IS DIRECT-TO-CONSUMER ADVERTISING ETHICAL WHEN LIVES ARE AT STAKE?

Statement

by

Yvonne Bokhour
Master's Candidate
Health Advocacy Program, Sarah Lawrence College

Written Testimony Submitted in Response to the
United States Food and Drug Administration Public Hearing
On Direct-to-Consumer Promotion of Medical Products
Held in Washington, DC, November 2005

Introduction

The often idyllic images portrayed in pharmaceutical advertising are perceived quite differently by concerned stakeholders. To some, they signify the promise of free enterprise. To others, they epitomize the danger of greed. The ads may well appeal on many levels. They offer hope to the afflicted. They reveal the wonders of scientific achievement. And they illustrate the power of our entrepreneurial spirit, which can produce remarkable results with profit as inspiration. Patients, frail and vulnerable, may gravitate to these ads as they once admired Marcus Welby—yearning for relief, eager to place their faith in the hands of a trustworthy healer.

But pharmaceutical ads are not created by physicians who treat patients or even researchers who develop drugs. They are created by marketers. These marketers may well believe quite sincerely in their products. However, their primary goal is not the public health of the nation, but profit—profit for one, specific company.

Does this matter? Are consumers at risk? Although, ultimately, it is physicians who write the prescriptions needed for purchase, direct-to-consumer advertising (DTCA), in full force since 1997, is groundbreaking in its direct appeal to untrained patients regarding complicated medical decisions. The products in question are not paper towels or vacuum cleaners, for which "buyer beware" may serve as adequate warning. They are potentially life-altering medications. Although it's true distressing symptoms may be markedly relieved, it's also true there are serious risks involved, even death. Is it ethical to allow direct-to-consumer advertising when lives are at stake? If so, how can we insure the public's safety? Who is responsible for ad content, and who is responsible for its consequences?

Peter Lurie, MD, MPH, a consumer advocate at Public Citizen, said recently DTCA should be judged like any medical intervention, "by comparing its risks to its benefits" (Lurie).

And Matthew F. Hollon, MD, MPH, assessing the impact of DTCA through October 2005 for the New England Journal of Medicine, characterized the phenomenon as a "massive and uncontrolled experiment" (Hollon). The scandal surrounding Vioxx, a pain relief medication recently withdrawn from the marketplace, is the most visible indication to date that DTCA might have a deleterious impact on patient health (Spence). Advertised to consumers more than any drug in 2000 (indeed, more than Pepsi and Budweiser), Vioxx was an extremely profitable medication that is now suspected of causing "between 88,000 and 140,000 excess cases of serious coronary heart disease" in the United States (Graham). The evidence also suggests many of these events may have been fatal (Graham). More than 6000 lawsuits have been filed against the manufacturer, Merck. Coincidentally, the journal has just accused Merck of misrepresenting important research results, published in 2000 while Vioxx advertisements ruled the airwaves (Berenson 2). However, even the published results, from the VIGOR study (Vioxx Gastrointestinal Outcomes Research), should have raised red flags regarding Vioxx commercials. Significant cardiovascular risks ("a five-fold difference in incidence of acute myocardial infarction" between those treated with Vioxx and those treated with naproxen) were known even then (Graham).

Experts agree more research is needed to fully assess the effects of DTCA on public health (Hollon, Spence). If, as Hollon suggests, direct-to-consumer ads are indeed experimental, and if research is ongoing with respect to their risks and benefits, perhaps we should conduct this experiment, or at least assess this experiment, using the well-established ethical principles that govern all clinical research. Ezekiel Emanuel, David Wendler and Christine Grady synthesized these principles in 2000, writing for JAMA. The authors delineated seven requirements for clinical research, based on the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, the International Ethical Guidelines for Biomedical Research Involving Human Subjects

and several other sources, which together comprise the basis of modern medical ethics. The authors state "the seven requirements…provide a systematic and coherent framework for determining whether clinical research is ethical," offering "fundamental protections" (Emanuel).

Rise of DTC Advertising

To place these ethical issues in context, a brief history of DTCA is in order. Pharmaceutical advertising is regulated by the Food and Drug Administration (FDA), a federal agency charged with assessing and monitoring the safety of drugs and medical devices. Until 1985, the FDA would only permit ads directed to physicians. Drug companies complied by pitching their products in medical journals, conducting sales calls to doctors' offices and sponsoring events. In 1985, however, the FDA agreed to allow DTCA, responding to the notion that consumers would benefit by the increased information supplied in ads. Campaigns were subject to severe restrictions, however, which kept their power to a minimum. In 1997, the advertising landscape changed dramatically when the FDA agreed to relax its rules. Drug companies were no longer required to provide exhaustive lists of risks in TV and radio commercials. It was now acceptable to supply only major side effects, as long as consumers were directed to other sources of information like web sites. The airwaves were soon inundated with advertisements (Abramson).

Perhaps surprisingly, there were many pharmaceutical executives who expressed serious reservations about DTCA when the concept was first proposed in the early 80s. The chairmen of SmithKline French, Eli Lilly and Abbott Laboratories were among several leaders who feared DTC ads might hurt the physician-patient relationship and pressure doctors to make inappropriate choices. Physicians, too, were worried the trend would lead to "self-medication" and "the subversion of the therapeutic relationship between doctor and patient" (Critser). But a Supreme Court case, *Virginia Citizens Consumer Council vs. Virginia's Board of Pharmacy*,

had, in the 1970s, established "the consumer's right to know," a philosophy that espoused the unrestricted flow of information in order to empower both individual consumers and free enterprise as a whole. Eventually the courts, the drug industry and even the American Medical Association (AMA) signed on to the notion that patients' access to information should not be limited and might even improve health by encouraging communication between consumers and their physicians. The FDA heard these arguments during a hearing in 1995 and relaxed its DTC regulations two years later. The modern DTC advertisement was born (Critser).

