed.[18] The FDA cannot dictate the label; it and the drug manufacturer must agree on the language, a negotiation process that can enable marketing concerns to shape a drug label's content.[19] Perhaps that influence explains why, when significant evidence of Vioxx's heart risks persuaded the FDA that Vioxx's label should contain some information about heart risks, that information was not placed in the "Warnings" section.[20] The FDA recognizes the difficulty it has in making drug labeling reflect drugs' risks and has asked for the authority to dictate the content of prescribing information.[21]

Despite the Regulations, Not All Ads Are Submitted to the FDA

Drug marketers do not always submit advertisements to the FDA for review, despite the regulations. The FDA is well aware of the problem.[22] Indeed, 32 of the false and misleading ads addressed in the FDA letters we reviewed had not been submitted to the FDA; the FDA found them by other means. Thus the universe of potentially false conventional advertising is larger than the one the FDA is given the opportunity to review.

The FDA Does Not Review All Ads Submitted To It

Not all ads submitted to the FDA for review may in fact be reviewed. As the Government Accountability Office (GAO) explained:

> FDA said that it receives numerous marketing and promotional materials for promoted prescription drugs and that while every effort is made to review the materials, it cannot guarantee that all materials are reviewed because of limited resources and competing priorities.[23]

Thus, the universe of ads the FDA reviews for accuracy is smaller than the one it is theoretically given the opportunity to review, which as noted is already smaller than the full universe of conventional prescription drug advertisements. Thus the data discussed above reflect the false and misleading ads detected in a subset of a subset of the true universe of ads.

The Data Mostly Reflect Ads, Not Placement of Ads

By the time the letter is issued, a print ad, for example, may have run in several professional journals, newspapers or magazines. Very few of the FDA letters identified the outlets in which the advertisements appeared; when FDA identified the outlets, it often was by example rather than comprehensive. Thus our findings understate the number of times the drug marketers disseminated the deceptive messages identified by the letters we reviewed.

Deceptive Ads Are Not (and often cannot be) Recalled

While the FDA may declare a "sales aid" advertisement false and forbid its further use, it may already be in thousands of doctors' offices, distributed during meetings between sales representatives and the doctors. While the sales aid in theory could be recalled, no FDA letter suggested that drug marketers attempt a recall. a false journal advertisement could not, nor could a television ad that has already completed its run. Thus a false ad may continue disseminating false messages long after the company agrees to stop using it.

The Best Measure Is How Many People Internalized a False Message

Finally, even if we could count how many times drug marketers communicated false or misleading advertising, that total would still grossly understate the problem of false and misleading drug advertising. In the end, the critical number is not how many false ads were disseminated, but how many people received and internalized them. A single false TV ad seen by millions of people may have prompted thousands of them to make a decision harmful to their health. There is no way to estimate how many people are being affected by the false messages, other than to say it is orders of magnitude greater than the number of messages being put out.

The FDA's Failures

The data in the tables, illustrated by the case studies in Appendix A, reveal a false and misleading prescription drug marketing problem that is endangering patients. The size and depth of the problem prove that current methods of addressing false advertising are failing.

Setting aside the fact that the FDA does not review much of drug marketers' activity for accuracy and fairness, the FDA letters fail to effectively police what marketing the FDA does review in at least three ways.

FDA LETTERS GO OUT TOO LATE TO BE EFFECTIVE.

To prevent the dissemination of deceptive messages, the FDA would have to review the materials in advance and release only accurate advertisements for distribution. Sending letters after deceptive material is distributed might prevent further distribution of the deceptive ads, but it does nothing to prevent doctors or the public from internalizing the already-distributed deceptive messages, nor does it ensure that doctors or the public do not continue to view the already-distributed deceptive materials. For example, a doctor might hold onto an issue of a professional journal for years and see a deceptive ad any time he returns to it to review an article. Only by preventing the dissemination of deceptive messages could the FDA eliminate the risk that prescriptions are written based on inaccurate information about risk or effectiveness. Unfortunately, at present the FDA does not have the necessary resources to review materials before they go out.

While reviewing the materials before dissemination would be best, sending letters at the beginning of an advertising campaign would be more constructive than present practice. At present letters can take weeks to months to be sent out, allowing the false messages to persist, even to fully run their course.[24]

LESS THAN A QUARTER OF THE LETTERS CALL FOR CORRECTIVE ADVERTISING.

Only 23% of the FDA letters call for corrective advertising, allowing whatever misperceptions the false ads created to remain unchallenged in three quarters of the cases. Moreover, corrective measures such as "Dear Doctor" letters and labeling changes may not correct doctors' understanding.

Serious risks with Propulsid, Rezulin, Posicor and Duract came to light after they were on the market and doctors had formed habits for prescribing them. The FDA addressed the risks by changing the drugs' labeling and requiring the drug marketers to send Dear Doctor letters announcing and explaining the labeling changes. The letters and labeling changes failed to change doctors' prescribing habits, and patients died. All four drugs are now off the market.[25] Since Dear Doctor letters failed in these cases—when drug marketers had every incentive to ensure they succeeded—the letters are unlikely to correct a false or misleading advertising message.

THE FDA LETTERS DO NOT DETER FUTURE DECEPTIVE ADVERTISING

We looked at two types of recidivism, general and specific: how many companies advertised falsely more than once, and how many companies advertised falsely about the same drug in the same way? In both cases, recidivism rates were high.

General Recidivism

Over One-Third of the Companies Received More Than One Letter.

Approximately one-third of the companies accounted for two-thirds of the letters sent in 2001-2005. In all, 28 companies accounted for 113 of the letters. However, even within the group

Table 4: General Recidivism
Companies Receiving More Than One Letter in the Study Period

Companies	# Letters received by each	Total letters
Pfizer, Inc.	15	15
Novartis Pharmaceuticals Corp.	9	9
AstraZeneca, Aventis, GlaxoSmithKline	7	21
Hoffman-LaRoche	6	6
Berlex Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb Company.	5	15
Abbot Laboratories, Alcon Research, Ltd. (including one received by Alcon Laboratories for the same drug at issue in one of Alcon Research, Ltd.'s letters)	4	8
Allergan, Inc., Alza Corporation, Bayer Corporation, Fujisawa Healthcare, Inc., SuperGen, Inc.	3	15
Actelion Pharmaceuticals US, Inc., Connetics Corporation, Elan Pharmaceuticals, Eli Lilly, Fujisawa Healthcare, Inc., Galderma Laboratories, Gilead Sciences, Inc., Janssen Pharmaceutica, Janssen Research Foundation, Pharmacia Corporation, Sanofi-Synthelabo, Inc., Schering Corporation.	2	24
Total number of letters received by general recidivists:		**113**

of recidivists, some companies were much more frequent disseminators of deceptive advertising than others. Pfizer, Inc. received 15 letters; the next closest company was Novartis with nine, and three companies tied for third with seven letters each. Table 4 shows the breakdown:

We also found several examples of specific recidivism; that is, marketing the same drug in the same deceptive manner after the FDA has demanded it stop.

Specific Recidivism
One example of specific recidivism and the FDA's frustration with it is the conduct discussed in a February 1, 2001 letter to Pharmacia:

> ***You have engaged in repeated promotional activities that minimize the potentially serious risk of using Celebrex and Coumadin (warfarin) concomitantly. Your minimization of this risk raises significant public health and safety concerns because it minimizes the risk of significant bleeding.*** Your promotional activities that minimize this risk are particularly troublesome because we have previously objected in two untitled letters to your promotional materials for Celebrex that among other violations minimized the Celebrex/ Coumadin drug interaction. ***Based on your assurances that corrective steps had been taken in order to prevent future violative practices of this type, we considered these matters closed. Despite your assurances, however, your violative promotion of Celebrex has continued***. (Emphasis added; Pharmacia Warning Letter, 2/1/01 at p. 1)

Of the 170 letters we reviewed, 27 (16%) discussed past letters that the FDA had sent regarding similarly false advertising.

An enforcement system that responds late, requires corrective advertising a quarter of the time, and experiences significant recidivism is a failure.

To get a fuller sense of the FDA's failures, please review the case studies in Appendix A, particularly Accutane and Tindamax.

Case Studies of Deceptive Marketing

INTRODUCTION

Case studies are the easiest, most intuitive way to convey how drug marketers disseminate false and misleading messages about risks and unproven uses to doctors and how ineffective the FDA is at addressing the problem.

We present six case studies: Vioxx, OxyContin, Paxil, Neurontin, Accutane and Tindamax. Each one highlights a different aspect of the deceptive marketing problem, although the stories have some overlap as well, which emphasizes that the issues are not unique to any one drug. The case studies describe drug marketers misrepresenting risks (Vioxx, OxyContin, Accutane), suppressing or misrepresenting clinical data (Vioxx, Paxil, Accutane, Neurontin), promoting unproven uses (Vioxx, Neurontin), promoting uses where the risks outweigh the benefits (OxyContin, Paxil), and disregarding the FDA's weak enforcement efforts (Accutane, Tindamax).

In all of these cases, the deceptive advertising had a single goal: persuade doctors to write more prescriptions than sound medicine would dictate, putting patients at risk.

CASE STUDY 1: VIOXX
TARGETING DOCTORS WITH DECEPTIVE MESSAGES ABOUT POTENTIALLY FATAL RISKS

Vioxx is an anti-inflammatory pain reliever approved in 1999 for osteoarthritis, acute pain, and menstrual pain. Eventually its approved uses expanded to include rheumatoid arthritis and acute migraine pain. It quickly became one of Merck, Inc.'s most important drugs, with $2.5 billion in sales in 2003 alone.[72] Merck withdrew Vioxx from the market in September 2004 after clinical data unequivocally demonstrated serious heart risks with its use. During its five years on the market, millions of people took Vioxx, resulting in an estimated 88,000-139,000 heart attacks of which some 26,000-55,000 were likely fatal.[73] Another estimate claims Vioxx caused some 160,000 heart attacks and strokes.[74]

Merck is now battling mass litigation alleging Vioxx caused heart attack deaths and injuries. Regardless of the outcome of those cases, the record shows that Merck hid and misrepresented the risks of Vioxx and the results of a landmark clinical trial, as well as promoted Vioxx for unproven uses.

Targeting Doctors

In September, 2001, the FDA wrote to Merck regarding its promotion of Vioxx. The Warning Letter described several different types of promotional activities that minimized the serious risks associated with Vioxx use—the same heart attack risks that Merck is now being sued for failing to warn about—and stated:

> "Your minimizing these potential risks and misrepresenting the safety profile of Vioxx raise significant public health and safety concerns. Your misrepresentation of the safety profile of Vioxx is particularly troublesome because we have previously, in an untitled letter, objected to promotional materials that also minimized Vioxx's safety profile." (FDA letter, 9/17/01, at p. 2)

The promotional activities the Warning Letter addressed were six audio conferences, events in which a doctor gave a Merck-initiated and supported presentation to colleagues; a press release; and oral statements by Merck sales representatives at two professional conferences.

The Vioxx letter and surrounding story involves several key features of the deceptive marketing problem, but it makes a good showcase for one in particular: doctors are being heavily targeted with potentially deadly false messages about risks.

Deceptive Doctor-to-Doctor Marketing

As the Warning Letter indicates, Merck was misrepresenting the risks of Vioxx to both the public (the press release) and doctors. The press release claimed that Vioxx had "a favorable cardiovascular safety profile," a claim the FDA found "simply incomprehensible."[75]

Nonetheless, the misleading marketing aimed at doctors was worse. With regard to doctors, Merck was spreading the false messages on risk in two ways, via sales representatives and via peer-to-peer (doctor-to-doctor) presentations.

Doctor-to-doctor marketing is a common strategy. Large drug companies, including Merck, commonly retain hundreds of doctors as speakers and consultants to give promotional presentations on their drugs, each of whom may speak at several such events each year, and the events are becoming ever more common.[76] In 2004, doctors spoke at 237,000 meetings and talks sponsored by pharmaceutical companies, up from 66,000 in 1999.[77]

Doctor-to-doctor marketing is particularly effective, because doctors see each other as credible sources of information, more so than pharmaceutical sales representatives. Merck understands the unique impact of doctor-to-doctor marketing on sales, according to company documents reported by the *Wall Street Journal*:

> In a Merck slide presentation dated December 2001, two Merck employees observed that doctors who attended lectures or more intimate roundtable-type discussions were much more likely to increase their prescribing of certain medications than those who spent time with a Merck sales representative.
>
> According to the document, doctors who attended a lecture by another doctor wrote an additional $623.55 worth of prescriptions for the painkiller Vioxx over a 12-month period compared with doctors who didn't attend. Doctors who participated in the more intimate discussions wrote an additional $717.53 worth of prescriptions for Vioxx...That compared to an increase of only $165.87 in Vioxx prescriptions by doctors who attended a meeting with a salesperson.[78]

The slide presentation described by the *Wall Street Journal,* dated only three months after the FDA sent Merck the Warning Letter, suggests that such tactics were an integral part of Vioxx's marketing.

The six doctor-to-doctor audio conferences addressed in the Warning Letter were misleading in five ways.

First, the doctor giving the presentations misrepresented Vioxx's heart attack risks. He gave inaccurate information about the heart attack rate in the Vioxx patients in the leading clinical trial. He then explained away that understated data by claiming as fact a wholly untested hypothesis: Vioxx did not hurt hearts; the comparator drug in the trial, naproxyn, protected hearts.[79] Second, the doctor suggested Vioxx was safe to use with patients taking another drug, Coumadin, when in fact in combination the drugs pose a serious risk of dangerous bleeding.[80] Third, the doctor omitted a large range of other risk information, including certain types of patients who should not be given Vioxx and what the most common adverse events with Vioxx use are.[81] Fourth, the doctor made a number of unsubstantiated claims about Vioxx's purported superiority to naproxyn and similar drugs and Celebrex. Finally, the doctor claimed Vioxx was safe and effective for use in rheumatoid arthritis, cancer prevention and treatment, Alzheimer's disease, and gout, all of which were "off-label" uses, that is, ones for which Vioxx had not been proven safe or effective.[82]

The Warning Letter does not suggest that Merck's representatives tried to correct the doctor's misleading presentation. As moderators of the presentations, they had the opportunity to correct the information; their silence amounts to a tacit endorsement of the doctor's statements, as does the fact that six equally misleading presentations occurred. Indeed, the FDA viewed Merck as responsible for the doctor's statements, which is why it discussed them in the Warning Letter to Merck.

