"DODGEBALL"

The Pharmaceutical Companies' Direct Marketing To Doctors and The Impact on Health Care Costs and Patient Safety

Written by:
Blair Horner
Michael Hartwell
Arthur Levin, MPH

Recommendations endorsed by:
AARP
Center for Medical Consumers
Consumers Union
New York Public Interest Research Group
New York State Alliance for Retired Americans
New York StateWide Senior Action Council

June 2006

Acknowledgements

Written by Blair Horner and Michael Hartwell of the New York Public Interest Research Group (NYPIRG) as well as Arthur Levin of the Center for Medical Consumers.

To receive a copy of this report, visit our website or send a check for $5 made payable to NYPIRG at the following address:

NYPIRG
107 Washington Avenue
Albany, N.Y. 12210
(518) 436-0876
www.nypirg.org

"DODGEBALL"

DRUG COMPANIES' DIRECT MARKETING TO DOCTORS AND THE IMPACT ON HEALTH COSTS AND PATIENT SAFETY

Health care costs in New York State are staggering. Well over $40 billion of state revenues are spent on health care with at least $80 billion more spent by the private sector.[1] And those costs have been increasing. One major reason for this on-going increase is the rise in the cost of pharmaceuticals. Some of the increasing cost in medicines is the result of important, but very expensive, new therapeutics. But a substantial portion of inflation in drug costs is the result of the introduction and promotion of new expensive products that are not only no more effective than older, cheaper alternatives but often prove to have more harmful side effects.

Although the industry defends its high prices as necessary to support the enormous investment behind medical progress, the reality is that some drug companies spend more on advertising and promotion than on research and development.

New and expensive drugs are heavily promoted directly to physicians in slick and expensive advertising campaigns. The most effective promotion is through pharmaceutical "detailing" – a marketing tactic that involves individual pharmaceutical sale representatives (detailers) meeting with doctors in their offices to promote specific medications. "Detailing" is a multi-billion dollar business employing tens of thousands of sales representatives; in fact there is approximately one detailer for every eight doctors in the United States.

The "detailing" process is abetted by information drug companies buy – often without the knowledge or prior consent of doctors – regarding individual prescribing histories. Purchased from retail pharmacies and then aggregated by data processing companies, this information gives "detailers" precise information about what each physician prescribes. Drug companies use this information for direct mail marketing to medical offices and "detailers" use it to specifically target their sales pitches when they meet with doctors.[2]

The use of pharmaceutical "detailing" is on the rise. As the practice becomes more prevalent, it becomes increasingly competitive. Industry sales reps have a harder time keeping a doctor's attention or even getting through the office door. As a way to make friends with office staff and get time with doctors, sales reps

[1] See www.statehealthfacts.org, New York statistics, "state health care expenditures," and "personal health care expenditures."

[2] Saul, S., Doctors Object as Drug Makers Learn Who's Prescribing What, *New York Times,* 5/4/2006.

commonly bring “gifts” and offer meals along with their promotional information and free drug samples.

This report examines the impact that practice of “gift-giving” by pharmaceutical sales representatives has had on the safety and costs of prescription drugs.

FINDINGS:

- The practice of direct marketing to physicians by pharmaceutical companies has increased dramatically and makes up the most significant portion of the industry’s promotional and marketing costs.

- The practice has contributed to high volume sales of drugs that are not only more expensive than therapeutically equivalent older medicines, but too often pose a health threat to patients.

- Internal documents obtained in recent court cases illustrate the tragic consequences of unmonitored and unregulated pharmaceutical companies’ direct marketing to doctors.

RECOMMENDATION:
New York State should make the practice of “detailing” transparent by enacting legislation that requires pharmaceutical companies to publicly disclose their “gift making” practices – including how much they give and to whom.

NOTE:
You will see throughout this report that we put quotations around the word “gift.” The definition of a gift is “something voluntarily transferred by one person to another without compensation.” Yet, drug companies do not deduct the costs of such “gifts” as charity, but as a marketing expense – just a cost of doing business.

THE IMPACTS OF PHARMACEUTICAL COMPANIES' DIRECT MARKETING TO DOCTORS

Background: Prescription Drug Costs Are On The Rise.
There are many factors that contribute to the rising cost of health care in New York today. The rapid rise in prescription drug prices has been a significant variable in driving these increases. According to the Kaiser Family Foundation, "retail prescription prices (which reflect both manufacturer price changes for existing drugs and changes in use to newer, higher-priced drugs) increased an average of 8.3 percent a year between 1994 and 2004 (from an average of $28.67 to $63.59), or more than triple the average annual inflation rate of 2.5 percent."[3]

Impact: Pharmaceutical Companies' Direct Marketing Steers On Doctors' Prescribing Practices.
Unfortunately, inflated prescription prices rarely correlate with meaningful improvements or innovations in drug safety and efficacy. Instead, many of the new drugs introduced to the market offer slight or no therapeutic advantage compared with already marketed alternatives, including less expensive generics.[4] Moreover, these new and costly drugs are explosively introduced by highly trained sales reps with specific marketing strategies designed to steer doctors to prescribe them, instead of older, better understood and less expensive equivalents. There is evidence from published studies that detailing has an immediate and significant impact on doctors' prescribing practices.[5]

The success of industry's marketing strategies in propelling new drugs to almost immediate blockbuster status lies behind an increasing direct-to-physician drug sales force. Just as the number of sales representatives and detailing budget allocations have grown in the past few years, so too have the sales of aggressively marketed drugs. In conjunction with direct marketing to doctors, direct to consumer advertising has helped develop an apparent consumer preference for new drugs, even if there is a lack of demonstrated advantage over existing, better understood products. The manipulation of physician and consumer demand in turn increases expenditures for drugs and has led to a drop in generic drug scripts. According to the Center for Policy Alternatives, "Studies consistently prove that the practice of detailing causes doctors to prescribe the newest drugs, even when overwhelming medical evidence shows that less

[3] Kaiser Family Foundation 'Prescription Drug Trends: November 2005.' See: http://www.kff.org/rxdrugs/3057-04.cfm.
[4] For information regarding the numbers and kinds of drugs approved by the FDA each year, see the Administration website at http://www.fda.gov/cder/rdmt/pstable.htm.
[5] Brennan, T. et al, Health Industry Practices That Create Conflicts of Interest, *Journal of American Medical Association,* Vol.295, No.4, p. 431.

expensive, tried and true remedies would be much cheaper, just as effective, and often safer".[6] *Simply put, if such marketing wasn't working to influence health care providers and increase pharmaceutical profit margins, why would the industry continue to pump money and resources into the practice?*

Impact: The Costs of Pharmaceutical Companies' Direct Marketing to Doctors.

It is difficult to get exact figures on how much the pharmaceutical industry spends on detailing because drug makers choose not to disclose this specific information. In the absence of any requirement to do so, detailing expenses are often grouped in with all other types of marketing and advertising costs. However, between 2001 and 2005, the known costs explicitly used for direct-to-doctors sales activities have risen from $5.5 billion to $$6.8 billion.[7] Given the number of doctors in active practice (which grew from 813,869 in 2000 to 884,975 in 2004[8]), that works out to about $7,700 per doctor.[9] Other sources, like the Journal of American Medical Association, are less frugal in their estimations, claiming, "approximately 90% of the $21 billion marketing budget of the pharmaceutical industry's marketing budget continues to be directed at physicians."[10] Either way these figures are large enough to push a seemingly endless bombardment of lavish gifts, but they might also account for some of the industry's soaring prescription costs.

Impact: Pharmaceutical Companies' Direct Marketing Can Affect Patients' Health.

When physicians listen to the messages delivered by sales reps, and have been the beneficiary of free samples, gifts and others perks, it is not simply a matter for patients' checkbooks. While industry maintains that sales reps help "educate" doctors about important new drug products, the message delivered may not be based on good science. In fact,

> "research suggests that physicians rely heavily on detailers for information and that the more doctors rely on commercial sources of information, the less likely they are to prescribe drugs in a manner consistent with patient

---

[6] Center for Policy Alternatives, Prescription Drug Marketing 2004. see: http://www.stateaction.org/issues/issue.cfm/issue/PrescriptionDrugMarketing.xml.

[7] IMS Health, Total US Professional Promotional Spending by Type, 2005. See: http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_78084568_78152318,00.html.

[8] *American Medical Association,* Physician Characteristics and Distribution in the US, 2006 Edition.

[9] Calculations by authors.