The Experiment

Today, many of these same issues are at play. The risks and benefits of DTCA have been clearly defined by stakeholders on all sides of the issue including doctors, manufacturers, patient advocates and government. However, a consensus has yet to emerge. Do DTC ads help or hurt the public's health?

According to Emanuel et al, clinical research is needed in order to determine whether a new intervention is better than conventional therapies. "There must be controversy within the scientific community" on this point, otherwise known as "clinical equipoise." Researchers may be unsure of the intervention or may actually disagree regarding its value. If there is consensus on its superiority (or that of the standard method), experiments are no longer needed (Emanuel).

There is no shortage of controversy surrounding DTCA. Proponents champion its ability to educate the public about frequently misdiagnosed or under-treated medical conditions (Kelly). They claim DTC ads may well reduce the stigma associated with problems such as depression or sexually transmitted diseases (Lenhardt, Mayer). The ads can prompt additional research by patients on the internet or through other venues (Kelly, Person), and encourage helpful, necessary trips to the doctor (Aikin). The physician, once contacted, will likely examine the patient both for the disease advertised and other, unpublicized, medical issues (Hollon). Perhaps

most important to proponents, patients are valuable members of the health care team and deserve information. DTC ads respect patient autonomy by providing them with awareness, opportunity and hope (Kelly, Lenhardt).

Opponents of DTCA believe the lust for profits distorts commercial messaging. Critics accuse Pharma of releasing "numerous inappropriate advertisements" (Lurie) that may mislead the public, a problem compounded by the FDA's limited ability to adequately enforce even the current, relaxed DTC regulations (Angell, GAO, Hollon, Lurie). Medication benefits may be inflated by beautiful imagery, while side effects may be downplayed with rapid fire dialogue, tiny print, or subtle advertising tricks (Day). Some have suggested that manufacturers "medicalise….normal human experience" (Mintzes) by broadening definitions for conditions such as "social anxiety disorder" in order to sell drugs, thereby encouraging essentially healthy consumers coping with common daily stressors to try risky medications (Koerner, Lenhardt, Mintzes). Critics fear DTC ads have led to inappropriate prescribing by physicians (Spence), who may bow to patient pressure as well as their own exposure to pharmaceutical advertising (Rosenthal, Wilkes). They also assert DTC ads increase national health care costs, which are rising at an alarming rate (Consumer Reports, GAO, Lurie).

In our experiment, we are questioning whether commercial pharmaceutical advertising aimed directly at consumers (the intervention) is superior or inferior to prior methods of pharmaceutical advertising (namely, ads aimed at physicians alone, who were—and are—also expected to consult independent sources of drug information). Two distinct populations, patients and physicians, require examination. Our research questions regarding patients are as follows: does DTCA improve patient knowledge and promote public health? Does DTCA put patients at risk? If so, how does this occur and what is the degree of danger? Our research questions regarding physicians are: does DTCA improve or harm the physician-patient relationship? Does

DTCA affect physician prescribing habits? If so, is there increased chance of inappropriate prescribing and adverse events including death?

Our study is well under way, although unfortunately it began in 1997 without structure or design of any kind. However, we have the required equipoise, since experts disagree on the value of the intervention in promoting patient health. While a substantial amount of data has been accumulated, its risks and benefits are still very much in question (Hollon). Our investigators are those conducting the experiment, pharmaceutical manufacturers, although we must concede they have not framed all the questions themselves. Our experiment will require independent review, a function we will assign to the FDA.

Ethical Requirement #1: Value

"To be ethical, clinical research must be valuable, meaning that it evaluates… (an) intervention that could lead to improvements in health or well-being…Only if society will gain knowledge...can exposing human subjects to risk in clinical research be justified…There are two fundamental reasons why…value should be an ethical requirement: responsible use of finite resources and avoidance of exploitation" (Emanuel).

Researching the impact of DTC advertising on population health must at this late date be considered valuable, since the horse is already out of the gate and the public's safety is in play. However, should DTC ads have been allowed considering this principle, and should it be banned from this point on? The United States is the only country in the world that currently permits DTC advertising (New Zealand did as well, but recently imposed a moratorium). The European Union weighed the pros and cons of DTCA, deciding against it (Lurie).

The possibility that DTC ads might improve patients' well-being was certainly a component of the FDA's decision to permit such marketing. DTCA arose within a specific cultural context, as concepts such as "the consumer's right to know" and "patient autonomy" took root in society. Our cherished belief in the first amendment right of free speech was also a factor (Abramson, Critser). Few if any would dispute the value of accurate, unbiased information to the consumer, and perceiving patients as valuable members of the health care team is increasingly encouraged. But in considering whether DTC advertising should have been allowed

in 1997, or should be permitted today, one must ask whether the FDA has given adequate consideration to the ads' potential for harming patients. In addition, do DTC ads use finite resources appropriately, and do they exploit study participants?

When the European Union elected to continue its ban on DTC advertising in 2003, it did so partially to protect its citizens from "commercially sponsored misinformation coming from the United States" (Abramson). Instead, European consumer advocates urged the Union to encourage education with information from "independent national sources" (Abramson). The world-wide reluctance to allow DTCA is certainly some indication that potential for harm should have been accorded more weight by the FDA when direct-to-consumer advertising was first proposed. Some have even suggested that possible safety issues such as the ads' potential to weaken the physician's role "were largely brushed aside by the FDA" at the 1995 hearings (Critser).