Deceptive Sales Representative-to-Doctor Marketing

Merck has a large staff of sales representatives who meet with doctors at their offices, over meals, at continuing education events and conferences on a regular basis. According to the Warning Letter, Merck sales representatives misrepresented the risks of Vioxx to people attending the 119th Annual Meeting of the Maryland Pharmacists Association and the Annual Meeting of the American Society of Health-Systems Pharmacists. The sales representatives, like the doctor in the audio conferences, claimed that the clinical data showing high risks of heart attacks with Vioxx use meant only that naproxyn protected hearts, not that Vioxx hurt them.[83] The fact that different sales representatives made similarly misleading statements at different conferences in different regions of the country (the first was in Maryland, the second in California) suggests Merck trained all its sales representatives to offer this explanation of the heart attack data.

Sales representative training is the drug marketers' opportunity to control and shape the messages that doctors receive from the sales force. Documents released because of the Vioxx litigation confirm Merck specifically trained sales representatives to mislead doctors about Vioxx's risks by teaching them to play "dodge ball." The sixteen page training handout had twelve tough questions about Vioxx's cardiovascular risks that doctors might ask, one per page, followed by four pages with only one word: "DODGE!"[84]

Clinical Trials and Data Manipulation as Promotional Tools

Merck's desire to sell more Vioxx and to capture a larger share of the painkiller market led it to manipulate the structure of its trials and ignore results from its own clinical trials that suggested Vioxx presented a cardiac risk.

Choosing Not to Investigate Heart Attack Risks

Pre-approval, Merck had data and theory to suggest that Vioxx harmed hearts and protected stomachs, but they did not have enough information about either to definitively say what the risks or benefits were.[85] Faced with these two possible areas for further investigation, Merck decided to see if Vioxx protected stomachs, but chose not to do a heart risk study.

Merck made two informative decisions related to the design of VIGOR, the "does-Vioxx-protect-stomachs?" study that compared Vioxx to naproxyn, a generic drug with similar pain relieving effectiveness but known risks to the stomach. First,

Merck decided that comparing cardiovascular events would not be a "pre-specified analysis," meaning determining the heart risks posed by Vioxx versus naproxyn was not an original intention of the study.[86] Second, Merck excluded patients at high risk of heart attack from the study. That decision lowered the chance that Vioxx's potential heart risks would appear in the trial's results.

Nonetheless, the VIGOR trial showed patients taking Vioxx had five times as many cardiovascular events such as heart attacks as the patients taking the comparator drug did, Merck told doctors and the public that Vioxx does not hurt hearts, the other drug protects them.[87] Only when another clinical trial—conducted five years and several billion dollars in sales after Vioxx came on the market—found that Vioxx patients had a significantly increased risk of heart attacks versus placebo, did Merck acknowledge the danger and remove Vioxx from the market.[88] That definitive trial, incidentally, was not intended to investigate heart risks. It was intended to determine Vioxx's effectiveness in preventing colon polyps and in the treatment of colon cancer.[89]

Heart attacks are potentially fatal, millions of Americans are already at elevated risk of heart attacks, and Vioxx was intended for a broad market: the millions of Americans needing pain relief. For those reasons, doctors needed to understand what risk, if any, Vioxx posed to hearts. By choosing to do two large studies designed to provide commercial advantage, designing at least one of them to reduce the chance of heart risks showing, and never choosing to do a large study designed to investigate heart risks, Merck revealed how deeply marketing concerns, not patient concerns, often shape which studies are done.

Misleadingly Explaining Away Clinical Data Demonstrating Risks
Merck completed the VIGOR study in March 2000. Even with the structural advantages given by excluding high risk patients, Vioxx's heart risks surfaced too strongly to be ignored: the Vioxx patients were five times as likely as the naproxyn patients to have heart attacks.

Merck decided to explain the VIGOR results in a way that minimized their negative impact: Vioxx does not endanger hearts, Merck asserted, naproxyn protects them, the way aspirin does.[90] The FDA's 2001 Warning Letter criticized Merck for promoting this idea, in particular for presenting it as truth rather than as hypothesis, since Merck had no evidence that naproxyn protected hearts.[91]

Misstating Clinical Data to Claim Reduced Risk
The Warning Letter also explains that Merck's misrepresentations about the VIGOR data included falsehoods, namely claiming that the Vioxx patients were only four times as likely to have a heart attack as the naproxyn patients, and after accounting for relatively high risk patients, the Vioxx patients were only twice as likely to have a heart attack as the naproxyn users were. In fact, the Vioxx users were five times more likely to have a heart attack over all and three times as likely once relatively high risk patients were excluded.[92]

Merck again gave doctors false information about the VIGOR data in a letter that Merck sent to thousands of doctors in 2001. That letter purported to describe the results from the VIGOR trial and asserted that only 0.5 percent of Vioxx participants had incurred "cardiovascular events," or heart and circulation problems. That would be only 20 of the 4,000 patients who took Vioxx during VIGOR. In truth, 590 Vioxx patients suffered cardiovascular adverse events while taking the drug, a fact Merck reported to the FDA, and 101 of the 590 people had serious problems, including heart attacks.[93]

In addition, the *New England Journal of Medicine*, the prestigious journal that published the VIGOR study, accused Merck of suppressing key VIGOR data and thereby misrepresenting the study's heart risk results.[94] Merck strongly contests the Journal's critique by emphasizing that the withheld data had arisen after a "pre-specified cut-off date."[95] The non-Merck authors of the VIGOR report similarly defend the report and add that they do not believe including the data would have led to different conclusions about the safety of Vioxx.[96] The *New England Journal of Medicine* rejected their explanations and reiterated its concerns, emphasizing that the "pre-specified" date was decided near the end of the study, that it was inexplicably a month earlier than the cut-off date used for the stomach-protecting data, and that it believed the omitted results were significant.[97]

Not an Isolated Incident
While the Warning Letter only addressed six audio conferences, two sales representatives' statements and a press release, it is unlikely that all of Merck's other promotional activities accurately portrayed Vioxx's risks. In fact, FDA had previously objected to promotional materials, in 1999, for similar reasons, suggesting a concerted effort by Merck to mislead doctors about Vioxx's potentially fatal risks.

CASE STUDY 2: OXYCONTIN
TARGETING DOCTORS WITH MESSAGES THAT MINIMIZED RISKS AND BROADENED THE INDICATION

OxyContin, like Vioxx, is a "blockbuster" drug that became the focus of mass litigation for its maker's alleged failure to warn of its risks—in this case, risks of addiction and death by overdose.

OxyContin is a controlled-release opioid designed to provide pain relief for 12 hours. Like nearly all opioids, OxyContin is a Schedule II controlled substance, reflecting its morphine-like addictiveness. FDA approved it in 1995 for the treatment of "moderate-to-severe pain where use of an opioid analgesic is appropriate for more than a few days;" [98] it came on the market at a time when treating pain became a medical priority.[99]

Unfortunately, crushing an OxyContin tablet destroys its time-release mechanism, releasing the large, 12 hour dose of oxycodone in the tablet all at once. By 2000, large numbers of people, particularly in Appalachia, figured this out and started crushing and snorting OxyContin or intravenously injecting it.[100] By March 2001, the media began to report OxyContin's new nickname: "Hillbilly Heroin."[101] "Hot spots" of abuse developed in many areas, and the Drug Enforcement Agency (DEA) began concerted efforts to combat it and the associated crime wave.[102]

The OxyContin story as related below is an important illustration of two parts of the false and misleading marketing problem: how drug marketers aggressively target doctors with misleading messages and increase the size of their potential market by "broadening the indication" of a drug. That is, promoting it for its approved use—pain relief—without regard to the safety-based limitations on that use. This type of off-label promotion is more subtle than recommending Vioxx as a cancer treatment, but is no less effective at increasing the drug's potential market while endangering patients.

OxyContin's original approved use had three significant limitations: "moderate to severe pain," "opioid analgesic is appropriate," and "for more than a few days." The record strongly suggests Purdue Pharma encouraged doctors to prescribe OxyContin much more frequently than those restrictions would dictate. Moreover, even after the FDA narrowed OxyContin's approved use to state "moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time," the record suggests Purdue continued promoting OxyContin for broader uses that FDA had judged do not justify the risks.

Purdue's marketing efforts worked. The drug quickly became a cash cow, bringing Purdue more than $1 billion/year by 2001, comprising approximately 90% of Purdue Pharma's revenues.[103]

Minimizing Addiction Risks to Ease Acceptance of a Highly Addictive Drug

Purdue Pharma promoted OxyContin for relatively mild pain relief, positioning it to replace take-as-needed drugs like Percoset.[104] The promotion involved minimizing the risks of addiction by suggesting that opioid addiction rarely occurred; Purdue claimed it happened less than 1% of the time, a figure FDA rejected as unsupported.[105] As early as 1998, Purdue Pharma distributed to doctors 15,000 copies of a video that contained the less than 1% claim[106] and "presented the pain relief experiences of various patients and the pain medications, including OxyContin, they had been prescribed."[107] Purdue distributed a revised version of this video in 2000, which the FDA said also appeared to minimize OxyContin's risks.[108] Doctors otherwise leery of morphine because of its addictiveness often turned to OxyContin, which they thought offered morphine's proven pain relief without its proven risks.[109]

Targeting Primary Care Physicians Instead of Just Cancer or Pain Specialists

While cancer doctors might seem to be the natural market for such a potent narcotic, from the outset Purdue Pharma ran a massive marketing campaign aimed at primary care physicians and other doctors.[110] By 2003, nearly half of all OxyContin prescribers were primary care physicians. The DEA feared these doctors lacked adequate training in pain management and were likely to prescribe OxyContin inappropriately.[111]

Purdue Focused On Marketing to Doctors, Not Patient Safety

Using Data to Target Doctors More Effectively But Not To Identify Problems

Over time, Purdue dramatically increased its sales force for OxyContin from 618 representatives in 1996 to 1,066 representatives in 2001. These representatives were calling on some 100,000 doctors a year.[112]

Purdue Pharma maximized the effectiveness of its sales representatives by using extensive data about doctors' prescribing habits to determine which doctors to target. Such targeting-by-prescribing-data-analysis is common practice for pharmaceutical marketers; they buy data from pharmacies, the federal government and the American Medical Association and use it to create detailed prescriber profiles. [113] Trade magazines such as *Pharmaceutical Executive* and *Pharma Marketing News* offer extensive advice on how to exploit the data for maximum benefit.[114] Nonetheless, not until the fall of 2002 did Purdue start using that vast trove of data to search for evidence that individual doctors were contributing to the OxyContin abuse problem.[115]

Beyond Sales Representatives

In addition to its sales force, Purdue's marketing efforts included:

> expanding its physician speaker bureau and conducting speaker training conferences, sponsoring pain-related educational programs, issuing OxyContin starter coupons for patients' initial prescriptions, sponsoring pain-related Web sites, advertising OxyContin in medical journals, and distributing OxyContin marketing items to health care professionals.[116]

Notably, other than the websites and starter coupons, the marketing was not aimed at consumers; doctors were the primary focus.

Purdue Pharma's OxyContin marketing items, such as "OxyContin fishing hats, stuffed plush toys, coffee mugs with heat-activated messages, music compact discs, [and] luggage tags,"[117] made it much easier for doctors to remember that OxyContin was an option but did nothing to convey its true abuse potential. Indeed, according to the DEA, the scale of the OxyContin marketing effort was unprecedented for a drug with OxyContin's abuse potential.[118] The DEA's concern with these items is clearer if one imagines Purdue distributing—and doctors using—fishing hats, stuffed plus toys, coffee mugs with heat-activated messages, music compact discs, and luggage tags labeled "morphine."

Abuse Rose as OxyContin Became a Mainstream Treatment

Despite OxyContin's potency and abuse potential, the marketing campaign made it a mainstream treatment. According to the Government Accountability Office:

> In 2001 and 2002 combined, sales of OxyContin approached $3 billion, and over 14 million prescriptions for the drug were dispensed. OxyContin also became the topselling brand-name narcotic pain reliever in 2001 and was ranked 15th on a list of the nation's top 50 prescription drugs by retail sales.[119]

In 2001, concerned by escalating abuse of OxyContin, the FDA required Purdue to change the prescribing information to narrow its approved use to "moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time" and added new warnings.[120] The FDA followed up the labeling change with an August 2001 letter to Purdue stating that thenceforth, all OxyContin promotional materials should prominently disclose the new warnings, precautions, and narrowed indication for OxyContin; Purdue agreed.[121] These changes were in part "intended to change prescription practices."[122] It is unclear what effect if any these changes had on prescriptions, however, as OxyContin sales increased another 7% in 2002 to $1.5 billion and 7.2 million prescriptions.[123]

The FDA Warning Letter

In January 2003, two years after the prescribing information was updated and three years after serious abuse problems had surfaced, the FDA wrote Purdue Pharma a Warning Letter regarding two print advertisements that Purdue ran in the *Journal of the American Medical Association*.

In the Warning Letter, the FDA castigates Purdue and emphasizes the possible consequences of false or misleading advertising, particularly broadening the indication and minimizing risks:

> Your advertisements thus grossly overstate the safety profile of OxyContin by not referring in the body of the advertisements to serious, potentially fatal risks associated with OxyContin, ***thereby potentially leading to prescribing of the product based on inadequate consideration of risk.*** In addition, your journal advertisements fail to present in the body of the advertisements critical information regarding limitations on the indicated use of OxyContin, ***thereby promoting OxyContin for a much broader range of patients with pain than are appropriate for the drug.*** The combination in these advertisements of ***suggesting such a broad use of this drug to treat pain without disclosing the potential for abuse with the drug and the serious, potentially fatal risks associated with its use, is especially egregious and alarming in its potential impact on the public health.*** (emphasis added; FDA letter to Purdue Pharma, 1/17/03)

The FDA required Purdue to not only stop using such ads, but to disseminate corrective information to the audience that saw the ads. According to a December 2003 GAO report, Purdue's corrective ad ran for three months and appeared in approximately 30 medical journals.[124] While significant progress has been made in reducing and limiting OxyContin abuse, it more likely results from extensive efforts made by the DEA, the hardest hit states, and Purdue, in contexts other than its advertising. These efforts are discussed in the GAO report.