[10] Brennan, T. et al, Health Industry Practices That Create Conflicts of Interest, *Journal of American Medical Association,* 1/25/2006, Vol.295, No.4, p. 430.

needs. Information provided by detailers is often biased, and sometimes dangerously misleading."[11]

According to the Food and Drug Administration, inaccurate statements made by pharmaceutical sales reps in their meetings with doctors were the fourth most common source of false or misleading drug information observed in pharmaceutical marketing.[12] Studies show that many doctors disregard even the most serious safety warnings required on prescriber information by the FDA. When patients taking the diabetes drug Rezulin (marketed by Warner-Lambert Company) started dying from drug-related liver failure in the late 1990s, the FDA repeatedly warned doctors to test patients' liver enzyme levels to spot early signs of trouble. Unfortunately, fewer than 5% of patients got the tests, and even more patients died.[13]

Warner-Lambert also over-promoted the anti-epilepsy drug, Neurontin. While the FDA had typically approved Neurontin for treating only one specific condition, company sales reps were encouraging doctors use the drug "off label" and prescribe it for conditions for which it had not approved. According to one doctor's testimony, a Warner-Lambert marketing executive had gone so far as to suggest "Neurontin for pain, Neurontin for monotherapy, Neurontin for bipolar, Neurontin for everything."[14] Although off label prescribing by doctors is not regulated by the FDA, the agency prohibits the promotion of off-label use by industry. Despite the fact that off-label promotion is not permitted, the company paid doctors to keep on prescribing off-label and "act as a surrogate sales force for the company."[15] By May 2004, Pfizer – which had taken over Warner-Lambert – pled guilty to Medicaid fraud and paid $430 million in fines.[16]

---

[11] Katz, D., Caplan, A., Merz, J., All Gifts Large and Small, *The MIT Press,* Summer 2003, Vol. #, No. 3, p. 40.

[12] FDA Warning and Untitled Letters from 2001-2005, posted at http://www.fda.gov/foi/warning.htm. Analysis by CalPIRG Education Fund, see Turning Medicine Into Snake Oil: How Pharmaceutical Marketers Put Patients At Risk, May 2006.

[13] Carey, J., Barrett, A., Cropper, C., Lessons From the Vioxx Fiasco, *Business Week*, 11/20/2004

[14] Petersen, M., Whistle-Blower Says Marketers Broke the Rules to Push A Drug, *The New York Times,* 3/142002; C1.

[15] Petersen, M., Court papers suggest scale of drug's use: Lawsuit says doctors were paid endorsers, *New York Times,* 5/30/2003; C1.

[16] "Pfizer Settles Neurontin Medicaid Fraud Case for $430 Million." KaiserNetwork.Org. 5/13/2004. See: http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=23702.

HOW PHARMACEUTICAL COMPANIES TRAIN THEIR SALES STAFF
A CASE STUDY: MARKETING VIOXX

Merck trained its sales representatives to view doctors' concerns about Vioxx's safety (causing heart attacks and stroke) "obstacles" to be avoided or dismissed. One internal marketing document obtained through legal action reveals how sales representatives were taught to play "Dodgeball" when doctors voiced concerns. In their training, sales reps were shown a series of "Dodgeball" slides and were prepped on how to respond. Below is one of those slides dealing with cardiac concerns about Vioxx:

In a training video, "an actress playing "an obstacle" to a Vioxx sales says, 'I'm afraid Vioxx causes M.I.'s' – a reference to myocardial infractions, or heart attacks. In response, an actress playing a Merck sales representative says, 'That's not true.'"[17]

Merck's marketing of Vioxx eventually came under fire from the FDA. In a "Warning letter" in September of 2001, the FDA criticized Merck's marketing stating "the Division of Drug Marketing, Advertising, and Communications

[17] Berenson, A., In Training Video, Merck Said Vioxx Did Not Increase Risk of Heart Attack, *New York Times,* 7/21/2005.

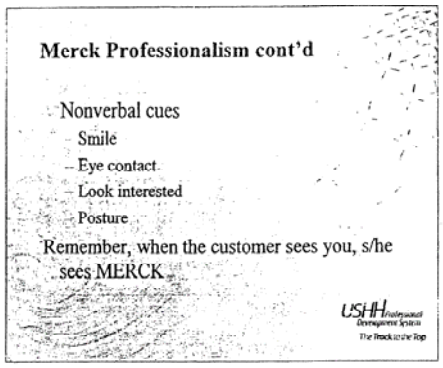
(DDMAC) has reviewed your promotional activities and materials and has concluded that they are false, lacking in fair balance, or otherwise misleading."[18]

The letter went on to state "Additionally, your claim in a press release that Vioxx has a 'favorable cardiovascular safety profile,' is simply incomprehensible, given the rate of MI and serious cardiovascular events compared to naproxen."[19]

The game of dodgeball went on during a period when researchers (including some at Merck) were becoming increasingly convinced that Vioxx, and its siblings, Bextra and Celebrex, had significant safety problems. According to a member of the FDA's Office of Drug Safety who testified at a Senate hearing:

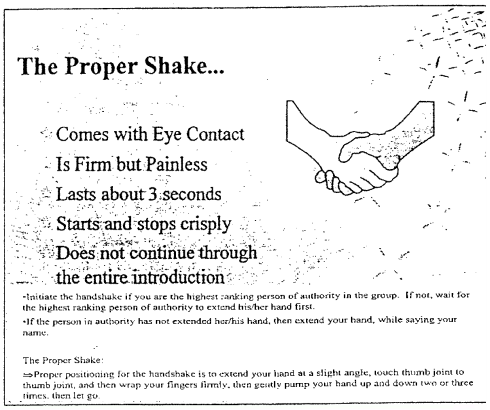
> "Among many things, this report estimated that nearly 28,000 excess cases of heart attack or sudden cardiac death was caused by Vioxx. I emphasize to the Committee that this is an extremely conservative estimate. *If a more realistic analysis was used, the range of heart attacks "ranges from 88,000 to 139,000. Of these, 30-40% probably died*."[20] [Emphasis added]

Not only were sales reps trained on how best to counter physicians' concerns, internal documents also show well they were trained in "people" skills.



4. Nonverbal cues - are just as important for professional presence. Make eye contact with the person your talking to; smile and look interested like you belong there to provide value added service

[18] See US Department of Health and Human Services, letter to Merck from the FDA, 9/17/2001. (see appendix)
[19] See US Department of Health and Human Services, letter to Merck from the FDA, 9/17/2001.
[20] Testimony of David Graham, MD, MPH, before the U.S. Senate Finance Committee, 11/18/2004. The testimony can be obtained at: http://www.saferdrugsnow.org/documents/vio/111804dgtest.pdf.



The point of this training? To create a positive impression on the doctor and to promote sales.

PHARMACEUTICAL COMPANIES' EFFORTS TO INFLUENCE DOCTORS' PRESCRIPTIONS

Strategies to Influence Doctors – The Rapid Increase In The Number Of Drug Companies' Sales Representatives.

Between 2001 and 2004, the number of pharmaceutical reps in the United States for the 40 largest companies grew from 81,588 to 101,531.[21] In 2004, there were roughly 884,000 doctors licensed in the nation.[22] That means there was at least 1 sales rep for every eight doctors. As these numbers have increased, the growing competition has resulted in the pharmaceutical industry pushing their products ever more aggressively. One example of this trend is most easily seen in the operation of pharmaceutical giant Pfizer, whose 38,000 (9,421 in the US alone[23]) sales reps ("roughly the size of three army divisions") "fan out around the globe… to make Pfizer drugs the treatment of choice."[24]

In order to make the most of their time with doctors, pharmaceutical sales reps employ a number of strategies to influence doctors to use their products. As various drug companies increase their sales fleets and storm hospitals and doctors offices, these tactics became all the more cutthroat. Thus, as competing marketing representatives congregate in certain areas and jockey for position, "sales territories are now as small as a single ZIP code."[25]

Strategies to Influence Doctors – Purchasing Doctors' Prescribing Patterns from Pharmacies.

These territories have been carefully selected and the doctors' prescribing practices have been well researched. By utilizing prescriber reports (weekly lists compiled of all prescriptions written and their respective prescribing doctors) from pharmacies, detailers are able to strategize whom they target and what they're selling.[26] One sales rep justifies the use of prescriber reports only "if I'm close to getting a bonus… [then] I can go to the doctors who I have a good relationship with… and ask them to write six prescriptions to get me there."[27]

---

[21] Arnold, M., Flexible Forces, *Medical Marketing & Media*, November 2005.
[22] *American Medical Association,* Physician Characteristics and Distribution in the US, 2006 Edition.
[23] *Ibid* at 22.
[24] Barrett, A., Pfizer's Funk, *Business Week*, 2/28/2005: Cover Story.
[25] Hensley, S., Side Effects: As Drug-Sales Teams Multiply, Doctors Start To Tune Them Out, *The Wall Street Journal,* 6/13/2003: A.1.
[26] Brownlee, S, Lenzer, J., Spin Doctored, Slate.com see: http://www.slate.com/id/2119712.
[27] Strout, E. Doctoring Sales, *Sales and Marketing Management*, May 2001: pgs. 52-60.

Strategies to Influence Doctors – Hiring Attractive Sales Reps.
Additionally, the new trend of hiring college cheer leaders as drug reps further calls the 'information only' argument into question. Indeed, "anyone who has seen the parade of sales representatives through a doctor's waiting room has probably noticed that they are frequently female and invariably good looking… less recognized is the fact that a good many are recruited from the cheerleading ranks."[28] But whether those making the rounds are cheerleaders or average Janes and Joes, drug reps continue to be a ubiquitous presence wherever health care providers are.