Have finite resources been used to best effect? Unlike most investigators, pharmaceutical manufacturers have huge sums at their disposal. DTC advertising is currently a 4.1 billion dollar industry (Davies, Mayer). In 2002, the General Accounting Office (GAO) found that spending for direct-to-consumer ads grew 145% between 1997 and 2001. This figure stood in sharp contrast to the growth of spending for research and development, which increased 59% during that period (GAO). The GAO also reported that drug companies spent more on research than marketing (30.3 billion vs. 19.1 billion in 2001, although experts such as Marcia Angell, MD, believe Pharma spent more on promotion than is publicly acknowledged) (Angell, GAO). Nevertheless, one might argue the billions allocated to DTCA might be better spent in other ways. For example, in addition to devoting more funds to research and development, Pharma could make contributions to independent agencies charged with disseminating objective information regarding diseases and treatments.

The GAO also found "DTC advertising appears to increase prescription drug spending and utilization." Between 1999 and 2000, drugs that were frequently advertised saw a 25% rise in prescriptions, whereas drugs that were not well promoted rose 4% (GAO). In addition, drug companies tend to promote newer, expensive drugs that are patented, rather than cheaper generic medications that may be just as effective (Angell, Hollon, Lurie).

National spending may also be affected by Pharma's tendency to advertise a limited number of drugs for chronic conditions, especially those with massive appeal (GAO, Hollon). A research report by The National Institute for Health Care Management Research and Educational Foundation (NIHCM) found that during the year 2000, "the 50 drugs most heavily advertised to consumers" (out of 9,850 available) accounted for 47.8% of the $20.8 billion increase in drug spending from 1999 to 2000. These same 50 medications were responsible for 31.3% of retail drug sales (which totaled $131.9 billion).

Considering the implications for our nation's budget, which will only grow more onerous now that Medicare has added a prescription drug benefit (and Pharma fully expects more scrutiny as a result) (The Pink Sheet 9/26/05), it is indeed reasonable to question the ethics of DTC advertising in terms of its use of, and its effect on, finite resources.

Do DTC ads exploit subjects? As mentioned above, since we went forward with DTCA despite international concerns, and are now the only country in the world to permit the practice, we have reason to suspect we may have placed patients at unnecessary risk. But Emanuel and his colleagues state that "researchers should not expose human beings to potential harms without some possible social or scientific benefit" (Emanuel). It might be said the FDA, the drug industry, the courts and other proponents of DTCA sincerely believe in the power of information to promote public health. This is still the position of the AMA (The Pink Sheet 11/7/05). The word "exploit," however, is key in this context, for DTCA impacts study participants for the

primary purpose of profit, not education, however well-executed the latter may be (and it may indeed be quite well-executed. The Merck website, for example, at www.merck.com, provides a vast array of resources and beautifully produced educational tools). The profit motive should have been examined more seriously at the start of our experiment in 1997, but can certainly be questioned in depth today.

According to Andrew McDonald of ThinkEquity Partners, banning DTCA could cost Pharma as much as $10 billion dollars in sales (Smith). With so much money at stake, to avoid the charge of exploitation it would be ethically imperative to show that patients have had or will derive substantial benefit from DTCA, either from taking the drugs advertised or from the promotion of overall health through better dialogue with physicians, etc. The benefits would have to be of significant value to justify any exposure to risk. Unfortunately, the impact of DTCA on health is an open question. As Dr. Hollon notes, "compelling evidence is difficult to obtain as it requires teasing out an independent effect for DTCA amid a range of other forces" (Hollon).

Various surveys, which are not considered definitive proof of public health effects (Hollon), have provided some insight into DTCA's influence on the patient-physician relationship. The Henry J. Kaiser Family Foundation tested three commercials to assess their effect on patient behavior. The ads inspired 30% of respondents to ask their doctor about the advertised drug. The overall results, reported in November 2001, were "mixed," because in some cases consumers were familiar with the disease and the medicine before the ad appeared, whereas in other cases they were not (Henry J. Kaiser). In 2004, Joel Weissman and colleagues reported on their survey of 643 physicians regarding DTCA. The doctors noted "improved communication and education" but felt the ads encouraged unnecessary therapies. Patient visits resulted in scripts for the advertised drug in 39% of cases, although 48% of the doctors

questioned felt another drug would have been equally effective. The ensuing dialogue, however, did enable physicians to suggest alternate treatments, including lifestyle changes (Weissman 2). Also in 2004, the FDA issued its own survey results. Conclusions were once again mixed. The agency concluded DTCA increases awareness of some conditions and treatments, and can inspire trips to the doctor as well as improved dialogue during the visit. However, some physicians may feel pressured to prescribe the advertised drug, and also question the ads' representation of risks and benefits (Aikin).

There is evidence that DTCA has encouraged patients to seek help for certain conditions such as osteoporosis, allergies and high cholesterol, although it's difficult to be sure the ads were the only stimulating factor and other problems such as hypertension have not been so affected. Direct-to-consumer ads may also improve compliance with medication regimens (Hollon).

Although the results above suggest DTCA may contribute in some measure to improved physician-patient communication and health service utilization, even if we assume the effects are substantial, we must ask: are such benefits outweighed by the risks? We will address this question in depth below, in "Ethical Requirement # 4: Favorable Risk-Benefit Ratio," but will state for the moment that the Vioxx case in and of itself would seem to outweigh the educational benefits of DTCA, since significant life-threatening risks were not considered reason enough to halt or even alter a massive, lucrative advertising campaign, thus exploiting tens of thousands of patients who later experienced serious cardiovascular events, many of which were fatal. With the evidence now suggesting repression of research results even as ads proliferated (Berenson), the value of this experiment must be called into serious question. The FDA must consider banning DTCA.

Ethical Requirement #2: Scientific Validity

"To be ethical, valuable research must be conducted in a methodologically rigorous manner…Scientifically unsound research on human subjects is ipso facto unethical in that it may expose subjects to risks or inconvenience for no purpose…invalid research is unethical because it is a waste of resources" (Emanuel).