It is impossible to say how many patients became addicted to opioids or died from an opioid overdose because of their unnecessary treatment with OxyContin, how many patients' existing opioid addictions were worsened or became fatal by moving to the more easily abused OxyContin, or how many drug abusers who were not patients were able to get the drug illicitly simply because it was so widely used and available. Nonetheless, even Purdue concedes that OxyContin's widespread use and availability may have contributed to its abuse.[125]

CASE STUDY 3: PAXIL CR
CONCEALING SUICIDE RISK DATA AND PROMOTING UNNECESSARY MEDICATION

GlaxoSmithKline made an aggressive effort to dramatically expand the size of Paxil CR's potential market. Glaxo did this by concealing data of suicide risks, ineffectiveness and withdrawal problems and by persuading doctors to prescribe, and patients to demand, the medication for treatment of the ordinary anxieties of life.

Paxil CR is an "SSRI" drug, a type of anti-depressant that includes Prozac. In addition to being an anti-depressant, Paxil won approval for the treatment of a then little known psychological syndrome known as Generalized Anxiety Disorder. By heavily promoting both the disorder and Paxil, GlaxoSmithKline was able to persuade doctors and consumers that Paxil was appropriate for the off-label use of the anxieties of every day life. Going from being a preferred treatment for an extreme condition to the preferred treatment for a relatively normal one transformed Paxil from a potentially niche drug to a blockbuster. In 2001 alone, GlaxoSmithKline sold $2.1 billion of Paxil.[126]

Promoting Paxil for the anxieties of everyday life is precisely the same kind of indication-broadening as promoting OxyContin for ordinary pain. The three major differences between the OxyContin story and the Paxil story are:

- GlaxoSmithKline targeted its Paxil ads at the public as well as doctors;
- Paxil is not proven to be effective in treating ordinary anxiety; and
- OxyContin's basic risk—drug abuse—was arguably obvious despite being consistently misrepresented. Paxil's most famous risk—causing adolescents to commit suicide or become psychotic—was deliberately concealed by GlaxoSmithKline for years.

Broadening the Indication—Medicating Unnecessarily and Dangerously

Dramatically Expanding Paxil's Market by Medicating the Ordinary

Unlike the other FDA letters discussed so far, the Paxil letter focuses on a "direct-to-consumer" advertisement that told the public to take Paxil to cope with everyday anxieties. The June 2004 "Untitled Letter" to GlaxoSmithKline discussed a TV advertisement called "Hello, my name is…", stating it was:

> "concerning from a public health perspective because it broadens the use of Paxil CR beyond the narrowly-defined and more serious condition of social anxiety disorder to people experiencing more ordinary degrees of anxiety, fear or self-consciousness in social or work situations, while also minimizing the serious risks associated with the drug." (FDA Letter to GlaxoSmithKline on June 9, 2004 at p. 1, emphasis added.)
>
> •
>
> "The TV ad suggests that *anyone* experiencing anxiety, fear, or self-consciousness in social or work situations is an appropriate candidate for Paxil CR. … ***Overall, the TV ad suggests that Paxil CR therapy is appropriate for patients with lesser degrees of performance anxiety or shyness, which do not generally require drug treatment***." (*Id.* at pp. 2-3; emphasis added.)

Others besides the FDA were critical of GlaxoSmithKline's messaging. One commentator suggested that GlaxoSmithKline essentially manufactured a disease in order to maximize sales.[127] The incentive for a drug marketer to broaden its consumers from those specifically identified by the FDA's narrow indications for a drug is obvious; the broader a drug's use, the more drugs sold. Furthermore, pharmaceutical companies are driven by Wall Street's expectations to manufacture "blockbuster" drugs.[128] As with Hollywood, manufacturing a blockbuster involves a slick marketing campaign aimed at creating the biggest audience for the drug possible.

> "Every marketer's dream is to find an unidentified or unknown market and develop it," Barry Brand, SmithKline's product director for Paxil, told *Advertising Age*. "That's what we were able to do with Paxil."[129]

Ad-Driven Consumer Demand Results in Unnecessary Paxil Prescriptions

How many thousands of people seeing the ad thought they should ask their doctor for a Paxil prescription and face the risks of taking it, when treatment was unnecessary? A recent study[130] from the *Journal of the American Medical Association* (JAMA) suggests many thousands or more.

The authors of the JAMA study trained actors to portray either "major depression" or "adjustment disorder with depressed mood" involving mild and short-term symptoms, and sent them to primary care physicians to seek treatment. Ostensibly, doctors would prescribe anti-depressant medication to patients with major depression relatively often and rarely, if ever, for adjustment disorder patients. As JAMA noted,

> Although several small trials suggest that antidepressants confer modest benefits on patients with minor depression, there are no data to support their use in adjustment disorder, especially when characterized (as in our study) by a clear precipitant, mild symptoms, and short duration.[131]

When the actors visited the doctors, they took one of three actions: one third of the time the actors requested Paxil, mentioning that they had seen an ad for it; one third of the time they made a general request for medication; and one third of the time they did not request medication from the doctors they visited. The researchers found that while major depression patients were prescribed drugs more often, doctors gave drugs to a significant number of the adjustment disorder patients. Moreover, requesting Paxil specifically affected what prescriptions were written:

> Among [patients] portraying major depression, [Paxil] was rarely prescribed (approximately 3%) unless the [patient] specifically requested Paxil; if Paxil was requested by name, 14 (27%) of 51 received Paxil/paroxetine, 13 (26%) received an alternative antidepressant, and 24 (47%) received no antidepressant.
>
> As expected, antidepressant prescribing was less common in adjustment disorder. …There was a strong prescribing gradient according to request type: 55% of [patients requesting Paxil] received an antidepressant compared with 39% of [patients] making a general request and 10% of those making no request.[132]

The study did not conclude that direct-to-consumer advertising for anti-depressants or any other drugs was necessarily bad, suggesting that it can guard against under-treatment for major depression as well as lead to over-treatment for lesser conditions.[133] Nonetheless, in light of this study, it is worth reiterating what the FDA letter said about the Paxil CR TV ad:

> Overall, the TV ad suggests that Paxil CR therapy is appropriate for patients with lesser degrees of performance anxiety or shyness, which do not generally require drug treatment.

The FDA's Untitled Letter criticizing the Paxil TV did not require corrective advertising and was received by GlaxoSmithKline fully a month after the ad had stopped running.[134]

Devastating Risks Without Benefit

Prescribing Paxil when it is not needed is dangerous and exposes patients to unnecessary risks. Paxil can cause birth defects,[135] suicide,[136] and severe withdrawal.[137] Although all of these side effects may occur rarely, when the number of people taking a drug is large, a rare risk still hits a significant number of people.

Putting Profits Before People: Suppressing the Risks of Withdrawal

In addition to criticism for the direct-to-consumer advertising addressed by the FDA in the 2004 letter, GlaxoSmithKline has come under fire for what it failed to say to doctors.

According to *ABC News*, a 1997 GlaxoSmithKline safety review noted that withdrawal effects were showing up in Paxil clinical studies in substantial numbers.[138] One study discussed in the safety review showed 25% of Paxil patients experienced withdrawal symptoms, versus only 5.9% of placebo patients. Another study, involving patients with major depression, found that 42% of Paxil patients had at least one withdrawal symptom. Nonetheless, a December 1, 1997-May 31, 1998 "business plan guide" reported by *ABC News* instructed sales representatives to "minimize concerns surrounding discontinuation symptoms" and tell doctors that they occurred in two of 1,000 patients.[139]

Nor could prescribers debunk these claims by turning to Paxil's official package insert; until December, 2001 it merely included the vague warning that a "withdrawal syndrome" was a rare potential side effect, and then GlaxoSmithKline simply added a "precaution" to Paxil's prescribing information to inform doctors "discontinuation" symptoms could occur in 2% or greater of patients.[140] (The company preferred the term "discontinuation" because it does not connote addiction as strongly as withdrawal does.)[141]

Why did GlaxoSmithKline misrepresent the risks of withdrawal? As a company memo explained:

> **Discontinuation: why this is an issue**
> '97 Seroxat/Paxil sales to end Sept already exceed
> **$1 Billion**

This heading was followed by a picture of a big money bag.[142]

Putting Profits Before Children: Suppressing Data Showing Paxil Ineffective for Adolescents and Suggesting It Created Suicide Risks for Them

In a 1998 memo first uncovered by the *Newark Star Ledger*,[143] GlaxoSmithKline discusses two clinical trials that showed Paxil was not effective, particularly in adolescents; placebo worked just as well. The memo states that the company would not submit the data—including safety data—to regulators because of the potential negative impact on sales and that it would withhold the data until the company could submit it without that negative impact:

> "…no regulatory submissions will be made to obtain either efficacy or safety statements relating to treatment of adolescent depression at this time. However, ***data (especially safety data) from these studies***

> ***may be included in any future regulatory submissions, provided we are able to able to go on and generate robust, approvable efficacy data.*** The rationale for not attempting to get a safety statement at this time is as follows…***it would be commercially unacceptable to include a statement that efficacy had not been demonstrated as that would undermine the profile of [Paxil].***"[144] (emphasis added.)

New York Attorney General Eliot Spitzer made headlines in 2004 when he sued GlaxoSmithKline for consumer fraud for its failure to disclose clinical trial data.[145] Spitzer's allegations were based on the fact that GlaxoSmithKline sponsored five trials of Paxil in adolescents suffering from major depression, but published only one of the trials, which had mixed results. The four unpublished trials failed to show any benefit for the drug and suggested that it might increase the risk of suicide in adolescents, and include those discussed in the memo above. With the support of a 2001 internal company memo to sales representatives that claimed: *"Paxil* demonstrates REMARKABLE Efficacy and Safety in the treatment of adolescent depression,"[146] Spitzer also alleged that GlaxoSmithKline sales representatives told doctors Paxil was appropriate for adolescents.[147]

Suppressing data showing that Paxil was not effective in adolescents and, worse, may cause them to commit suicide or become psychotic, boosted Paxil's sales. According to Spitzer, GlaxoSmithKline reaped $55 million from Paxil prescriptions to adolescents and children in 2002 alone.[148]

Without admitting wrongdoing, GlaxoSmithKline settled Spitzer's suit two months after it was filed for $2.5 million and agreed to post its clinical data on line.[149]

CASE STUDY 4: NEURONTIN
OFF-LABEL PROMOTION AS OFFICIAL MARKETING STRATEGY

Neurontin, an epilepsy medicine created by Warner-Lambert, is the archetype of off-label promotion. Unlike OxyContin and Paxil, Warner-Lambert could not broaden Neurontin's indication to include everyday ailments. Most people don't experience a mild form of epilepsy on a regular basis.

The Neurontin story came out because a whistleblower, Dr. Franklin, filed suit against Warner-Lambert. Dr. Franklin contended that Warner-Lambert was not satisfied with the limited on-label potential sales for Neurontin and hired an advertising agency to design an aggressive, comprehensive strategy to persuade doctors to prescribe it off-label.[150] That strategy, the *New York Times* reported,

> "included paying doctors to appear as authors of journal articles on off-label uses of Neurontin, articles that were actually written by nonphysicians working under the direction of the company's marketers. The company then paid hundreds of doctors to attend expensive dinners and weekend retreats, where they were urged to prescribe Neurontin.
>
> Other doctors, often frequent prescribers of Neurontin, were paid to speak to other physicians about Neurontin's benefits. Finally, the company paid doctors to prescribe Neurontin and include those patients in clinical trials, which Dr. Franklin contends were designed mainly for marketing purposes."[151]

Other reports noted that tactics marketing firms developed for Warner-Lambert's off-label campaign included "continuing medical education classes for physicians, "home study kits" for doctors who couldn't attend meetings, prepaid calling cards that would trigger recorded messages about Neurontin, Web sites, and special supplements to medical journals."[152]

According to Dr. Franklin, a senior Warner-Lambert marketing executive told his staff of doctors, whose job it was to market to other doctors, that:

> we need to be holding their hand and whispering in their ear, "Neurontin for pain, Neurontin for monotherapy, Neurontin for bipolar, Neurontin for everything."[153]

Dr. Franklin was among the doctors being given the instruction.

In these ways, Warner-Lambert promoted the drug to "doctors for more than a dozen medical conditions for which it was not approved, conditions like attention deficit disorder in children, neurological pain and bipolar disorder."[154] For at least one off-label use, migraine pain, Warner-Lambert had data showing Neurontin was ineffective, but suppressed the data and continued promoting for it.[155]

Driven by the concerted marketing campaign, sales for Neurontin soared, reaching over a billion dollars a year. Some 90% of sales were for off-label uses.[156] In 2004, Pfizer, which had acquired Warner-Lambert, pled guilty to criminal charges stemming from the suit and agreed to pay $430 million.[157]

CASE STUDY 5: ACCUTANE
CONCEALED RISKS AND A WEAK REGULATOR

Accutane is an effective but dangerous acne drug. It was developed in 1971 but not initially marketed because it causes birth defects.[158] It was approved in 1982 as a treatment of last resort for "severe, recalcitrant, nodular acne."[159] Few treatments are helpful for that kind of serious acne. For that reason, Accutane's known serious birth defect risks were outweighed, and the drug was approved. Overtime, evidence has emerged that Accutane can cause suicide as well as severe gastrointestinal problems. In the drug's 23 years on the market, the FDA has revised Accutane's labeling 29 times without expanding its "severe, recalcitrant, nodular acne" indication, presumably because the risks do not justify any other use.[160] Indeed, the birth defect risk is so high and has proved so unmanageable over the years that now patients and their doctors must register and patients must promise to use two forms of birth control and take regular pregnancy tests.

Nonetheless, Accutane has become commonly prescribed. The FDA estimates 100,000 Accutane prescriptions are filled each month.[161] Much of that use is likely off-label-by-broadened-indication, treatment of relatively mild acne. How much of the decision to use Accutane so lightly is a direct result of Hoffman-LaRoche's marketing of Accutane is not clear.