Strategies to Influence Doctors – "Gift-giving."
The drug companies have contracted with many hundreds of doctors to serve on their advisory boards or to serve on speakers bureaus for which they are well compensated. Offering the Continuing Medical Education (CME) which physicians are required to earn for their speciality certification at no cost is another powerful incentive. Payment for attending "scientific" meetings, payments for travel to attend such meetings or scholarships, provision of pharmaceutical samples, grants for research projects, and payment for consulting services round out the grab bag of gifts that industry has available to lavish on compliant doctors.[29]

The US Department of Health and Human Services Office of Inspector General found that nearly all doctors accept small "gifts" from drug salespeople.[30] The large majority of doctors meet with industry detailers several times a month, and many doctors cite these "gifts" as the sole or among the top reasons for seeing the drug detailers.[31]

"Show Me The Money" – Doctors Game The System Too.
Drug company giant Merck felt it had to "neutralize" physician concern about its pain reliever Vioxx. As revealed through court documents, in a 1999 dinner, "a Merck executive asked Dr. Altman, a Florida physician, what it would take to win his support, the doctor recalled. Dr. Altman said he told the executive that he wanted to run a clinical trial involving Vioxx, and, later, Merck put $25,000 for it. 'Show me the money,' appeared on an internal document near Dr. Altman's

[28] Saul, S., Gimme an Rx! Cheerleaders Pep Up Drug Sales, *The New York Times* 11/28/2005. A:1.
[29] Brennan, T. et al, Health Industry Practices That Create Conflicts of Interest, *Journal of American Medical Association,* Vol.295, No.4, p. 430.
[30] Katz, D., Caplan, A., Merz, J., All Gifts Large and Small, *The MIT Press,* Summer 2003, Vol. #, No. 3, p. 40.
[31] Katz, D., Caplan, A., Merz, J., All Gifts Large and Small, *The MIT Press,* Summer 2003, Vol. #, No. 3, p. 40.

name."[32] *[See attached internal document showing this quote and other efforts to monitor doctors' practices.]*

But the "gift" game is also a two way street. Doctors use the competition between drugs makers to their own personal advantage. In the competition between Celebrex and Vioxx, one Long Island, New York physician worked it to his own advantage.
According to internal documents, a review of this physician reported:

> "At the time, Dr. Hamburger was approaching drug companies to subsidize retreats for his group during which physicians would put together guidelines on what drugs to prescribe. 'Companies that provide funding will receive preferred status with its members and those that do not will have trouble accessing' the group, the Merck [internal] memo stated. 'Price tag is $25,000.'"[33]

[32] Meier, B., Saul, S., Marketing of Vioxx: How Merck Played Game of Catch-Up, *New York Times,* 2/1//2005.
[33] *Ibid*.

WHAT SHOULD BE DONE

The most obvious response should be to prohibit such "gifts" from detailers. However, as a first step policymakers should demand more public accountability of this practice by requiring reporting of such "gifts" – not only which companies offered the "gifts," but also which health care providers accepted them.

Four states – Vermont, Minnesota, West Virginia and Maine – have laws requiring "gift" reporting by drugmakers. California requires that drugmakers declare they are compliant with federal and industry "gift" guidelines.[34]

In New York, there are currently matching bills in the Senate (S.696-D) and the Assembly (A.5574-D) which call for the disclosure of gifts (over $75) by pharmaceutical companies to health care providers. The bill stipulates that the health commissioner must create a yearly report based on the submissions and information received from drug companies in New York. The bill also includes the following provisions:

- The information shall be compiled and must be made available free of charge, in both paper copy and on the Internet, to the public.
- The commissioner has the right to impose civil penalties of up to $3,000 if drug companies improperly file reports or fail to file completely.
- Exceptions to disclosure include: Payment for clinical trials; Support and/or scholarships for medical students; Grants for continuing education programs; and, prescription drug rebates and discounts.

[34] Appleby, J, States want info about drugmakers' gifts to doctors. *USA Today,* 2/16/2006.

OPPONENTS' ARGUMENTS AGAINST REFORM

Drug Companies' Argument – Disclosure Will Drive Up Costs By Requiring Burdensome Reporting.

One of the key points of opposition to disclosure legislation is that disclosure will raise costs for pharmaceutical companies, as well as the government, and, ultimately, the consumer. An excerpt from the pharmaceutical trade association opposition memo reads (page 2), "this bill would add to the cost of prescription drugs (the prodigious costs of accounting compliance) by creating a reporting nightmare affecting prescribers and patients."[35] *[See full memorandum attached.]*

Response – The Companies Already Keep Close Track of Their Gift-giving Practices, There Should Be No Cost Impact.

However, as seen through evidence in internal documents, drug companies already keep explicit records of their direct-to-doctor marketing expenditures and experiences, making the "reporting nightmare" argument a moot point *[See attached document].* Since it is clear that the information required to be disclosed already exists, the only cost would be having the information published and posted on the Internet.

Drug Companies' Argument – The State Should Rely on The Federal Government To Protect The Public.

Response – History Shows Such Reliance Would Be Misplaced.

Meanwhile those who argue that the federal government's oversight is sufficient to protect the public should heed the words of a key FDA staffer: *"After the Food and Drug Administration insisted for months that it did nothing wrong in its oversight of Vioxx, a top agency official acknowledged 'lapses' in the agency's actions"* when she testified before a Senate panel last March.[36] In addition, the FDA has no authority to oversee marketing – other than to review the materials provided about a drug for scientific accuracy and fairness.

Drug Companies' Argument – Look At Other More Important Problems.

Response – The Problems of "Gift-giving" By Pharmaceutical Companies Is A Problem All By Itself.

PhRMA spends nearly three pages of its memo stressing the need for attention (and disclosure) to be refocused on "those who would seek to reduce patient choice through restrictive formularies" (page 1). Namely, pharmacy benefit managers (PBMs) should be scrutinized and required to disclose information of

[35] Hinman, Straub memorandum on behalf of PhRMA is in appendix.
[36] Harris, G., F.D.A. Official Admits 'Lapses' on Vioxx, *New York Times,* 3/2/2005.

their own. While no one would dispute this suggestion (indeed our organizations support legislation requiring just such scrutiny), it has nothing to do with the problem at hand. The practice of "gift-giving" from pharmaceutical companies to doctors creates unique problems which impact on safety and cost. These problems are best resolved, at least initially, through public accountability.

Drug Companies' Argument – Disclosure Will Lead to "Rationing Patient Choices In Regard To Prescription Drugs" (see page 3).

Response – This Argument Is Absurd. Given The Costs – Both Economic and Moral – Justify Greater Public Oversight.

Making public the information on drug marketing expenditures will empower patients and their doctors to make better informed decisions about the use and prescription of drugs. The pharmaceutical industry argues that reporting marketing expenses is really "rationing patient choices in regard to prescription drugs." Patients should have the right to know how much money drug companies spend to persuade physicians to prescribe high cost brand name medicines instead of equally effective, and lower cost alternatives.

Drug Companies' Argument – Disclosure Will Create An Accounting Nightmare And Thus The Practice of Offering Free Samples Might Be Discouraged (see page 2).

Response – This Argument Seems Designed To Scare Policymakers. Internal Documents Make It Clear That The Industry Already Extensively Monitors It "Gifting" Practices. Offering Free Samples Would Likely Put Drug Companies In a Good Public Light. Therefore Disclosure of Free Sampling Practices Could Benefit The Companies.

Since the drug industry defends free samples as charity for humane purposes – reporting would document their generosity for all to see. Lastly PhRMA's threat that passage of this bill would result in the loss of needed patient access to free samples is the sort of "fear mongering" that should have no place in Albany.

CONTENT AND INADEQUACIES OF EXISTING INDUSTRY CODES AND VOLUNTARY GUIDELINES

The problems caused by pharmaceutical detailing have not gone unnoticed by regulators, doctors, consumers and the pharmaceutical industry itself. To address the concerns raised by various stakeholder groups, a number of voluntary guidelines have been developed.

American Medical Association (AMA) Guidelines

On December 4, 1990, in response to growing concern both inside and outside the medical community about the appropriateness of gifts from industry, the American Medical Association adopted a set of guidelines to help doctors determine appropriate limits for gifts and other industry supported programs. Two days later, the Pharmaceutical Manufacturer's Association (PMA), a predecessor of today's Pharmaceutical Research and Manufacturers of America (PhRMA), adopted the same voluntary guidelines.

The document consists of a number of guidelines that physicians should consider before accepting a gift, grant, subsidy or any other inducement from an industry representative. The recommendations advise physicians to avoid accepting any gift that is of substantial value or that does not entail a value for patients. They recommend that doctors only attend meetings and conferences where the primary purpose of the event and incentive for attending is the furtherance of medical knowledge. The guidelines also advise doctors against accepting any gift that is given conditionally.[37]

In 2001, as part of a campaign to remind doctors about the existence of the guidelines and to encourage compliance with them, the AMA published updated recommendations with a number of clarifications.[38]

Pharmaceutical Research and Manufacturers of America (PhRMA) Code

In response to heavy legislative and public scrutiny culminating in an $875 million settlement against TAP pharmaceuticals regarding its marketing practices, PhRMA (an industry trade group and the successor to PMA) adopted a new code of conduct in July 2002. The preamble to the code openly acknowledges the industry's desire to limit the negative public reaction to gift giving. It states that "[w]e are also concerned that our interactions with healthcare professionals not be perceived as inappropriate by patients or the public at large."[39]

---

[37] The original guidelines with updated recommendations can be found at: http://www.ama-assn.org/ama/pub/category/1904.html.