As noted above, direct-to-consumer advertising is an experiment that was initiated without structure or design. Indeed, Marcia Angell notes its health impact cannot be assessed using "properly controlled studies," because nearly everyone in the United States has seen the ads. Well-designed clinical research would compare the behavior of those who have been exposed to the ads with those who have not (Angell). Such a trial might have been a possibility prior to 1997, but not today (although the FDA could organize focus groups to anticipate the public's response to particular ads) (Lenhardt). Also, as noted above, there may now be too many confounding factors to be sure of DTCA's effect on health (Hollon).

The FDA regulations that govern DTC ads provide a bit of structure to our experiment, but not enough to assert the study has been conducted according to sound scientific principles. While the rules vary according to the advertising medium, in general manufacturers are encouraged to present accurate, not misleading, information; to make claims only if such assertions can be upheld with convincing evidence, and to warn consumers about consequences; to convey balance between risks and benefits; and to follow various requirements regarding labeling, etc. Print ads must reveal all risks, whereas broadcast commercials need only list major side effects as long as they direct consumers to additional sources of information. Drug companies are required to submit their ads to the FDA for approval before an ad campaign is launched, although the ads can run while the FDA checks (Angell, GAO).

Unfortunately, the FDA does not have the resources to adequately enforce its regulations. Also, new requirements have hindered the process. As of 2001, 30 reviewers were responsible for 34,000 ads (Angell); today the burden is even more onerous. Despite the FDA's limitations, however, "multiple, serious offenses or violations that raise public health issues" have been found. The FDA sends regulatory letters in order to change or halt misleading ads, but these letters do not necessarily prevent the companies in question from continuing to produce such ads

and sometimes arrive well after the ads have completed their run (GAO). Peter Lurie says "recidivism is common" (Lurie), a statement supported by GAO findings (GAO).

The trade association PhRMA, which represents our investigators, the drug companies, recently issued guidelines on DTCA (PhRMA). These guidelines, established eight years after DTC advertisements went full speed ahead, are the first attempt by Pharma to guide and self-monitor their advertising practices. Of note, they have not yet gone into effect and are completely voluntary. The document reiterates many of the same principles outlined by FDA regulations but also addresses specific areas of concern such as ad placement for adult products like Viagra. Reminder ads (which feature product names but no other details), while allowed by the FDA, are discouraged (PhRMA). Of special interest, manufacturers are urged to delay advertising new drugs (so doctors have a chance to see how well patients do), although campaign launch timing is left to the company's judgment (Mayer). PhRMA has established an "office of accountability" that will keep track of feedback from consumers, physicians and others. It will also issue regular reports. Manufacturers have the option of making their commitment public (PhRMA).

While this attempt to self-regulate may be helpful, critics question its worth, claiming drug companies have poor track records in this regard to date and are unlikely to fully comply unless rules are mandatory. Some believe the guidelines were produced as a public relations measure to counter negative Vioxx publicity and to prevent unpleasant interventions by the FDA and Congress itself (Lurie, Mayer).

The guidelines may indeed be an attempt at self-preservation in the wake of scandals like Vioxx. Trade and business publications are filled with stories that describe new marketing strategies designed to overcome the negative impressions Pharma sustained during this and similar incidents. Some companies have reduced DTCA spending, and many are advertising the

virtues of Pharma in general rather than specific drugs (Davies, Mayer, Monari, The Pink Sheet, Truelove). Although we cannot be sure of their impact, twenty three companies have now adopted PhRMA's guidelines, which may signal true change (Mayer).

However, neither current FDA regulations nor PhRMA's attempt at self-monitoring constitute a rigorous scientific protocol designed to test our intervention as safely as possible, using financial resources effectively and preventing exploitation of research subjects.

Ethical Requirement #3: Fair Subject Selection

"Selection of subjects must be fair. Subject selection encompasses decisions about who will be included both through the development of specific inclusion and exclusion criteria and the strategy adopted for recruiting subjects….Consistent with the scientific goals, subjects should be selected to minimize risks and enhance benefits to individual subjects and society….scientific goals, considered in dynamic interaction with the potential for and distribution of risks and benefits, should guide the selection of subjects" (Emanuel).

The entire population of the United States has been enrolled in this experiment. In fact, these commercials are seen in other countries as well (Abramson). Emanuel and his fellow authors have expressed special concern for subjects who are recruited for convenience sake, or subjects who are vulnerable for one reason or another and therefore not able to protect themselves (Emanuel). Some might well consider targeting the masses for profit convenient. Consumers with poor literacy might not have the sophistication to judge DTC ads with a wary eye, understand the significance of side effects, or investigate all their options. Others may lack the means to conduct such research. Those with low educational attainment levels or meager financial resources might therefore be at more risk than average for harm or exploitation. (On the other hand, we cannot accuse our investigators of excluding anyone unfairly!)

Lest we forget, doctors are also enrolled in this study. Their participation is confounded by exposure to a wide variety of promotional efforts sponsored by drug companies, including ads in medical journals, calls by sales representatives (who come with an assortment of delightful gifts), and symposia and other events underwritten by Pharma. In fact, while spending for DTCA may seem generous and has grown markedly in a short time, it actually accounts for only 15% of

Pharma's promotional budget (GAO). More than 80% is spent on health care professionals (GAO, Rosenthal). Studies have shown that Pharma's influence begins in medical school, where vulnerable students have repeated exposure to sales reps and other promotional methods of industry (Zipkin). Schools spend only 5% of teaching time training young doctors on medication use (Wilkes); drug companies have taken up the slack and have a substantial effect on developing prescribing patterns (Zipkin). The pharmaceutical industry employs 88,000 sales reps (known as "detailers") who are well trained and charming; this translates to one rep for every six doctors, or $9000 spent annually per doctor (detailers offer gifts both large and small, including food, flowers, pens, and mugs, as well as tickets to events and even trips). There is no question but that reps have significant influence. Physicians also receive a substantial amount of drug information from Pharma ads in medical journals, although questions have been raised about accuracy and balance in these ads, just as they have in DTC advertisements. Continuing medical education classes (CMEs) are additional sources of drug information, seemingly independent, but these events too are often sponsored by Pharma (Wilkes). Peer-reviewed articles in medical journals should be the ultimate source of reliable knowledge, but Pharma has been known to place ghost-written articles in journals, which companies later cite in ads to their advantage (Matthews). In additional, pervasive conflicts of interest among researchers, academia, government and industry may actually skew research results (Lenhardt).