What is clear, however, is the evidence suggesting that Hoffman-LaRoche has consistently hidden and downplayed the suicide risk of Accutane. As the case study will show, that behavior is an important illustration of two parts of the false and misleading marketing problem: the ability of companies to hide risk information for commercial advantage and the failure of the FDA to ensure accurate and timely warnings about risk.

Hiding and Misrepresenting Suicide Risks

Hiding Information from the FDA

By 1997, French regulators had seen enough data on Accutane's ability to cause suicide that they required a warning on the French packaging of Accutane. Hoffman-LaRoche did not tell the FDA of the French regulators' decision.[162] Also in 1997, a Hoffman-LaRoche doctor studied the suicide data and recommended in an internal report that a warning be added to Accutane's U.S. label. However, as Hoffman-LaRoche's Global Head of Regulatory Affairs testified, marketing concerns kept the company from acting on that recommendation. Instead they sent a copy of the report to the FDA that was edited to remove the recommendation about a warning.[163]

Disingenuous Advertising

Also in 1997, Hoffman-LaRoche ran a yearlong marketing campaign aimed at doctors, using ads in professional journals and brochures and possibly other materials that suggested Accutane was *an effective treatment* for depression, while failing to disclose that it had been associated with increased depression.[164] In February 1998 the FDA announced it was adding a suicide warning to Accutane's label.[165] The very next month FDA sent a Warning Letter to Hoffman-LaRoche criticizing the Accutane-is-good-for-depression ad campaign.[166] Hoffman-LaRoche took the letter in stride, with a company spokeswoman admitting: "Once the label changed, we knew we'd have to change our promotion."[167]

An Ineffective FDA

FDA Failure to Add a Warning

Despite the FDA's 1998 announcement of a labeling change to warn of suicide risks and the company's acknowledgement of it, the change itself did not occur until May 2000.[168] Why is unclear, although it may have been because of the FDA's inability to dictate labeling changes, as discussed earlier. As a result, Accutane's prescribing information inaccurately omitted the risk information for nearly two more years without penalty.

The FDA Untitled Letter on Misrepresenting Risks

As a 2002 FDA Untitled Letter describes, at a conference in March 2002, FDA representatives asked a Hoffman-LaRoche sales representative working an exhibit booth for Accutane if the package insert contained any information about psychosis and suicide. Not only did the sales representative fail to tell the FDA representatives the information that had been in the package insert for nearly two years, the representative stated:

> "We don't feel its an issue"
>
> "News has hyped it up"
>
> "Like any drug used in patients with depression, such as penicillin, it could bring it out."[169]

Given the consistency and tenor of the comments, the sales representative could have made similar comments to doctors during visits to their offices and at any other professional conferences the sales representative attended.

Reassuring and misleading statements like those made by the sales representative at the conference are are intended to persuade doctors to prescribe Accutane without regard to the serious risk of patient psychosis and suicide. Any doctor who internalizes statements like these could endanger their patients unnecessarily. Indeed, the July 2002 letter describing the incident notes that the statements "raise significant public health and safety concerns."

FDA Letter Was Late and Did Not Require Corrective Action

Despite acknowledging significant public health and safety concerns, and despite the fact that the representative was

making such misleading statements two years after the labeling had been revised, despite the company's history of disingenuous advertising and downplaying of risks, FDA sent Hoffman-LaRoche only an "Untitled Letter," telling the company to stop such advertising but not requiring any corrective action. Moreover, by sending the letter a full four months after the conference, the FDA's silence allowed the misleading promotional activities to continue for that time.

CASE STUDY 6: TINDAMAX
DISREGARDING THE FDA

Tindamax is not as well known as Vioxx, OxyContin, or Accutane, at least in part because it has not been the subject of mass litigation. Nonetheless, the FDA letter regarding it is noteworthy because it shows the extent to which companies will disregard the FDA's instructions and promote their drugs off-label. Simply put, Presutti Laboratories promoted Tindamax for conditions that the FDA, looking at Presutti's data, specifically said Tindamax could not be approved to treat.

Tindamax is an antibiotic approved to treat specific diseases. As the March 3, 2005 letter to Presutti Laboratories, Inc. notes, Presutti sought to add three new uses to its approved indication and submitted data in support of its request. The FDA denied the new uses because the data did not prove Tindamax safe or effective for them. Despite being specifically told no, Presutti promoted for those uses anyway by including them in a "Dear Doctor" letter it sent to prescribers.

As the FDA pointed out to Presutti: "you have encouraged the potentially unsafe use of Tindamax."

Table 5: Specific Recidivism
Companies Receiving More Than One Letter On the Same Drug and Same Issue

Company	Date of FDA Letters	Drug	Repeated Deceptive Issue
Abbott Laboratories	6/10/04 4/27/01	Norvir	Omitted material facts. The 4/27/01 letter was not posted on the FDA website and is otherwise omitted from this report.
Actelion Pharmaceuticals US, Inc.	7/20/05 10/30/02	Tracleer	Omitted risk information.
Alcon Laboratories	4/27/05 7/18/03	Cipro HC Otic	Made unsupported superiority claims.
Allergan, Inc.	9/6/05 3/26/01	Lumigan	Made unsupported superiority claims. Allergan also received a letter on 6/8/01 regarding a different Lumigan false/misleading promotion issue.
Aventis Pharmaceuticals	11/12/03 12/18/02	Taxotere	Omitted and misrepresented risk; overstated efficacy. Also, Aventis received a letter on 7/26/01 regarding a different Taxotere false/misleading promotion issue.
Baxter Pharmaceutical Products	3/26/01 10/1/99	Brevibloc	Minimized risks.
Berlex Laboratories	11/20/01 4/15/99	Magnevist	Promoted off-label.
Bristol-Myers Squibb Company	8/7/03 8/13/01 3/29/01	Pravachol	Broadened indication, overstated efficacy.
Cubist Pharmaceuticals	8/17/04 11/22/00	Cubicin	Omitted risks.
Cytogen Corporation	7/18/05 11/9/01	Quadramet	Made unsubstantiated efficacy claims. The 11/9/01 letter was not on the FDA website and is otherwise omitted from this report.
Elan Pharmaceuticals	8/5/2002 1/16/02	Zanaflex	Made unsubstantiated quality of life claims.
Endo Pharmaceuticals	6/28/05 11/24/99	Lidoderm	Omitted and minimized risks.
Genpharm, Inc.	6/18/03 2/20/03	Amnesteem	Made unsubstantiated claims and minimized risk. The 2/20/03 letter was not a warning or untitled letter; instead, it proactively forbade precisely the advertising at issue in the 6/18/03 letter.
Gilead Sciences, Inc.	7/29/03 3/14/02	Viread Tablets	Omitted and minimized risk information.
GlaxoSmithKline, Inc.	1/31/05 2/9/99 10/15/97	Coreg	Omitted and misrepresented risk information.

Company	Date of FDA Letters	Drug	Repeated Deceptive Issue
GlaxoSmithKline, Inc.	7/17/01 6/28/01 10/20/00 6/29/99	Avandia Tablets	Minimized risks.
Hoffman-LaRoche Inc.	5/29/03 1/9/02	Xeloda	Minimized risks, overstated efficacy, broadened indication.
Maxim Pharmaceuticals, Inc.	5/31/01 12/27/00	Ceplene	Promoted an investigational (not yet approved for anything) drug.
Merck, Inc.	9/17/01 12/16/99	Vioxx	Misrepresented risks.
Novartis Pharmaceuticals Corporation	4/21/04 11/4/99 9/23/99	Diovan	Promoted off-label use.
Organon Inc.	12/12/03 6/6/98	Follistim	Minimized risks.
Pfizer, Inc.	4/13/05 7/8/03 12/21/98	Zyrtec	Made unsubstantiated superiority claims. Pfizer also received a letter on 4/30/02 regarding a different Zyrtec false/misleading promotion issue.
Pharmacia Corporation	2/1/2001 4/6/00 10/6/99	Celebrex capsules	Misrepresented risks, made unsubstantiated superiority claims.
Shire Pharmaceutical Development, Inc.	5/7/01 3/12/01 1/23/01 7/19/00 7/6/00	ProAmatine	Overstated efficacy, minimized risks The 1/23/01 & 3/12/01 letters were not posted on FDA website and are not otherwise included in this report.
Supergen, Inc.	8/18/05 5/10/01 1/6/97	Nipent	Misrepresented risks.
TAP Pharmaceutical Products, Inc.	8/2/02 3/15/00	Prevacid	Misleadingly communicated indication.
VIVUS Inc.	5/24/04 4/1/98	MUSE	Failed to disclose a material fact.

False Marketing Beyond Routine FDA Review

Classic advertising—printed materials, commercials, branded office supplies and other "tchochkes"—is just one portion of drug marketing. As discussed above, the FDA has a system in place to address false classic advertising, albeit an ineffective and overburdened one. However, a huge portion of drug marketing is not classic advertising, and it occurs with little chance of FDA oversight. Two components are relatively visible—sales representatives and doctors hired has consultants or speakers.[26] A third component is largely invisible, although it has gained increasing and very important attention recently: the manipulation and suppression of clinical trial results.

Sales representatives and sponsored doctors making false or misleading statements about drugs are dangerous because of their many opportunities to instill those messages in doctors. Presenting clinical trial results to maximize commercial, rather than clinical, benefit or simply hiding negative data is scientific misconduct and is perhaps the most dangerous false marketing of all, as it is among the most difficult to detect and undermines the entire premise of pharmaceutical medicine.

All three of these types of marketing are currently outside FDA's ability to routinely monitor.

SALES REPRESENTATIVES: WHAT THEY SAY MATTERS

Sales representatives are a cornerstone of pharmaceutical marketing. In 2004, more than 90,000 sales representatives called on doctors, more than double the amount from a decade earlier.[27] Drug marketers use prescribing data to focus their sales representatives efforts and measure their success at increasing prescriptions.[28] According to IMS Health, a business that consults with the industry, those representatives focus on the 175,000 physicians who write 80 percent of prescriptions, resulting in a ratio of one sales representative for every two doctors.[29] According to a 2005 report in the *Journal of the American Medical Association (JAMA)*, sales representatives have a major impact on doctors:

> "Interactions with pharmaceutical representatives increase the likelihood of physicians making formulary requests for drugs with no clear advantage over existing ones, prescribing nonrationally, prescribing costlier drugs, and prescribing fewer generic drugs."[30]

As a Group, Sales Representatives Form Long and Deep Relationships With Doctors

Sales representatives may have such a great impact on doctors' prescribing habits because they begin relationships with doctors while the doctors are still in medical school, relationships that may condition doctors to be more receptive to sales representatives once they are in practice.[31] While in school, students interact with sales representatives in many ways, participating in drug company-sponsored meals, receiving small gifts, having conference admission paid and other items.[32] The 2005 *JAMA* study quoted above surveyed students at eight medical schools around the country to assess student attitudes toward pharmaceutical sales representatives and these gifts. The survey found that students felt "entitled" to the various sponsorships and gifts and commented that the results "suggest[] that as a group they are at risk for unrecognized influence by marketing efforts."[33]

Once doctors have begun their practices, sales representatives continue to interact with them in many ways. Perhaps one of the most unsettling, from a patient's perspective, is the practice of "shadowing" doctors while they examine patients, access for which they pay the doctors hundreds of dollars a day.[34] Once in the exam room with the doctor, the sales representative can ask patients about their experiences with medications.

As reported regarding Neurontin's marketing, shadowing enabled sales representatives to meet with patients, review charts, and recommend medications.[35] Not until 2003 did the American Medical Association vote to prohibit this practice without the patient's informed consent.[36]

Over time, individual sales representatives develop a relationship with individual doctors they see that can affect prescribing decisions in and of itself. Consider this comment from a sales representative:

> If I'm close to getting a bonus or making President's Club, I'll use the data," she says. "I can go to the doctors who I have a good relationship with and ask them why they're prescribing the competition. I'll tell them that I'm not far away from a bonus and ask them to write six prescriptions to get me there.[37]

These relationships are often cemented with free lunches for the doctor and the office staff and small gifts. As one former sales representative recently explained to *The Atlantic Monthly*:

> Bribes that aren't considered bribes… This, my friend, is the essence of pharmaceutical gifting. …Ideally, a rep finds a way to get into a scriptwriter's psyche…You need to have talked enough with a script-writer—or done enough recon with gatekeepers—that you know what to give.[38]

In the same article, another sales representative explained the purpose of all the free lunches, small gifts, and attention he lavishes on the doctors he visits as: "You're absolutely buying love."[39]

Sometimes, the gifts aren't small, and scandals about junkets and expensive presents prompted the pharmaceutical industry to adopt a voluntary code of conduct regarding gift giving, a code that may not be effective.[40]

Sales Representatives Make False and Misleading Statements

Considering how much physician contact sales representatives have, and how strong their relationships can become, the accuracy of their statements is critically important. Regrettably, the FDA letters discussed above prove that pharmaceutical sales representatives sometimes say things to doctors that are dangerously false about the drugs they are promoting.

In all, 30 of the 539 false or misleading messages aimed at doctors were statements by pharmaceutical sales representatives, a number which seems enormous when you consider how small the possibility is that such statements will come to the attention of the FDA. Almost all of the detected statements were discovered by FDA representatives asking questions of sales representatives at conferences, an activity the FDA lacks the resources to do comprehensively.

A 1995 study published in *JAMA* suggests that as much as 11% of sales representatives' statements are inaccurate.[41] The authors analyzed 106 statements made by sales representatives during 13 presentations. Statements were considered inaccurate if they contradicted the 1993 Physician's Desk Reference or materials the sales representative were distributing. The representatives made 12 inaccurate statements (11%), all of which were favorable to the drug they were promoting. The 27 physicians attending the presentations "generally failed to recognize the inaccurate statements."[42] Given that pharmaceutical marketing is a much bigger business now than it was in 1995, it is hard to say if the percentage of false statements remains accurate.

A number of doctors who prescribed themselves Vioxx are among the plaintiffs now suing Merck, Inc. for its failure to warn of Vioxx's cardiovascular risk. A critical feature of their allegations is that Merck sales representatives lied to them about Vioxx's risks.[43]

Most troubling of all about the evidence of false or misleading sales representative statements is that

nearly all of the promotional activity between sales representatives and doctors occurs without scrutiny of the FDA or any other regulator.

To learn more about sales representatives' role in deceptive marketing, please see the case studies in Appendix A, particularly Vioxx, OxyContin, Accutane, and Paxil.