[38] *Ibid*.

[39] The text of the PhRMA code can be found at http://www.phrma.org/files/PhRMA%20Code.pdf.

The PhRMA "Code on Interactions with Healthcare Professionals" lays out recommendations for many of the same situations addressed in the 1990 AMA guidelines. In addition to outlining advisable conditions for continuing medical education conferences and consulting agreements, the code recommends a few more specific limitations. It suggests that meals be only occasional and of modest value and that meetings no longer take place during entertainment and sporting events. The code advises that gifts only be offered occasionally, that they primarily entail a benefit to the patient and that no single gift exceeds $100 in value. It further states that cash and gifts intended for the personal use of a physician should no longer be offered. The code concludes with some clarifications as well as an admonition that "[e]ach member company is strongly encouraged to adopt procedures to assure adherence to this Code."[40]

Office of Inspector General (OIG) Guidance

In April 2003, to address concerns about abuses in federal healthcare programs, the Office of Inspector General of the U.S. Department of Health and Human Services issued a document entitled "Compliance Program Guidance for Pharmaceutical Manufacturers."[41] The OIG guide gives pharmaceutical manufacturers recommendations for establishing a program to ensure compliance with applicable statutes, regulations, and requirements of federal healthcare programs.

With regard to pharmaceutical marketing and detailing, the OIG report recommends that pharmaceutical companies carefully scrutinize certain types of relationships and promotional practices in order to avoid liability under existing federal law. The primary law addressed by the guidance is the federal anti-kickback statute (42 USC § 1320a-7b(b)).[42] The anti-kickback statute "is a criminal prohibition against payments (in any form, whether the payments are direct or indirect) made purposefully to induce or reward the referral or generation of federal health care business."[43] The statute and the guidance both deal exclusively protecting with public healthcare programs, including Medicaid and Medicare, from unscrupulous marketing and purchasing behaviors.

---

[40] *Ibid*.

[41] Office of Inspector General, "Compliance Program Guidance for Pharmaceutical Manufacturers," April 2003. see: http://oig.hhs.gov/fraud/docs/complianceguidance/042803pharmacymfgnonfr.pdf.

[42] Text of the anti-kickback statute is accessible at http://www4.law.cornell.edu/uscode/42/1320a-7b.html.

[43] Office of Inspector General, "Compliance Program Guidance for Pharmaceutical Manufacturers," April 2003, p.13. see: http://oig.hhs.gov/fraud/docs/complianceguidance/042803pharmacymfgnonfr.pdf.

Inadequacy – The Guidelines Are Too Limited and Vague.
There are significant shortcomings in the regulation of pharmaceutical detailing. The OIG guidance, while essential to safeguarding the integrity of federal healthcare purchases, is extremely narrow in scope. Neither the guidance nor the anti-kickback statute addresses two key aspects of pharmaceutical detailing. First, the federal statute has no provisions regulating detailer interactions with healthcare providers who have no connection to public health care business. Second, the anti-kickback statute does not address the offer, acceptance or reporting of any gift or other remuneration not intended to solicit or reward government contracts, regardless of the relationship between the recipient and the federal government. Thus, the OIG guidance or the anti-kickback statute does not regulate the everyday interactions between most physicians and detailers.

The AMA and PhRMA guidelines suffer from both their vagueness and their lack of enforcement mechanisms. While the revised AMA guidelines and the PhRMA code do recommend a few specific guidelines ($100 upper limit for gifts), they remain ambiguous in many areas. Suggestions that only "occasional meals" of "modest" value should be offered and that gifts "should not be offered on more than an occasional basis" are largely subjective and open to a tremendous degree of abuse. In an interview with the *Washington Post*, a pharmaceutical company spokesman admitted that the AMA guidelines "are not specific enough to be a practical guide for everyday practice in our industry."[44]

Inadequacy – The Guidelines Lack An Enforcer.
Because the guidelines are voluntary, they are essentially unmonitored and unenforceable.. The TAP Pharmaceuticals settlement and the fact that PhRMA was forced to issue a new code of conduct in 2002 reveal the failings of a voluntary system. TAP's marketing violations were not prevented by the code and were actionable only because they involved federal healthcare programs. PhRMA's new guidelines, while commendable, are a tacit admission of the failure of the first PMA code and still contain no legally binding enforcement mechanisms.

The Result – These Recommendations Are Useless.
The voluntary nature of the guidelines can also create a business quandary for manufacturers. If following the guidelines would put a company at a competitive disadvantage with a company that disregards the rules, the first company has little choice but to ignore the guidelines as well. As a former detailer posed the problem,

[44] Brubaker, B., Drug Firms Still Lavish Pricey Gifts on Doctors, *The Washington Post*, 1/19/2002.

> "Here you are, working for a company that wants to abide by the guidelines, and you can't compete with a guy who's giving away tickets."[45]

With no punitive mechanism for those who violate the recommendations, "gift giving" can escalate into an arms race with neither side willing to unilaterally disarm. A more uniform and enforceable standard for appropriate interactions would level the playing field for all companies.

[45] Ellen, E., Visits from Pharmaceutical Reps, *Psychiatric Times,* Volume XVIII, Issue 1, January 2001.

SECTION-BY-SECTION SUMMARY OF REFORM LEGISLATION S.696-D/A.5574-D

1. Reporting Requirements:
All pharmaceutical companies (manufacturers and wholesalers) that make at least one gift in excess of $75 (e.g. money, services, loans, travel, entertainment, hospitality) to health care providers will be required to report and file such gifts with the commissioner of the Department of Health for an annual report. Filing shall be done by June 1st of each year, beginning in 2008.

2. Annual Report:
The DOH shall issue a report containing the following:

A. The name, address, and telephone number of the pharmaceutical company.
B. An itemized, detailed listing of all gifts made by the companies and the name, address, and telephone number of the health care provider who received the gift(s).
C. The monetary value of each gift.
D. Any other information deemed necessary by the commissioner of the DOH.

By September first of each year (beginning in 2008), the commissioner shall publish and make available to the public, free of charge, a consumer guide on pharmaceutical gifting practices to health care providers. The guide will be made available on the Internet and in paper form, and shall be distributed throughout the state, at various county offices (e.g., education, aging, etc.).

3. Exemptions:
The following are exempt from disclosure:

A. Payments and/ or reimbursements for genuine clinical trials.
B. Gifts valued at or under $75.
C. Scholarships and/or support for medical students to attend educational, scientific, or policy-oriented conference.
D. Unrestricted grants for continuing education programs.
E. Prescription drug rebates and discounts.

4. Penalties:
For failure to report timely reports the commissioner may impose a fine of $50 a day until the report it filed or $3,000, whichever is less. The commissioner may also impose fines of no more than $3,000 to any person who violates other provisions of this bill.

THIS PAGE LEFT INTENTIONALLY BLANK

APPENDIX:

The following letter is from the FDA to Merck complaining about the promotional activities and materials for their Vioxx campaign. On page 7 of the memo, the FDA specifically criticizes Merck's sales representatives for having engaged in *"false or misleading promotional activities that also minimize the potentially serious MI results."* This conclusion stands in stark contrast to the "Dodgeball" training of sales reps.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

a1751d

TRANSMITTED BY FACSIMILE

Raymond V. Gilmartin
President and CEO
Merck & Co., Inc.
P.O. Box 1000, UG3BC-10
North Wales, PA 19454-1099

SEP 17 2001

RE: NDA 21-042
Vioxx (rofecoxib) tablets
MACMIS ID # 9456

WARNING LETTER

Dear Mr. Gilmartin:

This Warning Letter concerns Merck & Co. Inc.'s (Merck) promotional activities and materials for the marketing of Vioxx (rofecoxib) tablets. Specifically, we refer to promotional audio conferences given on behalf of Merck by Peter Holt, MD, a press release, and oral representations made by Merck sales representatives to promote Vioxx. As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed your promotional activities and materials and has concluded that they are false, lacking in fair balance, or otherwise misleading in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and applicable regulations. See 21 U.S.C. §§ 331(a) and (b), 352(a), (f), and (n), and 355 (a).

You have engaged in a promotional campaign for Vioxx that minimizes the potentially serious cardiovascular findings that were observed in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, and thus, misrepresents the safety profile for Vioxx. Specifically, your promotional campaign discounts the fact that in the VIGOR study, patients on Vioxx were observed to have a four to five fold increase in myocardial infarctions (MIs) compared to patients on the comparator non-steroidal anti-inflammatory drug (NSAID), Naprosyn (naproxen).

Although the exact reason for the increased rate of MIs observed in the Vioxx treatment group is unknown, your promotional campaign selectively presents the following hypothetical explanation for the observed increase in MIs. You assert that Vioxx does not increase the risk of MIs and that the VIGOR finding is consistent with naproxen's ability to block platelet aggregation like aspirin. That is a possible explanation, but you fail to disclose that your explanation is hypothetical, has not been demonstrated by substantial evidence, and that there is another reasonable explanation, that Vioxx may have pro-thrombotic properties.