The participation of physicians in the DTCA experiment is murkier than that of consumers. As highly trained professionals, doctors should in theory be alert to the risks of drug company influence on prescribing behavior. Academic institutions must take more responsibility to train both students and practicing physicians how to critically assess prescription medication, and how to avoid undue influence. Physicians must curtail their own greed (Wilkes), and Pharma must be held accountable for attempts to essentially bribe medical professionals (Angell). Until

these values are fully embraced, we cannot say our subjects have been chosen to minimize risks and enhance benefits for society. It would seem, rather, they have been targeted (and in some cases corrupted, or at least unconsciously influenced) in order to maximize profit.

Ethical Requirement #4: Favorable Risk-Benefit Ratio

"Clinical research involves drugs, devices and procedures about which there is limited knowledge. As a result, research inherently entails uncertainty about the degree of risks and benefits, with earlier phase research having greater uncertainty….Clinical research can only be justified if …potential risks to individual subjects are minimized, the potential benefits to individual subjects are enhanced, and the potential benefits to individual subjects and society are proportionate to or outweigh the risks…a favorable risk-benefit ratio embodies…nonmaleficence …not to inflict harm on a person…(and) beneficence…a moral obligation to act for the benefit of others" (Emanuel).

The risks and benefits of DTCA were summarized above in "The Experiment" and discussed in more detail in "Ethical Requirements" 2 and 3. They are also outlined in Table 1, attached. The crucial question now becomes, do benefits outweigh risks or vice versa?

Free speech is an essential and beloved component of our society. Does this value justify DTC advertising? Patients today are savvier than ever before. Surveys have shown as many as 43% of viewers will use DTCA as a springboard for further research and consults with healthcare professionals (Aikin). One survey found that 35% of respondents had discussed a DTC ad with their physicians. Of those, 25% were diagnosed with a condition unrelated to the drug advertised. Forty three percent of these newly discovered health issues were considered "high priority" (Weissman 1). It should be said this study was partially funded by several pharmaceutical companies (Hollon). Even so, the results are not out of line with other surveys that indicate DTCA can bring a fair number of patients to the doctor (Aikin, Hollon). If even a small portion of these patients receive diagnoses for serious conditions, it can be said DTCA saves lives.

But is it necessary or wise to achieve this effect with advertising? Do the risks of DTCA outweigh even this significant benefit? As noted above, Vioxx by itself may be responsible for thousands of deaths. Since Merck's primary purpose in designing its advertising campaign was to sell Vioxx, one wonders whether the drug might have been prescribed with more care had its

virtues been disseminated through physicians alone, or through independent educational agencies without profit as a motive.

The 2001 Kaiser survey found that consumers' understanding of potentially serious side effects and contraindications varied according to the ads they had seen (Henry J. Kaiser). Marketers employ many sophisticated techniques to minimize perception of risk (such as glittery butterflies floating by as side effects are enumerated), which can affect viewers' comprehension (Day).

Perhaps the most serious question raised by DTC advertising is whether it affects physician prescribing habits adversely, and if so, to what degree? Most doctors feel their judgment remains independent and sound, although they worry about their colleagues (Wilkes, Zipkin). Several studies show patient requests may well result in a script for the drug advertised (Aikin, Kravitz, Mintzes et al, Mintzes et al 2); such tendencies seem to be mirrored in sales trends for heavily advertised drugs (NIHCM). Physicians may prescribe these medications even against their better judgment, expressing ambivalence about need (Mintzes et al, Mintzes et al 2) or noting other drugs may have been equally effective (Weissman 2). Some doctors (about 22% of primary care physicians according to an FDA survey) feel "somewhat" or "very" pressured by their patients to prescribe advertised drugs; almost half of all doctors feel at least some pressure (Aikin). Risks to patients are highest if the condition is minor but the therapy is risky or expensive (Kravitz). This might be the case, for example, for "medicalised" conditions such as social phobia (Mintzes). On the other hand, patient requests can help prevent under-treatment of conditions like depression (Kravitz).

If physicians accede to patient pressure and prescribe advertised drugs, it does not necessarily follow they will show poor judgment and medicate inappropriately. Prescribing an expensive drug on patent vs. an equally effective generic has important implications for our

economy, but not for patient safety. Is there any evidence to suggest DTC causes inappropriate prescribing? Michael Wilkes, MD, Ph.D., in Congressional testimony on DTCA, said "there are example after example of where, despite sound evidence, doctors write prescriptions for inferior but heavily marketed products…ignoring or being unaware of the scientific evidence" (Wilkes). A study conducted in the Kaiser Permanente network prior to Vioxx's withdrawal from the marketplace found that physicians were more likely to prescribe Cox-2 inhibitors (such as Vioxx) when prompted by consumers as a result of an ad, even in cases where Cox-2s were not the safest choice according to clinical protocols. The authors concluded DTCA influence was pronounced, despite Kaiser's significant effort to provide its physicians with independent drug information and multiple guidelines (Spence).

If DTC advertising is to continue (and most observers feel it will, despite the criticism), more studies on prescribing will need to be conducted. However, the standards outlined by Emanuel and his colleagues state research on human beings should not proceed without a well-investigated analysis in advance of the risks and benefits to which subjects will be exposed (Emanuel). As the work of Kravitz, Spence and others implies, and as the deaths attributable to Vioxx suggest, the DTC experiment went forward prematurely and should at least be restructured if not stopped.