CLINICAL TRIALS

Data Suppression and Misrepresentation

The case studies in Appendix A illustrate four examples of how marketing shapes clinical trial research and data presentation. In the Vioxx case study, Merck, Inc. repeatedly chose not to do a study that would settle the Vioxx heart risk question. Moreover, when confronted with unfavorable data, the company tried to spin the data favorably by promoting an unsupported hypothesis as well as flatly misstating the numbers. In the Accutane case study, Hoffman-LaRoche analyzed clinical trial data, concluded that adding a suicide-risk warning to its prescribing information was appropriate, and then, concerned about its impact on marketing, omitted that recommendation when submitting the report to the FDA. As described in the Paxil case study, GlaxoSmithKline went further, choosing not to report four trials showing complete ineffectiveness and serious potential risks. Similarly, the Neurontin case study notes that Warner-Lambert reportedly suppressed clinical data showing Neurontin ineffective for migraine pain.

More recently, a scientist who conducted a clinical trial for Proctor & Gamble using the drug Actonel has accused the company of misrepresenting his data, withholding other data from him, and writing abstracts under his name that were impossible for him to appropriately review.[44] Finally, Northfield Laboratories, Inc. is currently conducting a clinical trial for its blood substitute PolyHeme without revealing the data from a past clinical trial that showed a much higher death rate for people taking PolyHeme instead of real blood.[45]

These six examples of drug marketers hiding or misrepresenting trial data are not the only ones uncovered in recent years. A report in the *New England Journal of Medicine* cited nine examples of trials where data unfavorable to the drug company sponsor were either suppressed or, the investigator believed, misrepresented in the article that was published.[46]

While suppressing or misrepresenting studies demonstrating serious risks or ineffectiveness are obviously the worst types of marketing-induced clinical trial fraud, the FDA letters reveal a different and likely more pervasive type: citing studies for product claims they do not support. Fully a third of the false and misleading messages in the FDA letters related to unsupported or overstated claims (third set of columns in Table 3); many of those were unsupported because, as the FDA explained, the studies cited to support them did not in fact provide support.

In the five years we studied, the FDA sent 25 companies a total of 38 Untitled and Warning Letters that involved more than 82 mis-cited studies.[47] The FDA noted some studies were too small for statistical significance or were poorly designed. In other cases, the company selectively presented only the favorable data from the studies. Some times the claims—particularly for effectiveness—were inconsistent with the data in the package insert, and no other data was cited. In a few cases the cited studies were not relevant or actually contradicted the claims.

Table 6 gives several examples.

Ghostwriters Allow Drug Marketers to Spin Data in Clinical Trial Reports

Suppressing or misrepresenting data that are commercially damaging, or citing studies for commercially favorable propositions they do not support, are unfortunately not the only forms of false and misleading marketing involving clinical trials. Sometimes drug marketers have marketing professionals—not medical professionals--ghostwrite clinical trial reports. Alternatively, drug marketers hire medical writers and have their

Table 6: Selected Studies Drug Marketers Cited for Product Claims They Do Not Support

Company	Drug, Where	# Mis-Cited Studies	Unsupported Claim	Letter Date & Type	Why the study Failed to Support the Claim
SuperGen, Inc.	Nipent Exhibit panel & handout	1	Nipent attacks only leukemia, not stem cells	8/18/05 Warning	Cited study involves preliminary in vitro data, and contradicts package insert.
Bristol Meyers Squibb	Ifex Journal Ad	7	Ifex "minimizes disruption of a patient's daily activities or lifestyle"	3/13/01 Untitled	"none of the 7 articles and abstracts discusses the use of Ifex and its effect on daily activities"
Sanofi-Synthelabo, Inc.	Visual Ad	1	Plavix works better than aspirin	5/9/01 Untitled	Selectively presented data and misstated data.
GelTex, Inc.	Renegal Press Release	1	Renegal reduces cardiac calicification; it's more effective and less risky than other treatments	8/17/01 Untitled	Interim data; study still on-going.
AstraZeneca LP	Zomig Detail aid	1	Zomig is effective treatment for migraines	10/9/01 Untitled	Cites a two part study. The first part is blinded, placebo controlled and randomized, and showed no benefit from using Zomig for migraines. Part 2 was open-label, uncontrolled and non-comparative. The detail aid cited part 2 to claim Zomig was effective for migraines.
Alcon	Cipro HC Otic	3	(a) Cipro HC Otic is safer than other treatments; (b) Cipro HC Otic is better than another treatment; (c) in vitro, Cipro HC Otic kills 99.9% of certain bacteria	7/18/03 Untitled	(a) Cited study involved in vitro data; (b) cited study was open label (allowing bias) and too small for statistical significance; (c) cited data do not involve Cipro HC Otic.
XCel	Migranal Detail Aid	More than 1	Migranal has comparable safety to Triptans, another type of drug, and also is better than Triptans	12/19/03 Untitled	Cited studies do not compare Migranal and triptans.
Janssen Pharmaceutica	Risperdal, "Dear Health Care Provider Letter"	8	Risperdal does not increase risk of diabetes	9/04/04 Warning	Risperdal's label has a warning on the risk of diabetes, the cited studies "do not represent the weight of the pertinent evidence" and two of the cited studies show Risperdal increasing the risk of diabetes.

marketers supervise their work. In both cases the reports are later published under doctors' names without revealing the marketers' input. This type of ghostwriting ensures that the commercially favorable results are highlighted and the unfavorable ones are downplayed.

Having marketers prepare/oversee preparation of articles for publication in scientific journals is particularly chilling because the published studies, granted the approval and gravitas of the journal, are what passes for scientific proof. Warner-Lambert hired an advertising firm to prepare 20 such articles for Neurontin.[48] Marketing ghostwriters were also hired to help promote fen-phen, the notorious diet drugs that have since been removed from the market.[49]

The *New England Journal of Medicine* published a report in 2000 that describes ghostwriting:

> "More recently, a practice that one might call the nonwriting author–nonauthor writer syndrome has developed. Many interviews conducted for this report confirmed the wide prevalence of this syndrome in publications of drug-trial reports, editorials, and review articles. The syndrome has two features: a professional medical writer ("ghostwriter") employed by a drug company, CRO, or medical communications company, who is paid to write an article but is not named as an author; and a clinical investigator ("guest author"), who appears as an author but does not analyze the data or write the manuscript.
>
> …In one study, 19 percent of the articles surveyed had named authors who did not contribute sufficiently to the articles to meet the criteria for authorship of the International Committee of Medical Journal Editors. Eleven percent had ghostwriters who contributed to the work but were not named as authors."[50] (Internal citations omitted.)

Two years later, the *New York Times* reported that advertising agencies had purchased or significantly invested in the companies that conduct clinical trials for pharmaceutical companies. With marketing firms profiting from and controlling these clinical trial companies, it seems likely that the prevalence of the tactic may have increased.[51]

Marketers ghostwriting for doctors is not limited to clinical trial results. A public relations firm working for GlaxoSmithKline ghostwrote a letter minimizing Paxil's withdrawal symptoms that was eventually edited and signed by Dr. Bruce Pollack of the University of Pittsburg and published in the Journal of Clinical Psychiatry.[52] Paxil sales representatives found the letter very helpful in responding to doctors' concerns about Paxil and withdrawal. While Dr. Pollack denies the letter was ghostwritten, GlaxoSmithKline documents reveal that a public relations firm hired by the company sought to have such a letter published, identified three doctors who would make good 'authors,' one of whom was Dr. Pollack, and prepared a draft that made the same points, in the same order, that Dr. Pollack's eventual letter did.[53]

Drug Companies Shape the Studies for Marketing Purposes

Embedding Marketing Concerns in the Clinical Trial Design

Even further in the shadows than the ghostwriters are the ways marketing drives the design of clinical trial studies themselves. The *New England Journal of Medicine* article quoted above reviewed the ways clinical trials can be designed to reliably produce results favorable to drug companies:

> "If a drug is tested in a healthier population (younger, with fewer coexisting conditions and with milder disease) than the population that will actually receive the drug, a trial may find that the drug relieves symptoms and creates fewer adverse effects than will actually be the case….If a new drug is compared with an insufficient dose of a competing product, the new drug will appear more efficacious….Clinical trials often use surrogate end points that may

> not correlate with more important clinical end points. Companies may study many surrogate end points and publish results only for those that favor their product."[54] (internal citations omitted.)

A similar critique was offered by Dr. Richard Smith, editor of the *British Medical Journal* for 25 years.[55] His 2005 essay entitled, "Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies," has this sidebar:

> "Examples of Methods for Pharmaceutical Companies to Get the Results They Want from Clinical Trials
> - Conduct a trial of your drug against a treatment known to be inferior.
> - Trial your drugs against too low a dose of a competitor drug.
> - Conduct a trial of your drug against too high a dose of a competitor drug (making your drug seem less toxic).
> - Conduct trials that are too small to show differences from competitor drugs.
> - Use multiple endpoints in the trial and select for publication those that give favourable results.
> - Do multicentre trials and select for publication results from centres that are favourable.
> - Conduct subgroup analyses and select for publication those that are favourable.
> - Present results that are most likely to impress—for example, reduction in relative rather than absolute risk."[56]

Dr. Smith also points out that drug marketers will publish the same data multiple times to magnify the effect of the positive results and that journal editors have a difficult time identifying the problem.[57]

An example of trying to design a study to get the desired results and no others is in the Vioxx case study in Appendix A. After choosing not to investigate heart risks, Merck, Inc. tried to not to find them in its VIGOR trial, which it conducted to see if Vioxx protected stomachs. In designing VIGOR, Merck chose to exclude people at high risk of heart attack, and at the outset did not intend to analyze any cardiovascular results.

Using Clinical Trials to Build Prescribing Habits

In trials conducted after a drug has been approved, the conduct of the trial itself is can be a marketing device to build prescribing habits in doctors. Consider what an executive of a company that conducts these post-approval trials said to the *Boston Globe*:

> "In addition, the studies are designed to get hundreds of doctors in the habit of prescribing a certain drug," said another panelist, Robert Deininger, executive vice president of AAI International of Natick, which also conducts these trials for drug companies. "It's also a platform for direct-to-consumer advertising."" [58]

Drug Companies Sponsor Most Research and Their Tactics Produce Self-Serving Outcomes

By 2001, more than 80 percent of all clinical trails were funded by the pharmaceutical industry.[59] Not surprisingly, given the influence drug companies have on the design and publication of studies, scholars have found that sponsorship by pharmaceutical companies is a strong predictor of results: trials of cancer drugs sponsored by the industry were eight times more likely to reach positive conclusions, and 98 percent of papers based on industry-sponsored research favored the drugs being examined.[60] In contrast, 79 percent of studies based on independent research were favorable. [61] Dr. Richard Smith, in his essay describing trial design manipulation by drug companies, stated that company sponsored trials were four times as likely to be favorable.[62]

Solutions

The FDA letter system, as discussed above, is ineffective at correcting or deterring deceptive classic advertising and does almost nothing to watchdog non-classic advertising. Whistleblowers and crusading attorney generals have been effective in isolated instances but cannot be counted upon to appear every time. Nor are personal injury lawsuits, the engine that eventually brings much of the truth to light and triggers other enforcement action, an efficient way to prevent and correct false advertising.

The most effective and possible changes that can be made are at the state level.

STEPS THE STATES CAN TAKE

Creating an Independent Information Resource for Prescribers and Patients-- A Publicly Accessible Clinical Trial Database

Clinical trial registries, i.e. searchable databases of trials and results, are one answer to clinical trial data manipulation and suppression.[63] Medical journals have made important headway in increasing the registration of clinical trials by refusing to accept reports from trials that are not registered.[64] Most researchers comply with this requirement by registering their trials with www.clinicaltrials.gov, a largely voluntary federal registry that does not serve the core purpose of ensuring that doctors and patients have the information they need to make sophisticated and tailored prescribing decisions. Drug marketers and researchers often take advantage of the registry's lax and minimal registration requirements by using vague and clinically useless language.[65]

Recognizing this problem—drug marketers can meet the registration requirement for publication and still not provide needed clinical data—the editors of the *New England Journal of Medicine* have urged researchers to register comprehensive, specific, clinically important information.[66] As a result, many medical researchers and organizations recognize that new laws are needed to ensure that registration of all trials is done consistently and with clinically meaningful information.[67]

To effectively address all of the methods of distorting clinical trials discussed above, a registry must include for each trial:

- The key features of a trial's protocol, with any amendments, including the trial's purpose, drugs involved, outcomes to be measured, when they are to be measured, etc.;
- an explanation for key features, such as the criteria used to include or exclude patients, and the dosages of drugs chosen for comparison purposes;
- the results of the trial, including the adverse events, and if the drug is already marketed in the U.S., where the adverse events are reflected in the drug's package insert, including a direct quotation of the relevant part of the package insert;[68] and
- whether any of the data were published, and where; the authors of any publication, the company who employs them and their role in the publication; trial funding sources; financial relationships between principal investigators and the pharmaceutical sponsor; financial relationships between authors and the pharmaceutical sponsor; and any other factor a competent regulator deems necessary.

Private Attorneys General

It would take vast resources to enable the FDA to effectively monitor sales representatives' promotional activities, ensure that drug marketers submit all materials for review, and ensure that all submitted materials are reviewed in a timely way. One solution is to deputize prescribers, the public, and their associations to bring enforcement lawsuits.

In order to ensure that a plaintiff will step forward, standing must be broadly available and attorneys' fees must be awarded to victorious plaintiffs. To guard against nuisance lawsuits, only injunctive relief rather than monetary damages should be available, and the threshold of actionable false advertising should be relatively high: to win, a plaintiff should show the advertising created a public health risk. (It's worth noting that in several of the letters discussed in this report, the FDA charged that the advertising posed significant public health risks.) In addition to injunctions, judges should be empowered to levy civil fines that range up to punitive levels, based on factors such as severity of the public health risk, whether the drug marketer had disseminated similar advertising before, etc. The fines would be payable to the state.