You have also engaged in promotional activities that minimize the Vioxx / Coumadin (warfarin) drug interaction, omit important risk information, make unsubstantiated superiority claims against other NSAIDs, and promote Vioxx for unapproved uses and an unapproved dosing regimen. In addition, in misrepresenting the Vioxx / warfarin drug interaction you also misrepresent Vioxx's safety profile by minimizing the potentially serious risk of significant bleeding that can result from using Vioxx and warfarin concomitantly.

Your minimizing these potential risks and misrepresenting the safety profile for Vioxx raise significant public health and safety concerns. Your misrepresentation of the safety profile for Vioxx is particularly troublesome because we have previously, in an untitled letter, objected to promotional materials for Vioxx that also misrepresented Vioxx's safety profile.

Background

Vioxx is a NSAID with selective cyclooxygenase 2 (COX-2) inhibitory properties. It was approved on May 20, 1999, for the treatment of primary dysmenorrhea, for the management of acute pain in adults, and for relief of the signs and symptoms of osteoarthritis.

Prior to approval, endoscopy studies were submitted to the original NDA database demonstrating that treatment with Vioxx 25 mg or 50 mg daily was associated with a significantly lower percentage of endoscopically apparent gastroduodenal ulcers than treatment with ibuprofen 2400 mg daily. Because the correlation between findings of endoscopic studies and the relative incidence of clinically serious upper gastrointestinal (GI) events was unknown, after approval, Merck sponsored the VIGOR study to obtain information regarding clinically meaningful upper GI events and to develop a large controlled database for overall safety assessment.

The VIGOR study included approximately 4000 patients per treatment arm (Vioxx 50 mg a day or naproxen 1000 mg a day) treated for a median time of 9 months. The primary endpoint of the study was the relative risk of confirmed PUBs (perforations, symptomatic ulcers, and GI bleeds) in patients with rheumatoid arthritis taking Vioxx 50 mg daily (two to four times the approved dosing regimen for Vioxx in osteoarthritis), compared to patients taking naproxen, 1000 mg daily. The study also compared the safety and tolerability of the two treatments in patients with rheumatoid arthritis. The results of the study demonstrated that patients on Vioxx had a significantly lower cumulative incidence of PUB's compared to patients on naproxen (2.08% and 4.49% for Vioxx and naproxen, respectively).

Other important results from the VIGOR study included the unexpected findings that investigator reported serious cardiovascular events occurred in 101 patients (2.5%) in the Vioxx treatment group compared to 46 patients (1.1 %) in the naproxen treatment group, and MIs occurred in 20 patients among 4047 in the Vioxx treatment group (0.5%), compared to four patients among 4029 in the naproxen treatment group (0.1%). These unexpected findings were extensively discussed at the FDA Arthritis Advisory Committee Meeting on February 8, 2001. Although, the reason for these differences is not clear, possible explanations include both an ability of naproxen to function as a cardioprotective agent and a pro-thrombotic property of Vioxx.

Promotional Audio Conferences

We are aware of six promotional audio conferences, presented on behalf of Merck by Peter Holt, MD that are in violation of the Act and its implementing regulations. These audio conferences were held on June 8, 2000, June 13, 2000, June 16, 2000, and three on June 21, 2000, and were moderated by Merck employees.

On December 12, 2000, we sent you a written inquiry about your involvement with and influence on the initiation, preparation, development, and publication of audio conferences given by Dr. Holt. We also asked you to describe the nature of the relationship between you and Dr. Holt. In your response dated January 5, 2001, you stated that, "Dr. Holt entered into a speaker contract with Merck on June 22, 1999." You also stated that, "Merck has determined that we arranged for Dr. Holt to speak at ten audio conferences in 2000. Merck Business Managers provided him with the topic for the audio conferences and, for two of the audio conferences, asked him to address the safety profiles of Vioxx and other NSAIDs."

The promotional audio conferences identified above, arranged by, and presented on behalf of, Merck were false or misleading in that they minimized the MI results of the VIGOR study, minimized the Vioxx / Coumadin drug interaction, omitted important risk information, made unsubstantiated superiority claims, and promoted Vioxx for unapproved uses and an unapproved dosing regimen. Our specific objections follow.

Minimization of MI Results

Statements made during the promotional audio conferences identified above minimize the potentially serious MI risk that may be associated with Vioxx therapy. For example, in your June 21, 2000, audio conference you begin your discussion of the MI rates observed in the VIGOR study by stating, "When you looked at the MI rate the rate was different for the two groups. The MI rate for Vioxx was 0.4 percent and if you looked at the Naprosyn arm it was 0.1 percent, so there was a reduction in MIs in the Naprosyn group." You then present your explanation as to why the Vioxx treatment arm had an increased rate of MIs compared to the naproxen treatment arm. Specifically, you state that,

> Vioxx is a wonderful, effective, selective COX-2 inhibitor that inhibits COX-2 but at the doses used does not inhibit COX-1. So therefore without the COX-1 inhibition you don't inhibit platelets, you don't prolong bleeding time and therefore it cannot be used as a cardiovascular protective drug. Naprosyn on the other hand is a wonderful platelet inhibitor, prolongs bleeding time and inhibits platelets identically to aspirin. Obviously the binding with Naprosyn is reversible and with aspirin is irreversible, but the effect on platelets and bleeding time is identical in terms of its effect and therefore functions as a wonderful drug for cardiovascular prophylaxis. So basically the MI rates are in sync with what we know about Vioxx and what we know about Naprosyn.

In fact, the situation is not at all clear. There are no adequate and well-controlled studies of naproxen that support your assertion that naproxen's transient inhibition of platelet aggregation is pharmocodynamically comparable to aspirin or clinically effective in decreasing the risk of MIs. Therefore, your representation that naproxen prolongs bleeding time and inhibits platelets identically to aspirin is misleading, and minimizes the potential seriousness of this finding. As you know, the

reason for the difference between Vioxx and naproxen has not been determined; it is also possible that Vioxx has pro-thrombotic properties. Also, the MI rate that you report for Vioxx is inaccurate; the MI rate for Vioxx in the VIGOR study was 20 MIs among 4047 patients (0.5%), not 0.4%, as you stated.

Your minimization of the seriousness of the MI rates observed in the Vioxx treatment arm of the VIGOR trial is further reinforced in your audio conferences by your discussion of a retrospective analysis of this trial. For example, in your June 21, 2000, audio conference, you state that,

> ...Merck went and pulled out those patients that again were enrolled in VIGOR and asked the question, who were those patients that really needed secondary cardiovascular prophylaxis from the get go, and that ended up being four percent of the study group in VIGOR based on whether there was a prior MI, stroke, TIA, angina, CABG or PTCA....Now if you look at the remaining part of VIGOR, which is 96 percent of the VIGOR population, and once again looked for the MI rate between Naprosyn and Vioxx, there's no statistically significant difference in the MI rate between Naprosyn and Vioxx. In fact, Naprosyn is 0.2 percent and Vioxx is 0.1 percent.

Your claim that the MI rate for naproxen was 0.2 percent and for Vioxx was 0.1 percent is again inaccurate. Contrary to your claim that there was a higher rate of MIs in the naproxen group compared to the Vioxx group, the MI rate for Vioxx in this subpopulation was 12 MIs among 3877 patients (0.3%) as compared to 4 MIs among 3878 patients (0.1%) for naproxen.

Moreover, you again minimize the Vioxx MI rate observed in the VIGOR study by your comparison of this rate to the rate of MIs observed for Celebrex (celecoxib) in the Celebrex Long-Term Arthritis Safety Study (CLASS). For example, in your June 21, 2000, audio conference you state, "Now if you remember the crude MI rate of Vioxx in VIGOR that number was 0.4 percent which is basically the same or in fact a little bit less then the crude MI rate of Celebrex in CLASS which is 0.5 percent." Your claim that the MI rates of Vioxx compared to Celebrex were basically the same, "or in fact a little bit less" is misleading. You are comparing MI rates from two different trials with different patient populations. For example, patients who had angina or congestive heart failure with symptoms that occurred at rest or minimal activity and patients taking aspirin, including low-dose (325 mg or less, daily or every other day) or other antiplatelet agents (e.g., ticlopidine) were excluded from the VIGOR trial. The CLASS trial in contrast, did not exclude patients of this type. The CLASS trial thus may have included patients at a higher risk for MIs.

Minimization of Vioxx / Coumadin Interaction

Statements made during your promotional audio conferences also minimize the risk of Vioxx therapy in patients who are taking warfarin. For example, in your June 16, 2000, audio conference you stated that, "...if you look at the thromboembolic events it's very clear that these selective COX-2 inhibitors have the benefit of not having platelet aggregation and bleeding time, and therefore, can be used safely in terms of post-op and with Coumadin." Your statement that Vioxx can be used safely with warfarin minimizes the precaution in the PI that states that "...in post-marketing experience, bleeding events have been reported, predominately in the elderly, in association with increases in prothrombin time in patients receiving Vioxx concurrently with warfarin." Your promotion minimizing the risk of using Vioxx and warfarin concurrently is particularly troublesome because Merck was aware of this potentially dangerous drug interaction in 1999, well before these audio conferences occurred. In fact,

Merck began disseminating a revised PI in October 1999, which included new information about this risk.