Ethical Requirement #5: Independent Review

"Investigators inherently have multiple, legitimate interests….These diverse interests can generate conflicts that may unwittingly distort the judgment of even well-intentioned investigators regarding the design, conduct and analysis of research….Independent review by individuals unaffiliated with the clinical research helps minimize the potential impact of such conflicts of interest….Independent review…assures members of society that people who enroll in trials will be treated ethically and that some segments of society will not benefit from the misuse of other human beings" (Emanuel).

We have charged the FDA with the task of independent review. As our medical ethicists have stated, such oversight is essential under the best of circumstances, when many "legitimate interests" may create conflicts. In the case of DTCA, where profit motivates our investigators more than public health, the need for objective guidance is crucial.

DTC ads are created to persuade more than educate (Lenhardt), even when information is tendered in a balanced manner. As long as persuasion to generate sales underlies advertisements, society cannot rely on the goodwill of even the most sincere, well-meaning marketers.

However, the profit motive affects more than the ads themselves; it pervades the entire medical culture, as described in "Ethical Requirement #2." Financial conflicts of interest, particularly those involving the pharmaceutical industry, affect so many components of our health care system, it is difficult to be sure of anything or anyone, even scientists at the FDA, who may themselves have conflicts such as consulting arrangements with drug companies (Angell, Lenhardt, Matthews). If research funded entirely by Pharma or ghost written surreptitiously by PR firms is cited in ads as independent verification of drug safety and effectiveness, DTCA simply cannot be trusted.

Many experts are calling for increased scrutiny of the FDA and its decision-making capacity, as well as additional DTCA regulations (Lurie, Mayer, Monari, Smith). Senator Bill Frist, a physician himself, is asking that Pharma wait two years before advertising new drugs, since it takes time to see the true effects of these medications (Davies, Smith, PhRMA). A total ban on DTCA is not likely, and PhRMA's efforts to self-regulate may have beneficial effects. Nevertheless, the crucial function of independent review would be enhanced by additional regulations and better enforcement. New drugs deserve special attention, but so do gift-giving practices (if we can't ban ads, we should at least ban bribes). Ads should be approved before they air. In addition, the FDA should consider imposing monetary fines on drug companies that fail to meet their obligations in protecting the public's health with balanced ads.

Ethical Requirement #6: Informed Consent

"…individuals must be accurately informed of the purpose, methods, risks, benefits and alternatives to the research; understand this information and its bearing on their own clinical situation; and make a voluntary and uncoerced decision whether to participate….Informed consent embodies the need to respect persons and their autonomous decisions" (Emanuel).

While it may be argued that our physician participants had fair warning regarding their involvement in this experiment, it is certainly difficult to know whether the majority would have provided their enthusiastic assent in 1997 (although the AMA did endorse the concept). It is doubtful, without careful assessment and full disclosure by our investigators, they could have anticipated the impact on their prescribing habits, especially because even now, although many fear for their colleagues, they do not believe themselves to be unduly influenced (Wilkes, Zipkin). The majority do not even realize how often they encounter drug company promotions (Wilkes).

Consumers had little understanding of DTCA's implications in 1997 and even years into the phenomenon. One telling survey result: half of those questioned by the University of California at Los Angeles and Davis were sure DTC ads were "preapproved by the FDA, and 43% thought only "completely safe" medicines could be advertised (Consumer Reports). These respondents were certainly not well informed.

How many consumers know that pharmaceutical companies are allowed to produce videos that essentially mimic news stories? Video News Releases (or VNRs) can be distributed for a price to media outlets throughout the nation, who then edit the pieces or air them whole, even substituting the voice of their own reporters as they please. While this practice has come under fire and is not used as frequently as it once was, it still happens with the knowledge of the FDA. The segments appear to be the work of objective reporters, but are actually produced to subtly persuade viewers about the need for a drug (Price). Although VNRs are technically a different entity than DTCA (subject to looser regulations), they are used to supplement advertisements. Consumers exposed to VNRs cannot be considered adequately informed.

As noted above, proponents cite DTCA's informative role in healthcare education. However, even if we acknowledge educational value for DTCA—even if industry adheres

rigidly to FDA and PhRMA principles with balanced, accurate ads that clearly delineate the risks and benefits of individual drugs—it must be said consumers, and perhaps to a lesser extent physicians, were not given adequate warning in advance regarding the potential of DTCA as a practice, as an intervention in and of itself, to impact health adversely.

A Pfizer executive recently stated, "An individual DTC advertisement should not be viewed as a single comprehensive source of all possible benefit and risk information. There are other complementary vehicles that allow for more detail (Kelly)." This is good to know, and would have been better to know in 1997. Such a statement should be required in ads, as should an independent source of information.

In order to provide true informed consent as outlined by Emanuel and colleagues above, patients need balanced information, presented as objectively as possible. Unfortunately, our investigators and even our independent reviewers did not fully inform the public in advance about the pros and cons of the DTCA experiment. The flaws inherent in this initial introduction to the concept of DTC advertising are compounded each and every time an ad appears, even in those that are exceptionally well-produced and balanced, since the ultimate purpose of these commercials is to persuade, not inform (Lenhardt). While it's true our research participants may benefit by exposure to ads, we might also argue they are but "means to an end," if Pharma's concern for its return-on-investment in any way compromises patient safety.

Perhaps ironically, the public's impressions of DTCA have become increasingly negative since the Vioxx incident. They are much more likely to be suspicious now than they were when surveyed by the Kaiser Foundation (Henry J. Kaiser, Berenson 1). As many as 46% of survey respondents trusted DTCA in 2001 (Henry J. Kaiser). In contrast, a recent poll found 9% of those surveyed thought drug companies were honest. Pharma recognizes this slide and is taking aggressive steps to "build consumer confidence" with various marketing strategies, including one

that "embraces error" so viewers understand "being an innovator means making mistakes (Monari)."