More Sunshine

States must require better disclosure of the FDA Untitled and Warning Letters and any other evidence of deceptive marketing, including company documents that were made public as a result of litigation. Drug marketers should be required to prominently display them on their websites and disseminate them to the press. Similarly, the state's Director of Consumer Affairs or Department of Health should issue an annual report highlighting the FDA letters and any other evidence of deceptive drug marketing relating to any drug sold in the state. In addition, the department should post that information on its website, along with plain English summaries as necessary to be sure the public can understand how and why the messages were deceptive. Finally, the state should require drug marketers to disseminate the FDA letters, in envelopes easily recognized as containing such letters, to every person licensed by the state to prescribe drugs.

The comprehensive clinical trial registry, the new enforcement action and the improved publicity of evidence of deceptive marketing would both be corrective and deterrent.

Counter-Advertising

Pennsylvania's Department of Aging has hired an "unsales" force to counter the effects of what drug representative say. While the Pennsylvania effort was initiated as a cost containment effort, the project also should improve doctors' information about risks and benefits. The "unsales" representatives go to doctors' offices much like drug company sales representatives do, but they practice "academic detailing"—efforts to educate doctors about the evidence relating to all treatments, with at least one goal being shifting prescribing patterns to cheaper drugs that are just effective as the new ones being pushed by the drug company sales representatives. That effort is too new to see results; however, it is an experience states should monitor, and if effective, mimic.[69]

FDA APPROACHES IMPROVING FDA ENFORCEMENT

To improve patient safety, we must restructure the FDA, particularly to separate drug safety from drug approval.[70] Such reform would undoubtedly improve oversight of drug marketing. Short of a complete overhaul, however, we could take significant albeit expensive steps to improve the federal regulation of deceptive drug marketing.

Fixing the FDA Letter System

To make the FDA letter system an effective enforcement system, we recommend several changes, nearly all of which require substantial investments of new resources.

- **FDA must review every piece of 'classic' advertising before it is disseminated.** Given FDA's current inability to review all pieces of advertising even after the fact, and industry's need for quick, commercially relevant review, preventative screening would require a sharp increase in staffing.

- **FDA must review all the training materials for sales representatives and observe training sessions unannounced.** Without such powers and resources, FDA cannot effectively police what sales representatives say when they are meeting with doctors. Given the number of sales forces and trainings, serious monitoring would require a sharp increase in FDA staff.

- **FDA must send personnel to a substantial number of conferences where sales representatives are staffing exhibit booths and check their promotional activities.** Again, without these resources it is impossible to ensure that large-scale deceptive advertising does not happen at these events. Because of the large number of events each year, and the large number of exhibit booths at each, implementing this recommendation also requires a sharp increase in FDA staff.

- **For deterrence purposes, FDA must have, and use, punishments short of removing a drug from the market.** If false advertising recidivism quickly and consistently resulted in punitively large fines, FDA could deter drug companies from repeating the offense.

- **FDA must make the letters more useful to doctors and the public.** FDA should post all FDA Warning and Untitled Letters for false and/or misleading marketing on a single website, indexed and searchable by type of violation, company, drug and date.[71] Such organization would make it much easier for prescribers and patients alike to see who is committing the most dangerous sorts of violations and for which drugs. Similarly, every Warning and Untitled Letter should be accompanied by a plain English summary so that non-medical professionals can understand what was wrong with the marketing.

- **FDA must require corrective action in every case.** Because false and misleading drug advertising poses a serious public health risk, FDA should require the drug marketers to correct their misleading claims. FDA should also require drug marketers to send to all relevant prescribers a copy of the Untitled or Warning Letter in a uniquely and prominently marked envelope so that the letters catch the attention of doctors otherwise inundated with unsolicited mail. Dissemination of the regulatory letters is a critical component of corrective advertising.

THE MEDICAL PROFESSION'S ROLE

Improve Prescriber Education and Information Resources

The medical profession and the independent organizations and academic institutions that service it can help.

- Doctors need better access to independent, accurate, digested information about drugs. The information produced by the clinical trial registry should be packaged by an independent group or agency into a form easily useable by prescribers who want information about treatment options. The information provided should include not only the clinically important information about each drug, but also how the drug compares to other treatments in terms of safety, efficacy, and cost.

  The Drug Effectiveness Review Project (DERP) generates this information, but it is aimed more at policy makers than prescribers. Similarly, Consumers Union takes DERP's data and packages it for patients, as part of its BestBuyDrugs project. To the extent that the information is already accessible (for example, The Medical Letter), the profession must find a way to ensure that doctors use it. Only by breaking their reliance on sales representatives and other sources of promotional information can doctors ensure they are getting unbiased information.

- Medical schools and teaching hospitals should heavily invest in training students and residents to be skeptical of pharmaceutical sales representatives and to rely on independent sources of information.

Conclusion

Deceptive marketing of prescription drugs is pervasive and dangerous. Most Americans take prescription drugs at some point in their lives, and many take medications every day. When the doctors prescribing those medicines have internalized the deceptive messages about drugs' risks and effectiveness, those prescribing decisions may harm patients, not heal them. Taken by the wrong patient, a medicine is a poison.

Doctors must recognize that drug marketers are regularly targeting them with deceptive messages about risk and effectiveness, and increase their skepticism of sales representatives, promotional materials, and even drug company-sponsored clinical trials by an order of magnitude.

Patients must understand that the deceptive marketing sometimes works.

Endnotes

[1] *See,* "**FDA Oversight of Direct-to-Consumer Advertising Has Limitations**" United States General Accounting Office, October 2002, available at http://www.gao.gov/new.items/d03177.pdf, hereinafter "GAO DTC Report"; "**Influence of Patients' Requests for Direct-to-Consumer Advertised Antidepressants: A Randomized Controlled Trial**", *R. L. Kravitz; R. M. Epstein; M. D. Feldman; C. E. Franz; R. Azari; M. S. Wilkes; L. Hinton; P. Franks*. JAMA. 2005;293:1995-2002, at 2000. (JAMA Paxil Study). "**Do Ads Really Drive Pharmaceutical Sales?**" *S. Findlay*. Marketing Health Services Chicago :Spring 2002. Vol. 22, Iss. 1, p. 20-25; "**DTC Ads Influence Majority Of Consumers, Say Doctors**" *R. Thomaselli*, Advertising Age Chicago: Jan 20, 2003. Vol. 74, Iss. 3, p. 6.

[2] "**Medical Students' Exposure to and Attitudes About Drug Company Interactions A National Survey**" *F. S. Sierles, A. C. Brodkey, L. M. Cleary, MD, F. A. McCurdy, M. Mintz, J. Frank, D. J. Lynn, J. Chao, B. Z. Morgenstern, W. Shore, J. Woodard* JAMA, September 7, 2005—Vol 294, No. 9 pp. 1034-1042; "**Influences on GPs Decisions to Prescribe New Drugs—the Importance of Who Says What**" *H. Prosser, S. Almond, and T. Walley*, Family Practice 2003, 20:61-68.

[3] "**Influences on GPs Decisions to Prescribe New Drugs—the Importance of Who Says What**" *H. Prosser, S. Almond, and T. Walley*, Family Practice 2003, 20:61-68

[4] "**Gifts to Doctors Is Effective Marketing, Some Drug Firm Employees Say**" *S. Murphy*. Knight Ridder Tribune Business News Washington: Nov 17, 2002. p. 1 (company memos released as part of litigation reveal effectiveness of tactics.) "**'Tis Always the Season for Giving**" *E. Clayton*, CALPIRG, Sept. 2004.

[5] **"Do Drug Samples Influence Resident Prescribing Behavior? A Randomized Trial"** *R. F. Adair, L. R. Holmgren*. The American Journal of Medicine. New York: Aug 2005.Vol.118, Iss. 8; pg. 881; **"Drug Samples Sway Doctors"** *J. Olson*. Knight Ridder Tribune Business News. Washington: Jul 28, 2005. pg. 1

[6] **"Kaiser goes generic / HMO limits senior coverage, raises co- payments"** *V. Colliver*. San Francisco Chronicle. San Francisco, Calif.: Oct 25, 2003. pg. B.1 In addition, patients without insurance are more likely to be influenced by a drug's cost.

[7] "**Patients trust their doctors**" *A. Branch Jr.* Pharmaceutical Executive Eugene: Mar 2003. Vol. 23, Iss. 3, p. 102 (discussing a Wall Street Journal Online/Harris Interactive Healthcare poll)

[8] "**Paternalism Costs Lives**" *H. I. Miller* Wall Street Journal Mar. 2, 2006 at p. A14.

[9] "**Reform of Drug Regulation — Beyond an Independent Drug-Safety Board**," *W. A. Ray and C. M. Stein,* N. Engl. J Med. 354;2 at 194. (Describes how limited risk and efficacy information is under the current FDA process, with examples.)

[10] 21CFR202.1

[11] Re accurate understanding of risks deterring both doctors and patients from a treatment, albeit in the context of surgery, not prescription drugs, *see* "**Medicare Says It Will Pay, but Patients Say 'No Thanks'**," *G. Kolata* New York Times, New York, Mar. 3, 2006 at C.1, C.3.

[12] We reviewed all the letters at this website: http://www.fda.gov/cder/warn/warn2005.htm. Four of the letters made reference to Untitled Letters from the time period we studied but which were not posted at the site. See Table 5. As a result, it is not possible to know how many letters were sent out in the time frame we studied, and from the very beginning our numbers understate the true problem.

[13] Abbot Laboratories, Actelion Pharmaceuticals US, Inc., Alcon Research, Ltd., Allergran, Inc., Alza Corporation, Amgen, AstraZeneca, Aventis, Barr Research, Inc., Baxter Pharmaceuticals, Bayer Corporation, Berlex Laboratories, Biovail Pharmaceuticals, Boehringer Ingelheim, Bracco Diagnostics, Bradley Pharmaceuticals, Braintree Laboratories, Bristol-Myers Squibb, Centocor, Inc., Cephalon Inc., Connetics Corporation, Corixa Corporation, Critical Therapeutics, Inc., Cubist Pharmaceuticals,

Cytogen, Dutch Ophthalmic USA, Elan Pharmaceuticals, Eli Lilly, Endo Pharmaceuticals, Forest Laboratories, Fujisawa Healthcare, Galderma Laboratories, GelTex Pharmaceuticals, Inc., Genentech, Inc., Genzyme Corp, Gilead Sciences, Inc., GlaxoSmithKline, Guilford Pharmaceuticals Inc., Hoffman-LaRoche, ICN Pharmaceuticals, Inc., ISTA Pharmaceuticals, Inc., Janssen Research Foundation, Janssen Pharmaceutica, Johnson & Johnson, King and Spaulding/Genfarm, Kos Pharmaceuticals, Lifecyle Ventures, Lilly ICOS LLC, Mallinckrodt Inc., Maxim Pharmaceuticals, MedImmune, Merck & Co., Nephrx, Novartis Pharmaceuticals Corporation, Novo Nordisk Pharmaceuticals, OraPharma, Inc., Organon, Ortho-McNeil Pharmaceutical, Inc., Pfizer, Pharmacia Corporation, Pharmacia & Upjohn, Pharmacyclics, Inc., PharmaMar, Praceis Pharmaceuticals, Presutti Laboratories, Inc., Procter & Gamble Pharmaceuticals, Purdue Pharma L.P., Roche Laboratories, Sanofi-Synthelabo, Inc., Santen, Inc., Schering Corporation, Shire Pharmaceutical Development, Inc., SkyePharma, Supergen, Inc., Takeda Pharmaceuticals North America, Inc., TAP Pharmaceutical Products, Inc., United Therapeutics Corporation, VIVUS, Inc., Watson Pharmaceuticals, Women's Capital Corporation, Wyeth-Ayerst, Wyeth Pharmaceuticals, Xanodyne Pharmacal, Inc., Xcel Pharmaceuticals

[14] ***Warning Letter to Pharmacia regarding Celebrex marketing on 2/1/01,*** total deceptive messages disseminated: 43 (5 audio conferences by a Pharmacia-sponsored doctor promoted 2 unapproved uses, claimed superiority to three treatments without support, omitted risks, minimized a dangerous drug-drug interaction, and minimized a contra-indication (5 x 8 = 40); a sales aid, a card, and a wall chart all minimized a contra-indication (3 x 1 = 3)). ***Warning Letter to Merck regarding Vioxx marketing on 9/17/01***, total deceptive messages disseminated: 45 (6 audio conferences by a Merck-sponsored doctor minimized heart attack risks, omitted other risks, minimized a dangerous drug/drug interaction, promoted at least 3 unapproved uses and made an unsubstantiated claim versus other NSAIDs (6 x 7 = 42); 2 sales reps each minimized risks at a conference (2 x 1 = 2); and one press release misrepresented safety (1 x 1 = 1)) ***Untitled Letter to Cephalon regarding Provigil marketing on 1/3/02,*** total deceptive messages disseminated: 44 (8 journal ads minimized abuse potential, promoted for unapproved use of daytime sleepiness and misleadingly claimed the drug's mechanism of action was known (8 x 3 = 24); 4 sales aids promoted unapproved use of daytime sleepiness (4 x 1 = 4); 5 sales aids promoted a misleading switch protocol and misleadingly claimed the drug's mechanism of action was known (5 x 2 = 10); 3 sales aids made unsubstantiated claims of superiority to other treatments (3 x 1 = 3); 1 website promoted for unapproved use of daytime sleepiness, promoted a misleading switch protocol and misleadingly claimed the drug's mechanism of action was known (1 x 3 = 3).

[15] GAO DTC Report at 17.

[16] "**'Off-label' drugs take their toll**" *A. Young and C. Adams* Knight Ridder Newspapers Nov. 02, 2003 (http://www.realcities.com/mld/krwashington/news/special_packages/riskyrx/7146578.htm?template=contentModules/printstory.jsp)

[17] Ibid.

[18] The FDA's difficulty in getting warnings and other labeling changes made post-marketing is not the only evidence of drug marketers' post-approval power. Recent reports indicate that the clinical trials companies promise to do after a drug is approved—studies that are part of the reason the FDA agrees to approve the drug—usually are not done. Prior to approval, the FDA can force a company to do any study the FDA wants, provided the drug marketer is sufficiently interested in getting the right to market. *See* "**New Drugs Hit the Market, but Promised Trials Go Undone**," *G. Harris* New York Times New York, Mar. 3, 2006 at B. 1.