The seriousness of this interaction is further minimized by your suggestion that COX-2 inhibitors, including Vioxx, can be used safely with warfarin because it "has the benefit of not having platelet aggregation and bleeding time." This claim implies that Vioxx is safer than other NSAIDS used in combination with warfarin. However, Vioxx has not been studied in head-to-head trials prospectively designed to assess this specific endpoint. Your superiority claim is therefore misleading.

We note that earlier in your June 16, 2000, promotional audio conference you state, "It can be used in people with Coumadin, although with Coumadin you've got to check their INR three and four days after you add the Cox inhibitor to the Coumadin because there may be a bump in the INR." This disclosure does not correct the overall misleading message, however, nor does it correct your suggestion that Vioxx is safer than other NSAIDs in patients taking warfarin.

Omission of Important Risk Information

Your promotional audio conferences fail to present serious and significant risks associated with Vioxx therapy. For example, your promotional audio conferences fail to state that Vioxx is contraindicated in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. You also fail to present the gastrointestinal (GI) warning about the possibility of serious GI toxicity such as bleeding, ulceration, or perforation in patients taking Vioxx. Moreover, you fail to present Vioxx's precautions for use in patients who have liver and kidney disease, information about patient populations in which Vioxx's use is not recommended, such as women in late pregnancy, and information about Vioxx's most common adverse events.

Unsubstantiated Superiority Claims

You make several unsubstantiated superiority claims for Vioxx throughout your promotional audio conferences. For example, in your June 16, 2000, audio conference, you claim that, "The importance of [VIGOR and CLASS] is that the data is going to really help change I believe the package inserts for [Vioxx and Celebrex] down the road because it really shows once again that they are safer than non-steroidals." Your suggestion that COX-2 inhibitors, including Vioxx, have an overall safety profile that is superior to other NSAIDs is misleading because such an advantage has not been demonstrated. In fact, in the VIGOR study the incidence of serious adverse events was **higher** in the Vioxx treatment group than in the naproxen treatment group (9.3% and 7.8% for Vioxx and naproxen, respectively). The results of safety analyses that were pre-specified in the protocol for the VIGOR trial, such as CHF-related adverse events and discontinuations due to edema-related adverse events, hepatic-related adverse events, hypertension-related adverse events, and renal-related adverse events were all numerically higher (in some cases statistically significantly higher) in the Vioxx treatment group than in the naproxen treatment group. Furthermore, your claim that the VIGOR and CLASS trials "show once again that they are safer than non-steroidals" is also misleading because it implies that the results of the VIGOR trial (i.e., patients on Vioxx had a significantly lower cumulative incidence of PUBs than patients on naproxen) can be applied to the entire class of NSAIDs.

In your June 16, 2000, audio conference you state, "...if you look at the thromboembolic events it's very clear that these selective COX-2 inhibitors have the benefit of not having platelet aggregation and

bleeding time, and therefore, can be used safely in terms of post-op and with Coumadin." This claim suggests that Vioxx is safer, or has fewer side effects, than other NSAIDs used in the post-operative setting because COX-2 inhibitors do not affect platelet aggregation and bleeding time. Vioxx has not been studied, however, in head-to-head trials prospectively designed to assess its safety compared to other NSAIDS in the post-operative setting. Your superiority claim is therefore misleading.

Further examples of your unsubstantiated superiority claims include your claim that, "In terms of half life Vioxx has a half life of 17 hours and is truly a once a day drug, whereas Celebrex has a half life of 11 hours and is a BID (twice a day) drug," stated in your June 16, 2000, audio conference. This claim is misleading because it suggests that Celebrex must be dosed twice a day for all of its approved indications. In fact, Celebrex is approved for use either twice a day, or once a day, for the treatment of osteoarthritis. Therefore, your claim that Celebrex is a "BID drug" is misleading.

Promotion of Unapproved Uses

Your audio conferences are misleading because they promote Vioxx for unapproved uses. For example, in your June 21, 2000, conference, you claim that in the VIGOR study, "...the Vioxx 50 milligrams a day and the Naprosyn, a gram a day, were absolutely equally effective in terms of treating the patients with rheumatoid arthritis." Your claim is misleading because it suggests that Vioxx is effective for the treatment of rheumatoid arthritis when this has not been demonstrated. The VIGOR study was not designed to assess the efficacy of Vioxx for the treatment of rheumatoid arthritis. Your claim that Vioxx is "absolutely equally effective" to naproxen in treating patients with rheumatoid arthritis is also misleading because this has not been demonstrated by adequate and well-controlled clinical studies, and because the VIGOR study was not capable of assessing their comparative effectiveness.

Your promotional audio conferences are also misleading because they suggest that Vioxx is safe and effective for other unapproved uses such as the prevention of cancer and invasive cancer, and for the treatment of Alzheimer's disease and gout. Examples of claims that promote Vioxx for unapproved uses, include, but are not limited to, your claims in your June 16, 2000 audio conference that, "...COX-2 seems to be able to interfere with...programmed cell death. Therefore, you get this increased cell growth which allows polps to form, cancer and then invasive cancer. And by blocking COX-2 you can actually prevent the development of colon polyps, cancer and invasive cancer." Additional examples include your claims that "So we tried it [Vioxx] after Vioxx was released and really within one or two pills acute attacks of gout were being shut down," and "Specifically, if you looked at potential uses of these drugs, the most exciting right now I guess in two areas, one is Alzheimer's disease...."

Press Release

We have identified a Merck press release entitled, "Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx," dated May 22, 2001, that is also false or misleading for similar reasons stated above. Additionally, your claim in the press release that Vioxx has a "favorable cardiovascular safety profile," is simply incomprehensible, given the rate of MI and serious cardiovascular events compared to naproxen. The implication that Vioxx's cardiovascular profile is superior to other NSAIDs is misleading; in fact, serious cardiovascular events were twice as frequent in the VIOXX treatment group (101 events, 2.5%) as in the naproxen treatment group (46 events, 1.1%) in the VIGOR study.

Oral Representations

Merck sales representatives have engaged in false or misleading promotional activities that also minimize the potentially serious MI results observed in the VIGOR trial. Specifically, Merck sales representatives made false or misleading statements to DDMAC reviewers at two different professional meetings. At your exhibit booth during the 119th Annual Meeting of the Maryland Pharmacists Association (MPhA), in Ocean City, Maryland, June 9 – June 12, 2001, your representative stated that the increased MI rate seen in patients on Vioxx in the VIGOR study is due to the fact that naproxen works just like aspirin (i.e., inhibits clotting and platelet aggregation). In addition, during the Annual Meeting of the American Society of Health-Systems Pharmacists (ASHP), in Los Angeles, California, June 3 – June 6, 2001, your representative stated that Vioxx had a greater MI rate in the VIGOR trial because naproxen is cardioprotective, having platelet effects similar to aspirin. These statements made by your sales representatives are misleading for the reasons stated above.

Conclusions and Requested Actions

The promotional activities and materials described above minimize the potentially serious cardiovascular findings that were observed in the VIGOR study, minimize the Vioxx / Coumadin drug interaction, omit crucial risk information associated with Vioxx therapy, contain unsubstantiated comparative claims, and promote unapproved uses. On December 16, 1999, we also objected to your dissemination of promotional materials for Vioxx that misrepresented Vioxx's safety profile, contained unsubstantiated comparative claims, and lacked fair balance.

Due to the seriousness of these violations, and the fact that your violative promotion of Vioxx has continued despite our prior written notification regarding similar violations, we request that you provide a detailed response to the issues raised in this Warning Letter on or before October 1, 2001. This response should contain an action plan that includes a comprehensive plan to disseminate corrective messages about the issues discussed in this letter to the audiences that received these misleading messages. This corrective action plan should also include:

1. Immediately ceasing all violative promotional activities, and the dissemination of violative promotional materials for Vioxx.

2. Issuing a "Dear Healthcare provider" letter to correct false or misleading impressions and information. This proposed letter should be submitted to us for review prior to its release. After agreement is reached on the content and audience, the letter should be disseminated by direct mail to all healthcare providers who were, or may have been exposed to the violative promotion.

3. A written statement of your intent to comply with "1" and "2" above.

Your written response should be received no later than October 1, 2001. If you have any questions or comments, please contact Lesley Frank, Ph.D., JD, by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #9456 in addition to the NDA number.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for Vioxx, and may determine that additional remedial messages will be necessary to fully correct the false or misleading messages resulting from your violative conduct.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

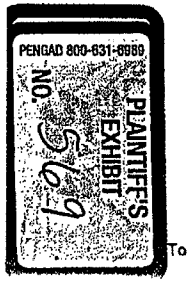
Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug Marketing,
Advertising, and Communications

The following internal document was obtained from a court action. The memo clearly shows how carefully the drug company monitors its sales strategies and undermines the argument that a state law requiring disclosure of gifts is too administratively burdensome. Moreover, the memo shows the strategies the industry uses to cultivate doctors and to enlist them in the cause. The infamous “Show me the money” quote is shown at the top of the third page.