Ethical Requirement #7: Respect for Potential and Enrolled Subjects
Conclusion

"Individuals must continue to be treated with respect from the time they are approached…throughout their participation and even after their participation ends….risks or benefits discovered in the course of research…should be (disclosed)….the welfare of subjects should be carefully monitored throughout their research participation" (Emanuel).

It would be pleasant to judge "respect for subjects" according to the behavior of individual manufacturers, because attitudes and practices have surely varied. If a drug company does its best to follow FDA regulations (and now PhRMA guidelines) in producing DTC ads, it will have shown respect. If it develops balanced, comprehensive educational materials, it will have shown respect. If it promotes honest communications, thorough research, and objective assessment of its own products, it will have shown respect. However, our experiment has been conducted nationwide. If we leave "respect for subjects" in the hands of individual companies, we leave millions of people at risk.

Unfortunately, the entire industry has fallen pray to the notion gifts to doctors are acceptable. It has lost perspective on the dangers inherent in ghost-writing research papers, sponsoring physician education, and developing financial arrangements with government scientists. Perhaps this is because as workers proceed in their daily lives, answering to employers and stockholders, they feel a certain loyalty to the products they are paid to promote. It's easy to believe whole-heartedly in these products, and feel you are providing a service when you sell them. It's also easy when doctors, scientists and even institutions are eager to take your generous gifts. There too, you might feel you are in some measure helping society.

But many people know better, and it is their responsibility to educate the misinformed and protect the vulnerable. Even giving Pharma every benefit of the doubt, assuming DTCA is indeed educational—assuming DTCA can save lives—government must step in. It is not

possible to provide completely objective information in an ad designed to sell. And, although there may be ethical companies determined to promote their products honestly, there is tremendous evidence that unscrupulous activity, in ad production and general marketing methods, exploits uneducated patients and influences busy doctors. If Merck did indeed repress research results even as it conducted a massive advertising campaign, it displayed the most profound disrespect.

In the end, we must all take responsibility for the health effects of prescription pharmaceuticals. Consumers can never assume medicine is completely safe; they must learn to consult independent sources of information including doctors, pharmacists, web sites and literature. Medical schools must train students and practicing physicians to critically assess the drugs they prescribe, and rely on objective scientific data more than drug reps. Academic institutions, medical societies, and scientific journals must institute stricter policies regarding financial conflicts of interest. And drug companies must step up to the plate, adhering to PhRMA guidelines and, most especially, recognizing that their gift-giving practices and marketing methods may increase sales but cost lives.

However, the history of DTCA is such that we cannot rely on anyone's goodwill, or the public's ability to educate itself. Government, more than any other stakeholder, is responsible for the effects of DTCA. Government has the power to structure our experiment so safety comes first. Government has the power to oversee our experiment so that financial conflicts are minimized. Government has the power to police our experiment, so that public health is advanced and not harmed.

Asserted Risks	Asserted Benefits
Conflicts of interest—profit vs. public health—may affect overall content of ads.	Reflects and promotes patient autonomy. Contemporary patients are now respected members of the health care team.
Pharma may inflate positive qualities of drugs and minimize negative, increasing possibility consumers receive distorted impression of drugs' safety.	In line with American belief in free speech and free enterprise. Consumers have the "right to know." They are entitled to unrestricted access to information.
Pharma may exaggerate "conditions" like "social phobia," stimulating essentially healthy adults to request medication that may be unnecessary.	May improve awareness of health concerns, especially those often undiagnosed or misdiagnosed.
Consumers may mistakenly assume drugs are completely safe because ad is allowed on the air.	Can reduce stigma associated with conditions such as depression and sexually transmitted diseases.
Ads may encourage patients to pressure physicians for drugs that are unnecessarily expensive or inappropriate, affecting or even weakening their relationship.	May promote hope with potential solutions.
Physicians may bow to patient pressure and their own exposure to pharma ads, rather than assert their best judgment.	Might inspire consumers to conduct further research into conditions and treatments (for example, on the internet).
DTC ads may lead to inappropriate prescribing with the potential to cause adverse events including death.	May drive patients to physicians who can assess overall health, not only condition specified in ad.
Physician knowledge of drugs may be limited. They may rely too heavily on pharma sales reps, appearing conveniently bearing gifts.	Might promote dialogue between patients and physicians.
FDA has limited resources/cannot monitor ads effectively, so consumers may be exposed to dangerous messages despite rules in effect.	Alerts consumers to potentially valuable (and FDA approved) therapies for patients who are suffering physically or emotionally.
DTC ads do not usually suggest treatment alternatives like generic drug formulations, exercise or diet that might be less dangerous, just as effective and cheaper.	
DTC ads may increase national health care costs by promoting the overuse of expensive new drugs without a track record, by encouraging "me too" drugs where cheaper drugs might be as effective, and by promoting drugs for a limited number of chronic diseases in order to generate sales.	