[19] "**Better Warning Labels For Drugs Urged by FDA**" *G. Hess*. Chemical Market Reporter New York:Mar 7, 2005. Vol. 267, Iss. 10, p. 24 (citing testimony of FDA before a Senate Committee), "**FDA Seeks More Say On Drug Labels; Regulators Want Greater Authority To Dictate Warnings**" *C. Rowland* Boston Globe Boston, Mass.:Mar 2, 2005. p. C.1 (same)

[20] "**Testimony Before the Senate Finance Committee**" *Dr. David Graham*, Nov. 18, 2004.

[21] "**Better Warning Labels For Drugs Urged by FDA**" *G. Hess*. Chemical Market Reporter New York:Mar 7, 2005. Vol. 267, Iss. 10, p. 24 (citing testimony of FDA before a Senate Committee), "**FDA Seeks More Say On Drug Labels; Regulators Want Greater Authority To Dictate Warnings**" *C. Rowland* Boston Globe Boston, Mass.:Mar 2, 2005. p. C.1 (same)

[22] "**OxyContin Abuse and Diversion and Efforts to Address the Problem**" United States General Accounting Office Report, December 2003, at p. 28, (Hereinafter "GAO OxyContin Report").

[23] Id. *See Also,* GAO DTC Report at 17, 21-22. (Discusses FDA's inability to review all direct-to-consumer advertising and its methods of prioritizing what does get reviewed.)

[24] For example, the Warning Letter sent to GlaxoSmithKline for its Paxil advertising, discussed in Appendix A, was received a month after the deceptive TV ad stopped running. The problem is systemic, and reflects a procedural change instituted in 2002. GAO DTC Report at 17 and 24. ("FDA's oversight has been adversely affected by a January 2002 change in its procedures for reviewing draft regulatory letters that was directed by the Department of Health and Human Services (HHS). This change has significantly increased the time between DDMAC's identification of a misleading advertisement and FDA's request to remove it from dissemination, with the result that some regulatory letters may not be issued until after the advertising campaign has run its course.")

[25] *See,* "**Complex Drug Labels Bury Safety Message Warnings Elude Patients, Doctors Alike**" *R. Rubin* USA Today McLean, Va.: May 3, 2000. p. 01A; "**The Fine Print: Are Too Many Doctors Missing Safety Alerts on Drugs?**" *C. Adams* Wall Street Journal New York, N.Y.:Mar 24, 2000. p. B1. "**The Weak Link in the Drug-Safety Chain: Doctors**" *P. Raeburn.* Business Week New York:April 10, 2000. Iss. 3676, p. 50 *See Also,* FDA talk paper Jan 2000 (The FDA found that 229 adverse events from Propulsid, including 70 deaths, involved patients with risk factors listed in Propulsid's label) and "**Adherence to Black Box Warnings for Prescription Medications in Outpatients**," *K. E. Lasser, D. L. Seger, D. T. Yu, A. S. Karson, J. M. Fiskio, A. C. Seger, N. R. Shah, T. K. Gandhi, J. M. Rothschild, D. W. Bates*, Arch Intern Med. 2006;166:338-344 (showing that doctors prescribe drugs with black box warnings to precisely the patients the warning counsels against).

[26] Doctor-to-doctor deceptive marketing is not a focus of this report, but to understand the role it can play, please see the case studies in Appendix A, particularly Vioxx and Neurontin.

[27] "**Marketing to Doctors a Key Approach for Drug Sales Representatives**" *C. T. Zaneski*. **Knight Ridder Tribune Business News** Washington: Jun 17, 2004. p. 1

[28] See the discussion in the OxyContin case study in Appendix A at FNs 115 and 116 infra, and the accompanying text, for more information on how pharmaceutical companies target doctors.

[29] "**Marketing to Doctors a Key Approach for Drug Sales Representatives**" *C. T. Zaneski*. **Knight Ridder Tribune Business News** Washington: Jun 17, 2004. p. 1

[30] Quote is from: "**Medical Students' Exposure to and Attitudes About Drug Company Interactions A National Survey**" *F. S. Sierles, A. C. Brodkey, L. M. Cleary, MD, F. A. McCurdy, M. Mintz, J. Frank, D. J. Lynn, J. Chao, B. Z. Morgenstern, W. Shore, J. Woodard* JAMA, Sept. 7, 2005—Vol 294, No. 9 1034-1042 at 1034-35. A comprehensive review of the studies documenting the power of sales representatives is "**Physicians and the Pharmaceutical Industry, Is a Gift Ever Just a Gift?**" *A. Wazana*, JAMA 2000; 283:373-380. *See Also*, "**Influences on GPs Decisions to Prescribe New Drugs—the Importance of Who Says What**" *Prosser H., Almond S. and Walley T.*, Family Practice 2003 20:61-68 (finding sales representatives were one of the largest influences on English doctors' prescribing decisions.) Despite this demonstrated power, pharmaceutical marketers are increasingly disenchanted with traditional sales representative strategies; some advocate a shift to more on-line promotion. See, e.g., "**Pharma Marketing News Special Supplement, eDetailing**" published by VeriSci Newton, PA 2005.

[31] "**Effect of Restricting Contact Between Pharmaceutical Company Representatives and Internal Medicine Representatives on Post-Training Attitudes and Behavior**" *B. B. McCormick, G. Tomlinson, P. Brill-Edwards, A. S. Detsky*, JAMA, October 24/31, 2001 Vol 286, No. 16 (med students at school that forbade interactions with representatives during school were more skeptical of the sales representatives, and saw them less often, once in practice than students from a school that allowed sales representatives to interact with students and sponsor events.) "**Medical Students' Exposure to and Attitudes About Drug Company Interactions A National Survey**" *F. S. Sierles, A. C. Brodkey, L. M. Cleary, MD, F. A. McCurdy, M. Mintz, J. Frank, D. J. Lynn, J. Chao, B. Z. Morgenstern, W. Shore, J. Woodard* JAMA, September 7, 2005—Vol 294, No. 9 1034-1042 (citing one other study).

[32] "**Medical Students' Exposure to and Attitudes About Drug Company Interactions A National Survey**" *F. S. Sierles, A. C. Brodkey, L. M. Cleary, MD, F. A. McCurdy, M. Mintz, J. Frank, D. J. Lynn, J. Chao, B. Z. Morgenstern, W. Shore, J. Woodard* JAMA, September 7, 2005—Vol 294, No. 9 1034-1042 at 1036

[33] Ibid., at 1040.

[34] "**Marketing to Doctors a Key Approach for Drug Sales Representatives**" *C. T. Zaneski*. Knight Ridder Tribune Business News Washington: Jun 17, 2004. p. 1 *See Also*, "**Suit Says Company Promoted Drug in Exam Rooms**" *M. Petersen* New York Times New York, N.Y.: May 15, 2002. p. C.1 (discusses allegations about shadowing program of Warner-Lambert, also mentions shadowing by Alza Corporation.) and "**The Drug Pushers**," *C. Elliott*, The Atlantic Monthly, Vol. 297, No. 3, pp. 82-93.

[35] "**Suit Says Company Promoted Drug in Exam Rooms**" *M. Petersen*. New York Times New York, N.Y.: May 15, 2002. p. C.1

[36] "**Medical Group Votes to Bar Drug Salespeople from Witnessing Patient Exams**" *B. Japsen*. Knight Ridder Tribune Business News Washington: Jun 18, 2003. p. 1

[37] "**Doctoring sales**" *E. Strout*. Sales and Marketing Management New York: May 2001. Vol. 153, Iss. 5, p. 52-60.

[38] "**The Drug Pushers**," *C. Elliott*, The Atlantic Monthly, Vol. 297, No. 3, pp. 82-93 at p. 90.

[39] Ibid.

[40] Ibid. at p. 92

[41] "**The accuracy of drug information from pharmaceutical sales representatives**" *M. G. Ziegler, P. Lew and B. C. Singer* JAMA Vol. 273 No. 16, Apr. 26, 1995

[42] Ibid.

[43] "**Vioxx Doctors Wooed by Merck Are Now Its Foes**" *H. Won Tesoriero* Wall Street Journal, Mar. 10, 2006 at B1.

[44] "**Scientist Presses Claim P&G Misrepresented Actonel Data**," *S. Ellison*, Wall Street Journal, Feb. 23, 2006 at B6.

[45] "**Amid Alarm Bells, A Blood Substitute Keeps Pumping**" *T. M. Burton*, Wall Street Journal, Feb. 22, 2006 at A.1.

[46] "**Uneasy Alliance — Clinical Investigators and the Pharmaceutical Industry**," *T. Bodenheimer* NEJM Vol. 342 May 18, 2000 **No. 20 1539-1544 at 1541-42.**

[47] Aventis 3/8/01 Untitled Letter; Bristol Meyers Squibb 3/13/01 Untitled Letter; Bristol Meyers Squibb 3/29/01 Untitled Letter; Pfizer, Inc. 4/1/01 Untitled Letter; Sanofi-Synthelabo 5/9/01 Untitled Letter; SuperGen Inc. 5/10/01 Untitled Letter; Allergan, Inc. 6/8/01 Untitled Letter; Pfizer 6/29/01 Untitled Letter; Connectics, Inc. 8/13/01 Untitled Letter; GelTex, Inc. 8/17/01 Untitled Letter; Merck, Inc. 9/17/01 Warning Letter; AstraZeneca LP 10/9/01 Untitled Letter; Fujisawa 11/13/01 Untitled Letter; Connectics 11/15/01 Untitled Letter; Berlex 11/19/01 Untitled Letter; Forest Laboratories 9/13/02 Untitled Letter; Janssen Research Foundation 11/20/02 Untitled Letter; Aventis 12/15/02 Untitled Letter; Pfizer, Inc. 10/24/03 Untitled Letter; Organon, Inc. 12/12/03 Untitled Letter; XCel 12/19/03 Untitled Letter; Wyeth-Ayerst Laboratories 3/18/04 Untitled Letter; Novartis 6/27/03 Untitled Letter; Alcon 7/18/03 Untitled Letter; Novartis 8/22/01 Untitled Letter; Janssen 9/3/04 Warning Letter; Janssen Pharmaceutica 9/04/04 Warning Letter; GlaxoSmithKline 1/31/05 Warning Letter; Centocor, Inc. 2/11/05 Untitled Letter; AstraZeneca 3/8/05 Untitled Letter; Boehringer 3/22/05 Untitled Letter; United Therapeutics Corp. 4/13/05 Warning Letter; Alcon Laboratories 4/27/05 Warning Letter; Endo 6/28/05 Warning Letter; Abbott Laboratories 7/15/05 Untitled Letter; Pfizer, Inc. 7/20/05 Warning Letter; SuperGen, Inc. 8/18/05 Warning Letter; Allergan 9/6/05 Warning Letter; Alcon 9/29/05 Untitled Letter

[48] "**Whistle-Blower Says Marketers Broke the Rules To Push a Drug**" *M. Petersen*. New York Times. New York, N.Y.: Mar 14, 2002. p. C.1

[49] "**Madison Ave. Has Growing Role In the Business of Drug Research**" *M. Petersen*. **New York Times**. New York, N.Y.: Nov 22, 2002. p. A.1

[50] "**Uneasy Alliance — Clinical Investigators and the Pharmaceutical Industry**," *T. Bodenheimer* NEJM Vol. 342 May 18, 2000 **No. 20 1539-1544 at 1542.** *See Also,* **"Developing an open relationship with the drug industry**" *P. Vallance* The Lancet London: Sep 24-Sep 30, 2005. Vol. 366, Iss. 9491, p. 1062-1064. (discusses ghostwriting at FN 3 and 19 and the accompanying text.)

[51] "**Madison Ave. Has Growing Role In the Business of Drug Research**" *M. Petersen*. **New York Times**. New York: Nov 22, 2002. p. A.1

[52] "**Drug Maker Withheld Paxil Study Data**" *Primetime Live* ABC News December 9, 2004, available at http://abcnews.go.com/Health/story?id=311956&page=1 at page 4, viewed March 31, 2006.

[53] Ibid. The marketers' letter and Dr. Pollack's letter are available at http://abcnews.go.com/images/Primetime/paxil_pollock.pdf

[54] "**Uneasy Alliance — Clinical Investigators and the Pharmaceutical Industry**," *T. Bodenheimer* NEJM Vol. 342 May 18, 2000 **No. 20 1539-1544 at 1541. The problem of industry's profit motive distorting scientific research is not limited to prescription drugs. A stark example is tobacco industry research;** *see* **"Research from tobacco industry affiliated authors: need for particular vigilance,"** *S. Chapman* **Tob. Control 2005;14;217-219.**

[55] "**Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies**" *R. Smith* PLoS Med 2(5): e138, published May 17, 2005 (available at http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0020138)

[56] Ibid. at p. 0365.

[57] Id. and at FN 15 and 16.

[58] "**Critics Say Drug Trials Often A Marketing Tool**" *A. Dembner,* **Boston Globe** Boston, Mass.: Jun 25, 2002. p. A.1

[59] "**Undue influence**" *J. Washburn*. The American Prospect Princeton:Aug 13, 2001. Vol. 12, Iss. 14, p. 16-22.

[60] Ibid.

[61] Id.

[62] "**Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies**" *R. Smith* PLoS Med 2(5): e138, published May 17, 2005 (available at http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0020138)

[63] See, "**Next steps in trial registration**," *K. Abbasi and F. Godlee* BMJ 2005;330;1222-1223 (at FNs 1-6 and accompanying text) and "**Registries and Registration of Clinical Trials**" *C. Haug, P. Gøtzsche, and T. V. Schroeder,* N Engl J Med 353;26 2811-13 (at FNs 1-7 and accompanying text).

[64] "**Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication Updated February 2006**" *International Committee of Medical Journal Editors* at III.J. available at http://www.icmje.org/ (requirement of registration)

"**Trial registration at ClinicalTrials.gov between May and October 2005.**" *Zarin DA, Tse T, Ide NC.* N Engl J Med Dec. 29, 2005;353:2779-87. (evidence of effectiveness of registration requirement for publication on registration rates; also evidence for clinical insignificance of many compliant registrations.)

65 "**Trial registration at ClinicalTrials.gov between May and October 2005**." *Zarin DA, Tse T, Ide NC.* N Engl J Med Dec. 29, 2005;353:2779-87; "**Trial Registration Report Card**." *J. M. Drazen, and A. J.J. Wood* N Engl J Med Dec. 29, 2005;353:2809-11.