NAME (Highlighted = National)	RBG	POINT RESPONSIBILITY	CONTACT INFO	AFFILIATIONS
Altman, Roy	SE (S)	1. R. Bartholomeo 2. A. Martinez 3. K. Woomer	P.O. Box 016960 Miami, Fl 33101 305-243-5735 305-243-5655 (FAX)	Professor of Medicine, Chief of Arthritis, Division of Rheumatology, University of Miami, School of Medicine V.A. Hospital
Arakawa, Ken C.	WE	1. M. Redden 2. D. Stael	Queens POB II 1329 Lusitana St. Suite 206 Honolulu, Hawaii 96813	Queens Medical Center; International Rheumatism Center; Hawaii Medical School
Berney, Steven **NEUTRALIZED**	MA	1. B. Nzerem	Broad & Ontario Streets 1 Jones Hall Philadelphia, PA 19141 Phone: (215) 707-3606	Chief-Division of Rheumatology at Temple University Hospital; Managed Care: Aetna/US Healthcare-35% Blues-15% Misc HMO-25% Medicare-5% State Aid-4% Cash-5% Other-11%
Box, Jane and Pat	SE (N)	1. L. Burk 2. T. Baker 3. L. Orlando	1001 Blythe Boulevard, Suite 403 Charlotte, NC 28203	Rheumatologists; affiliated with CMC, Carolinas Medical Center
Calabrese, Len	MA	1. T. Williams 2. G. Foster 3. D. Hartenbaum	9500 Euclid Avenue Cleveland, OH 44195 216-444-5258	Cleveland Clinic
Caldwell, Jacques R.	SE (S)	1. D. Meyers 2. J. Turnback-Grp B Mgr 3. M. Halpin	311 N. Clyde Morris Blvd. Suite 510 Daytona Beach, Fl 32114 904-253-1155	Member of the Board of Directors for the state's chapter of the Arthritis Society; officer and very highly regarded member of the state's Rheumatology Society



To Protective Order

NAME (Highlighted = National)	BACKGROUND PROVIDED BY A&A SPECIALISTS (with additional comments from National HSAs, RMDs, TBG, etc.)
Altman, Roy	Extremely influential physician in the rheumatology community; major thought leader in the field; very poor relationship with us, dating back to the early 1980s; a task force has been formed to try and bring him back to neutral in his perception of us; personal visit by Bruce Freundlich; bad feelings from FOSAMAX, but wants to be perceived as non-biased; submitted for a grant through Bruce; recommend a brainstorm with local reps, OSRs and A&A specialists for tactics and may also try Jim Kessinger (past Fosamax launch manager covering Altman) for ideas; provide OARSE funding every year
Arakawa, Ken C.	# 1 writing branded NSAID user in the state as well as the #1 prescriber of Celebrex; local rheumatologists respect him for his reputation and talent in the field; advocate for FOSAMAX and has given a couple lectures in the local area; left out of the various meetings over the last year and a half (including consultant meetings) while a few of his colleagues have attended these meetings; really wants to attend a Consultants' Meeting to get up to speed; very satisfied with the manner in which Searle/Pfizer have kept him in the loop with information and data on Celebrex post-launch through to the present; feels that their presenters have been very biased and feels like they would like him to be the same way; has written 127 prescriptions for Celebrex according to the February data; has given two lectures for Searle/Pfizer but is somewhat disgusted by the use of Dr. Singh in the area (Dr. Singh came to Hawaii last year and presented against the use of COX-2, but recently changed his story); currently disgruntled; Hawaii is leading the uptake of Celebrex
Berney, Steven **NEUTRALIZED**	Not quite anti-Merck; major advocate for Searle/Pfizer; Searle/Pfizer set up a very large Preceptorship Practicum at Temple with Dr. Berney and using him extensively throughout the Mid-Atlantic as a speaker; initial presentations not balanced and sometimes promotional for Celebrex; continuing work by HSAs; participating in our preceptorship/tutorial initiatives; willingness to speak for Merck when VIOXX is launched; however, suspicious of his relationship with the Searle/Pfizer camp; may be harboring some bad feelings toward Merck due to a perceived under-utilization as an advocate for FOSAMAX and not being selected as a clinical study site for VIOXX; excellent speaker; attended National Consultants' Meeting, but has not been given as much attention as others at Penn have gotten; outstanding feedback on recent program in Cleveland; CME faculty
Box, Jane and Pat	Key rheumatologists within the Charlotte area; large writers; not advocates for FOSAMAX; hard to approach in the office setting (Jane is much more approachable than her husband); research department in the office and do a ton of research projects (National HSA working with them); currently doing studies for VIOXX; working with Searle in the hospital setting
Calabrese, Len	Nationally respected for work in arthritides related to Hepatitis C and HIV; has been on Charlotte's Advisory Board and has been involved in Merck studies; presentations of the data for Celebrex have been very powerful and he has down-played issues related to sulfa and P450; may be just as enthusiastic for Merck once he is speaking for VIOXX; have made many attempts to get him involved in national level programs - all to no avail; already exposed to MRL researchers; filled out P&T request and wrote 6-page letter to get VIOXX on formulary at Cleveland Clinic (field report 7/22/99)
Caldwell, Jacques R.	Eighth largest prescriber of NSAIDs in the SERBG; he and his partner virtually control one of the "must win" clusters in the SERBG; this cluster has historically been a "poor launching" cluster; runs a very extensive Rheumatology practice in central Florida which encompasses a huge clinical trial arm as well; very much sitting on the fence right now with the competitive agent, because of his relationship with them over the past five or six years

NAME (Highlighted = National)	RECOMMENDATIONS (in addition to continued focus by the Specialists and HSAs)
Altman, Roy	"Show me the money"- Clinical Trials - Funding >$50,000 Rheum Fellowship Program - Task Force to continue to work with him Task force in place - Dr. Bruce Freundlich, SBD (J.G.) RMD K. Edwards, M. Halpin & local reps
Arakawa, Ken C.	- Consultant Meeting - any place in USA / international - SBD / RBG VP-level visit as first step
Berney, Steven **NEUTRALIZED**	Clinical studies Probably does not belong on this list
Box, Jane and Pat	Continue to support with clinical studies Visit by Dr. Greg Geba, CDP If continue to support, will be neutralized
Calabrese, Len	Visit from Lou Sherwood might be useful. Visit from upper sales or marketing management not necessary.
Caldwell, Jacques R.	Clinical Trials - Visit from RMD (if he can deliver trial then we are OK) and a visit from VP is not required

NAME (Highlighted = National)	RBG	POINT RESPONSIBILITY	CONTACT INFO	AFFILIATIONS
Condemi, John J. **NEUTRALIZED**	NE	1. T. Hassett 2. F. Ornskov	919 Westfall Road Building B Rochester, NY 14618 Tel. 716-442-0150 Fax. 716-271-8704	Strong Memorial Hospital University of Rochester Medical Center, Blue Cross Blue Shield of Rochester, Preferred Care

NAME (Highlighted = National)	BACKGROUND PROVIDED BY A&A SPECIALISTS (with additional comments from National HSAs, RMDs, TBG, etc.)
Condemi, John J. **NEUTRALIZED**	Thought leader in the community and Upstate NY; speaking on behalf of Searle as an advocate and investigator; recently enrolled him in a clinical trial (RA) after many months of promises and hard effort; not entirely certain this wasn't too little, too late; speaking to community physicians at programs sponsored by Rochester Blue Cross Blue Shield (80% market share in a 90% managed care market); have not been in attendance at these meetings, but can imagine that VIOXX has not been mentioned nearly as often as Celebrex; has trained many of the RHU in the Upstate area and is considered the expert by many (thus, the reason BC/BS has used him as a speaker); has done studies on FOSAMAX and SINGULAIR but for some reason was slighted by us for VIOXX; wants to be involved with VIOXX

NAME (Highlighted = National)	RECOMMENDATIONS (in addition to continued focus by the Specialists and HSAs)
Condemi, John J. **NEUTRALIZED**	Provide scientific information; research; interested in NSAID-induced asthma; provide investigator slides to balance presentations; personal visit by a "heavyweight" from MRL or CDP (Greg Bell or Greg Geba) to discuss where we want to go with VIOXX; could work with him to develop a clinical pathway for COX-2 inhibitors in a managed care setting; panel with Dr. Singh of Stanford and some others to focus on pharmacoeconomic studies which verify reductions in PPI or H2 blocker use - He is in a clinical trial - He is attending a program given by Dr. Geba - Speaker - doing a good job

The following document is the memorandum issued by PhRMA opposing disclosure of the industry's gifts to doctors. The memo was drafted and issued by PhRMA's Albany-based lobbying firm, Hinman Straub in March of 2006.

L 872

HINMAN STRAUB
ATTORNEYS AT LAW

121 State Street
Albany, New York 12207-1693
Tel: 518-436-0751
Fax: 518-436-4751
E-Mail: reception@hspm.com

March 22, 2006

RE: AN ACT to amend the public health law, in relation to disclosure of certain gifts provided by drug manufactures or wholesalers to healthcare providers.

A.5574-D (Grannis)
S.696-D (Maziarz)

MEMORANDUM IN OPPOSITION

Submitted on behalf of the Pharmaceutical Research and Manufacturers of America ("PhRMA")

We continue to oppose the enactment of this bill. This bill has not been merely amended from its original version, it has been completely changed to match up with S.696-D the so called Pharmaceutical Drug Manufacturer and Wholesaler Disclosure Act. This bill in our view is fatally flawed as a one-sided regulatory scheme, requiring no disclosure by those who would seek to reduce patient choice through restrictive formularies (e.g., PBM's).

This completely new bill, underscores our concern about the adverse consequences of a single state's attempt to regulate the marketing of pharmaceuticals. This bill purports to fairly require that prescription drug manufacturers and wholesalers disclose all gifts over $75 in value. The bill only seeks disclosure of such gifts aimed at those trying to bring medicines to the marketplace on behalf of patients. The bill would not require the disclosure of gifts to and from those business entities seeking to implement prescription drug formularies on behalf of businesses or associations (e.g., the contractual relationships between PBM's and those entities providing prescription drug plans or the gifts provided in the negotiation of such contracts).

In short, the bill would require the disclosure of samples valued at $76 or more, but require no disclosure of those gifts attending a multi-million dollar contract between a national association offering prescription drug coverage through a PBM. Nor is any disclosure required of a PBM's underlying financial compensation, which could be directly affecting a patients' access to drugs prescribed by their physicians, due to the restrictive formulary enforced by that PBM.

In addition, this bill would add to the cost of prescription drugs (the prodigious costs of accounting compliance) by creating a reporting nightmare affecting prescribers and patients, especially in regard to free samples. The penalty provision of this bill would set up a potential $3,000 penalty if samples were misreported under this bill's strictures. Yet, samples are enormously popular, particularly for young mothers with sick children. Physicians use free samples in many instances, to help their most financially pressed patients.

While creating this Codes trap in regard to samples, the bill ignores a report by the Pharmacists Society of the State of New York (PSSNY) which has described PBM "misbehavior" to the detriment of the payor and the patient. Craig Burridge, PSSNY's Executive Director, in a seminal report entitled "A No-Nonsense Guide to Pharmacy Benefit Managers," describes a problem which is "a crisis in accountability." Burridge's report highlights that unregulated PBM's often engage in "tricks of the trade" to the disadvantage of payors (including the State) and patients (e.g., manipulation of package sizes, multiple discount lists, varied reimbursement formulas for pharmacy and payor, and package size differentials, etc.), via hidden costs and shifted expenses.

Burridge also spotlights how PBM's oftentimes manipulate the rebates negotiated by the manufacturers with PBM's, so that payor and patients do not properly, much less fully, benefit from these rebates. Burridge delineates "tricks of the trade" whereby PBM's do not either fully or fairly pass along the benefits of rebates to their customers or the patient beneficiaries. Among the rebate strategies, Burridge highlights are:

1. PBM's, keeping the rebates for themselves in lieu of administration fees.

2. Re-classifying rebates as education grants, research, advertising promotion, access fees, formulary management fees and data collection fees.

3. Making formulary decisions that are in the best interest of the PBM but not either the payor or the patient.

Despite this report and Mr. Burridge's many excellent presentations to legislators and staff on this subject, when questions about why PBM's were excluded from this bill's reporting requirements, the response at the Health Committee was there have been no reports of problems. We believe this one-sided approach to disclosure is a fatal flaw in this bill. Why create a potential disclosure trap for samples, but give PBM's a free pass?

This goes to the heart of our argument for opposing this bill. This bill presumes that we need only be concerned about the disclosure of marketing by pharmaceutical manufactures and wholesalers, and that we need not be concerned about the marketing and reimbursement practices of PBM's who seek to administer prescription drug benefits for companies and national associations.

For example, should not AARP disclose any entertainment received by their executives related to the compensation packages negotiated by the PBM's servicing insurance packages run under the auspices of AARP? AARP is pushing hard to enact this disclosure bill, why should any of their PBM reimbursement contracts and packages be exempt from such disclosure?

While AARP implicitly argues that sunlight is a disinfectant, why do they pull down the shades in their own house? Could it be that such accounting would be unproductive and expensive? Providing little more than employment opportunities for accountants. But if this bill is so necessary for the pharmaceutical goose, why not applicable to the PBM gander?

If PBM's require no scrutiny, why did the Legislature work so hard to insist that patient protections be included in the PDL language accompanying the budget? If we need not be concerned about either the marketing practices or the contract provisions regarding the compensation arrangements of PBM's in administering these contracts, why didn't the Legislature just grant the Governor his original wish and turn over the PDL process, to a vendor like First Health? We are glad that the Legislature on a bipartisan basis, put patients first, by insisting on the prescriber prevails in the PDL and made no presumption giving PBM's carte blanche. This bill should be brought in line with that policy imperative.

At one of the Health Committee meetings considering this bill, a member asked if the bill required the disclosure of health care provider information and was told no. Yet, the bill would require the disclosure of the name, address and telephone number of every health care provider where the $75 threshold is triggered. That information could be of great interest to those who impose restrictive formularies, via their control over provider reimbursement. That information could be FOILED under this bill, even if it was not in the Consumer Guide. Might PBM's seek to harass physicians who were seeking to stand up for the best interests of their patients by challenging PBM denials? Should not the prescriber prevail, without a one-sided tool of potential restrictive access harassment placed in their path?

We do not believe the name of the game here is marketing disclosure, we believe the name of the game here is rationing patient choices in regard to prescription drugs. Informed patients asking hard questions of their doctors about problems and potential remedies, will frustrate the ability of vendors to deny the advances of modern science in the realm of prescription drugs. Yet this bill places no disclosure requirement either for gifts from or to PBM's, or for disclosure of compensation to PBM's, whose decisions can override the prescriber's medical judgment.

There are also four additional practical reasons we oppose this bill.

Trade Secrets are Legally Protected Property

This bill threatens to violate federal laws protecting fair trade practices. The bill does not adequately describe how the state will ensure confidentiality of the requested information, nor indicate the extent of the state's liability and a manufacturer's recourse for unauthorized

disclosure. Requiring disclosure of trade secrets could constitute a violation of federal trade secret law. Compilations of data, pricing, marketing techniques, and the identity of customers are "sufficiently valuable and secret to afford an actual or potential economic advantage over others." *Restatement (Third) of Unfair Competition § 39 (1995)*. Given the secrecy and competitive value of manufacturers' marketing and promotional activities, New York courts are likely to recognize this information as a trade secret, and thus, not available to the state for public use or distribution. The bill, in fact, seeks to disclose all information through a guide, containing no provision for protecting trade secrets.

Marketing Disclosures are Anti-Competitive and Anti-Free Market

Mandatory disclosure of the expenses associated with advertising and promotional efforts are anti-free market and represent unwarranted government interference. No other entities doing business in New York must disclose their marketing costs. Public disclosure of competitive information could decrease competition. This bill seems totally inconsistent with the investments made by the State through the RESTORE, GEN•NY•SIS and Centers of Excellence programs. Investments designed to enhance the pharmaceutical employment in NYS.

Investments geared to grow what already exists. In New York State the biopharmaceutical industry employs over 36,000 individuals that and the industry generates a total economic impact of approximately $8.5 billion. These jobs are the very sort of well paying high tech jobs NYS needs to retain and expand. Moreover, the industry contributes over $500 million in local and state taxes and supports the Medicaid program to the tune of $330 million in rebates.

HHS and PhRMA marketing guidelines make A 5574-D unnecessary and duplicative

The pharmaceutical industry has issued its own voluntary guidelines (the "PhRMA Code") related to communications with health care practitioners. The HHS Office of the Inspector General also issued mandatory marketing guidelines exacting even stricter standards enforced by the U.S. Department of Justice. These marketing guidelines already prohibit *quid pro quos* between manufacturers and health care professionals. Given the presence of both sets of guidelines, existing legal sanctions for non-compliance, and at a time when most people are concerned about rising health care costs, PhRMA believes legislators should ask why New York is attempting to increase administrative costs in health care. This bill does nothing to improve access to care, improve health care quality, or lower overall healthcare costs.

In addition, PhRMA has just announced that it will develop a voluntary code of conduct for the advertising of prescription medicines (*New York Times* May 17, 2005 at par. 16). This code of standards is to be issued in July, aimed at emphasizing "the need for advertisements to be serious and to highlight a drug's risks as well as benefits." (Id.).

Fourth, this bill requires an annual consumer guide on pharmaceutical drug manufacturer and wholesaler gifts to be prepared and distributed by the Health Department. Yet, the bill carries no

provision or fiscal mechanism to pay for the preparation or distribution of this guide. How many millions of unbudgeted state dollars will accompany the enactment of this bill? We therefore request that the Ways & Means Committee to prepare an analysis of the cost issues involved in this bill.

In summation, this bill will add compliance costs to the bottom line costs of prescription drugs. Is that a wise approach? Or is this bill's policy mechanism analogous to raising gas prices to lower gas consumption, which only hurts consumers. Why add disclosure which could discourage free samples, but don't add disclosure to put sunlight on reported PBM abuses? What policy does that posture serve?

For all these reasons we respectfully recommend that this bill not be enacted.

Respectfully submitted,

Hinman Straub P.C.

HINMAN STRAUB P.C.
Legislative Counsel for PhRMA