66 "**Trial Registration Report Card.**" *J. M. Drazen, and A. J.J. Wood* N Engl J Med Dec. 29, 2005;353:2809-11. *See Also,* "**The Ottawa Statement, Part One: Principles for international registration of protocol information and results from human trials of health-related interventions**" Edited by *K. Krleža-Jerić, A. Chan, K. Dickersin, I. Sim, J. Grimshaw, and C. Gluud, for the Ottawa group*, at p.10, E.5 available at www.ottawagroup.ohri.ca

67 "**The Ottawa Statement, Part One: Principles for international registration of protocol information and results from human trials of health-related interventions**" Edited by *K. Krleža-Jerić, A. Chan, K. Dickersin, I. Sim, J. Grimshaw, and C. Gluud, for the Ottawa group*, at p.10, E.5 (statement registration must be an enforceable legal requirement) available at www.ottawagroup.ohri.ca and "Trial Registration Report Card." *J. M. Drazen, and A. J.J. Wood* N Engl J Med Dec. 29, 2005;353:2809-11, at 2810.

68 This component is necessary because drug marketers have the right to negotiate the language of the package insert with the FDA, and they exercise that right to minimize any negative commercial impact of the label and maximize any positive commercial impact. The FDA has asked Congress for the authority to dictate drugs' labeling but to date has not received it. See FN 19 above.

69 "**Negative Advertising As Drug Bill Soars, Some Doctors Get an 'Unsales' Pitch**" *S. Hensley* Wall Street Journal New York NY: Mar. 13, 2006 p. A1.

70 "**Testimony Before the Senate Finance Committee**" *Dr. David Graham*, Nov. 18, 2004; "**Reform of Drug Regulation — Beyond an Independent Drug-Safety Board**," *W. A. Ray and C. M. Stein,* N. Engl. J Med. 354;2 at 194.

71 While all the letters reviewed for this report were from a single site, some of them referred to letters that were not posted. See supra at FN 12 and Table 5.

72 "**Struggling Merck Names New Boss**," BBC World News May 5, 2005, at http://news.bbc.co.uk/2/hi/business/4517351.stm (viewed February 16, 2005)

73 "**Testimony Before the Senate Finance Committee**" *Dr. David Graham*, Nov. 18, 2004.

74 Estimate by cardiologist Eric Topol, cited by Dr. Graham in his testimony. Ibid.

75 FDA Warning Letter to Merck, 9/17/01 at p. 6. (Herein after "Vioxx Warning Letter)

76 "**New Treatment: To Sell Their Drugs, Companies Increasingly Rely on Doctors; For $750 and Up, Physicians Tell Peers About Products**" *S. Hensley and B. Martinez* Wall Street Journal. New York, N.Y.: Jul 15, 2005. pg. A.1

77 Ibid.

78 Id.

79 Vioxx Warning Letter at pp. 3-4

80 Vioxx Warning Letter at pp. 4-5

81 Vioxx Warning Letter at p. 5

82 Vioxx Warning Letter at p. 6. Importantly, Vioxx was eventually proven to be effective for rheumatoid arthritis and such use was added to its label. However, the other uses were never demonstrated.

83 Vioxx Warning Letter at p. 7.

84 "**Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage; As Heart-Risk Evidence Rose, Officials Played Hardball; Internal Message: 'Dodge!'; Company Says 'Out of Context'**" *A. W. Mathews and B. Martinez.* Wall Street Journal. New York, N.Y.: Nov 1, 2004. pg. A.1.

85 Ibid. Dr. David Graham, an FDA official, testified that pre-approval Merck Inc. did a study named 090 that showed a 7-fold risk of heart attacks. "**Testimony Before the Senate Finance Committee**" *Dr. David Graham*, Nov. 18, 2004.

86 "**Response to Expression of Concern Regarding VIGOR Study**," *C. Bombardier, L. Laine, R. Burgos-Vargas, B. Davis, R. Day, M. Bosi Ferraz, C. J. Hawkey, M. C. Hochberg, T. K. Kvien, T. J. Schnitzer, A. Weaver* N Engl J Med 2006 (March 16 edition; posted early at http://content.nejm.org/cgi/reprint/NEJMc066096.pdf (viewed Feb. 24, 2006)) at p. 1

87 VIoxx Warning Letter

88 *See, e.g.,* "**The $20bn drugs disaster**" *T. Boles.* Knight Ridder Tribune Business News Washington:Aug 28, 2005. p. 1.

89 *See* "**Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage; As Heart-Risk Evidence Rose, Officials Played Hardball; Internal Message: 'Dodge!'; Company Says 'Out of Context'**" *A. W. Mathews and B. Martinez.* Wall Street Journal. New York, N.Y.: Nov 1, 2004. pg. A.1 (study was to test efficacy of preventing colon polyps.) "**The $20bn drugs disaster**" *T. Boles.* Knight Ridder Tribune Business News Washington:Aug 28, 2005. p. 1. (Treatment of colon cancer.)

90 Vioxx Warning Letter at p. 1

91 Vioxx Warning Letter

92 Vioxx Warning Letter at p. 4

93 "**At Vioxx Trial, a Discrepancy Appears to Undercut Merck's Defense**" *A. Berenson* New York Times Jul. 20, 2005.

94 "**Expression of Concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis,"**" *G. D. Curfman, S. Morrissey, and J. M. Drazen* N Engl J Med 2000;343:1520-8.

95 "**Response to Expression of Concern Regarding VIGOR Study**," *A. Reicin, D. Shapiro* N Engl J Med 2006 (March 16 edition; posted early at http://content.nejm.org/cgi/reprint/NEJMc066096.pdf (viewed Feb. 24, 2006)).

96 Ibid.

97 "**Expression of Concern Reaffirmed**" *G. D. Curfman, S. Morrissey, and J. M. Drazen* N Engl J Med 2006 (March 16 edition; posted early at http://content.nejm.org/cgi/reprint/NEJMc066096.pdf (viewed Feb. 24, 2006)).

98 GAO OxyContin Report at p. 35.

99 GAO OxyContin Report at p. 8

100 Ibid. at pp. 9-10. The problem arose first and primarily in rural areas of Maine, Kentucky, Ohio, Pennsylvania, Virginia, and West Virginia.

101 The first news reference to the phrase found in Lexis-Nexis was "**This painkiller can kill OxyContin abuse makes attacks on pot seem laughable OxyContin Mountain curse or miracle drug ?**" *G. Stone* Charleston Gazette (West Virginia) at p. 1A.

102 Beginning almost immediately after OxyContin was approved, in 1996, the DEA began addressing abuse problems. However, the DEA's efforts were significantly scaled up in 2001, when it developed an "Action Plan" to deter OxyContin abuse and joined national education efforts. The DEA's efforts continued at a high level from then on. GAO OxyContin Report at pp. 36-38.

103 Ibid. at 14.

104 Originally OxyContin was marketed as "The One to Start with and Stay with," a slogan promoting using OxyContin as a pre-emptive replacement for weaker and lower dose opioids on the market. Id. at 17.

105 Id. at 28. Purdue distributed a revised version of this video in 2000, which the FDA said also appeared to minimize OxyContin's risks. Purdue distributed 12,000 copies of another video that, although submitted to the FDA, was not reviewed by it. These videos became obsolete with the 2001 labeling change but were not recalled or replaced. Id.

106 Id. at 27-28. Purdue distributed 12,000 copies of another video that, although submitted to the FDA, was not reviewed by it. These videos became obsolete with the 2001 labeling change but were not recalled or replaced. Id.

107 Id. at 27.

108 Id.

109 Doctors' aversion is so commonplace as to have a name, "morphine stigma." See, "**What's the Fuss Over OxyContin and Other Long-Acting Opioids?**" *L. Broadman, J. P. Rathmell* American Society of Anesthesiologists Newsletter, Nov., 2001 at http://www.asahq.org/Newsletters/2001/11_01/broadman.htm

110 GAO OxyContin Report at p. 17

111 Ibid at 17-18.

112 Id. at p. 20 (The numbers include 300 sales representatives provided by Abbott pursuant to a co-promotion agreement. The report notes that in 2000, 671 Purdue reps were calling on 70-94,000 doctors; no estimate is given for the 300 Abbott representatives at the time. "Some 100,000" is our conservative estimate of how many doctors were being called on after the Purdue sales force expanded to 766 and Abbott's 300 reps are considered.)

113 *See,* "**Doctoring sales**" *E. Strout*. Sales and Marketing Management New York: May 2001. Vol. 153, Iss. 5, p. 52-60, and "**The Drug Pushers**," *C. Elliott*, The Atlantic Monthly, Vol. 297, No. 3, pp. 82-93 at pp.88-89.

114 "**No Margin for Error**" *M. Tenaglia, P. Angelastro*. Pharmaceutical Executive Eugene:Sep 2005. Vol. 25, Iss. 9, p. 90-92,94,96,98; "**Pharma Marketing News Special Supplement, Increase Physician Access and Effectiveness**" published by VeriSci Newton, PA 2005. (same).

115 GAO OxyContin Report at 34.

116 Ibid, at 21.

117 Id. at 25.

118 Id.

119 Id. at p. 30.

120 New label available at http://www.fda.gov/cder/foi/label/2001/20553s022lbl.htm

121 GAO OxyContin Report at 36.

122 FDA Talk Paper, 7/25/01, available at http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01091.html

123 GAO OxyContin Report Table 2 at p. 31.

124 Ibid. at 26.

125 Id. at p. 30.

126 "**Paxil is Forever**," *B. Hawkins* City Pages, Vol. 23, Iss. 1141 Oct. 16, 2002

127 "**Health: First, you market the disease then you push the pills to treat it**" *B. I Koerner*. The Guardian Manchester (UK):Jul 30, 2002. p. 2-8

128 See, e.g., "**Merck: Out Of The Ivory Tower: Its pragmatic strategy includes tweaking the vitamin niacin to make it a blockbuster**" Business Week Online at http://www.businessweek.com/magazine/content/06_10/b3974082.htm (visited Mar. 1, 2006) (discusses Wall Street expectations and need for Merck to develop a new blockbuster) or "**Antibiotic work afflicted by the bottom line blues**" *L. Beil* The Dallas Morning News, Mar. 1, 2006 (noting impact of Wall Street expectations on what types of drugs get researched).

129 "**Paxil is Forever**," *B. Hawkins* City Pages, Vol. 23, Iss. 1141 Oct. 16, 2002

130 "**Influence of Patients' Requests for Direct-to-Consumer Advertised Antidepressants: A Randomized Controlled Trial**", *R. L. Kravitz; R. M. Epstein; M. D. Feldman; C. E. Franz; R. Azari; M. S. Wilkes; L. Hinton; P. Franks*. JAMA. 2005;293:1995-2002. (JAMA Paxil Study).

131 JAMA Paxil Study at p. 2000.

132 Ibid. at p. 1998.

133 Id. at p. 2000

134 "**Glaxo Is Rebuked By FDA Over Ad For Paxil CR Drug**" *J. Whalen* Wall Street Journal New York, N.Y.:Jun 14, 2004. p. B.5

135 "**Antidepressant Risk for Newborns**" *J. C. Dooren*. Wall Street Journal New York, N.Y.: Feb 9, 2006. p. D.3 (increased risk of infants with persistent pulmonary hypertension when drug is taken in second half of pregnancy); "**U.S. Food & Drug Administration; Agency advises of risk of birth defects with Paxil**" Women's Health Law Weekly Atlanta: Jan 15, 2006. p. 4 (increased risk of heart defects in infants when mothers take Paxil in first trimester)

136 "**Suicide Warning Ordered On Drugs; Antidepressant Risk Seen In Youth**" *C. Y. Johnson*, Boston Globe Boston, Mass.: Oct 16, 2004. p. A.1

137 "Trouble In Prozac Nation," *D. Stipp, J. L. Yang* Fortune New York: Nov 28, 2005. Vol. 152, Iss. 11, p. 154-169.

138 "**Drug Maker Withheld Paxil Study Data**" *Primetime Live* ABC News December 9, 2004, available at http://abcnews.go.com/Health/story?id=311956&page=1 at page 3, viewed March 31, 2006.

139 Ibid. Business plan guide available at http://abcnews.go.com/images/Primetime/paxil_bpg.pdf (minimize at p. 2 and 2 in 1,000 at p. 3) Viewed March 31, 2006.

SmithKline Beecham, GlaxoSmithKline's predecessor, appears to have been somewhat flip about the issue. In a May 1997 memo to the "Paxil Sales Team", the company explained how to respond to concerns about Paxil and withdrawal and concluded: "Let's face it in the end. The only thing an anxious and agitated patient [anxiety and agitation are common Paxil withdrawal symptoms] will be saying is: Where's My Paxil!!!!!!" See http://abcnews.go.com/images/Primetime/paxil_wheresmy.pdf at p.2

140 Ibid.

141 "**Drug Maker Withheld Paxil Study Data**" *Primetime Live* ABC News December 9, 2004, available at http://abcnews.go.com/Health/story?id=311956&page=1 at page 3, viewed March 31, 2006.

142 http://abcnews.go.com/images/Primetime/paxil_moneybag.pdf viewed March 31, 2006. The font size and bolding approximates the original.

143 "**Paxil Memo Raises Questions**" *E. Silverman* The Star Ledger, Newark, NJ Feb. 18, 2004 at p. 21.

144 October, 1998 company memo, " http://www.ahrp.org/risks/SSRI0204/GSKpaxil/pg1.html at p. 5.

145 **"Spitzer Sues a Drug Maker, Saying It Hid Negative Data"** *G. Harris.* **New York Times** New York, N.Y.: Jun 3, 2004. p. A.1

146 The memo is available at http://abcnews.go.com/images/Primetime/paxil_remarkable.pdf, viewed March 31, 2006.

147 **"Spitzer Sues a Drug Maker, Saying It Hid Negative Data"** *G. Harris.* **New York Times** New York, N.Y.: Jun 3, 2004. p. A.1 and "**Sales Reps Told Not to Divulge Paxil Data, Drug Maker Memo Cited Risks to Youths**", *E. Silverman*, The Star Ledger, Newark, NJ September 29, 2004 at p. 1.

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