Bibliography

- Abramson, John. *Overdosed America: The Broken Promise of American Medicine.* New York: HarperCollins Publishers, 2004.
- Aikin, Kathryn, et al. US Department of Health and Human Services/Food and Drug Administration/Center for Drug Evaluation and Research. "Patient and Physician Attitudes and Behaviors Associated with DTC Promotion of Prescription Drugs—Summary of FDA Survey Research Results." 19 November 2004.
- Angell, Marcia. *The Truth about Drug Companies*. New York: Random House Trade Paperbacks, 2004.
- Berenson (1), Alex. "Big Drug Makers See Sales Decline with Their Image." *The New York Times*, 14 November 2005.
- Berenson (2), Alex. "Medical Journal Criticizes Merck Over Vioxx Data." *The New York Times*, 9 December 2005.
- Consumer Reports. "Free Rein for Drug Ads?" *Consumer Reports*, February 2003. Available at: www.consumerreports.org. Accessed 6 November 2005.
- Critser, Greg. *Generation Rx*. New York: Houghton Mifflin Company, 2005.
- Davies, Paul, et al. "Drug Makers Scramble to Respond to Ad Curbs." *The Wall Street Journal*, 5 July 2005.
- Day, Ruth. Duke University. "Comprehension of Benefits vs. Risks: Fair balance in DTC?" Presentation at US Food and Drug Administration Public Hearing on Direct-to-Consumer Promotion of Medical Products, 1 and 2 November 2005. Available at: http://www.fda.gov/cder/ddmac/dtc2005/presentations.htm. Accessed 3 December 2005.
- Emanuel, Ezekiel J, David Wendler, Christine Grady. "What makes clinical research ethical?" *JAMA* 283, No. 20 (24, 31 May 2000): 2701.
- General Accounting Office (GAO). Report #GAO-03-177: "Prescription Drugs: FDA Oversight of Direct-to-Consumer Advertising Has Limitations." October 2002.
- Graham, DJ, D. Campen, R. Hui et al. "Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. *The Lancet* 365, No. 9458 (5, 11 February 2005): 475-481.
- Henry J. Kaiser Family Foundation. "Understanding the Effects of Direct-to-Consumer Prescription Drug Advertising." November 2001.
- Hollon, Matthew F. "Direct-to-Consumer Advertising: A Haphazard Approach to Health Promotion." *JAMA* 293, No.16 (27 April 2005): 2030-2033.
- Kaiser Family Foundation. "National Survey of Physicians Part II: Doctors and Prescription Drugs." March 2002.
- Kelly, Pat. Pfizer. "Advancing Public Health through Effective Consumer Health Communication." Presentation at US Food and Drug Administration Public Hearing on Direct-to-Consumer Promotion of Medical Products, 1 and 2 November 2005. Available at:http://www.fda.gov/cder/ddmac/dtc2005/presentations.htm. Accessed 3 December 2005.
- Koerner, Brendan I. "Health: First you market the disease then you push the pills to treat it." *The Guardian,* Manchester (UK), 30 July 2002, pg. 8.
- Kravitz, Richard L., et al. "Influence of Patients' Requests for Direct-To-Consumer Advertised Antidepressants." *JAMA*, 293, No. 16 (27 April 2005): 1995-2002.
- Lenhardt, Erin. "Why So Glum? Toward a Fair Balance of Competitive Interests in Direct-to-Consumer Advertising and the Well-Being of the Mentally Ill Consumers It Targets." *Health Matrix*, 15, No. 1 (Winter 2005): 165-204.
- Lurie, Peter. Public Citizen's Health Research Group Publication #1751. "Seniors' Health and Health Care Costs: Testimony before the Senate Committee on Aging on the Impact of Direct-to-Consumer Advertising on Seniors' Health and Health Care Costs." 29 September 2005.
- Matthews, Anna Wilde. "At Medical Journals, Writers by Industry Play Big Role." *Wall Street Journal*, 13 December 2005, pg. 1.
- Mayer, Rebecca. "DTC Redefined." *PharmaLive/Med Ad News*, 2005. Available at: www.pharmalive.com/magazines/medad/view.cfm?articleID=2596. Accessed 6 November 2005.
- Mintzes, Barbara. "Direct to consumer advertising is medicalising normal human experience." *BMJ* 324 (13 April 2002): 908-909.
- Mintzes, Barbara, et al. "Influence of direct to consumer pharmaceutical advertising and patients' requests on prescribing decisions: two site cross sectional survey." *BMJ* 324 (2 February 2002): 278-279.

- Mintzes, Barbara, et al (2). "How does direct-to-consumer advertising (DTCA) affect prescribing? A survey in primary care environments with and without legal DTCA." *CMAJ* 169, No. 5 (2 September 2003): 405-412.
- Monari, Gina-Louise. "Weight of Risk: A Heavy Consideration." *Med Ad News*, May 2005.
- National Institute for Health Care Management Research and Educational Foundation (NIHCM). "Prescription Drugs and Mass Media Advertising, 2000." November 2001.
- Person, Bill. 50PlusWebHealth. "Consumer Directed Promotion of Regulated Medical Products." Presentation at US Food and Drug Administration Public Hearing on Direct-to-Consumer Promotion of Medical Products, 1 and 2 November 2005. Available at:http://www.fda.gov/cder/ddmac/dtc2005/presentations.htm. Accessed 3 December 2005.
- PhRMA. "PhRMA Guiding Principles: Direct to Consumer Advertisements About Prescription Medicines." Available at www.phrma.org. Accessed 6 November 2005.
- Price, Daniel. "Doctor, Doctor, Give Me the News." *Center for Media and Democracy*. Available at: www.prwatch.org/prwissues/2005Q2/abrax.html. Accessed 13 December 2005.
- Rosenthal, Meredith B. et al. "Promotion of Prescription Drugs to Consumers." *N Engl J Med* 346, No. 7 (14 February 2002): 498-505.
- Smith, Aaron. "Banning Drug Ads Could Cost $10B." *CNN/Money*. 1 August 2005. Available at: http://money.cnn.com/2005/08/01/news/fortune500/directconsumer/index.htm. Accessed 23 October 2005.
- Spence, Michele M. et al. "Direct-to-Consumer Advertising of Cox-1 Inhibitors: Effect on Appropriateness of Prescribing." *Medical Care Research and Review*, 62, No. 5 (October 2005): 544-559.
- The Pink Sheet. "Pharma Industry 'Institutional Public Relations' Ads Expected to Increase." *The Pink Sheet*, 26 September 2005.
- The Pink Sheet. "FDA Needs Health Communications Advisory Committee for DTC Policy, Pitts Says." *The Pink Sheet*, 7 November 2005.
- Truelove, Christiane. "Beyond image problems." *Med Ad News*, September 2005, 4-8.
- Weissman (1), JS, et al. "Consumers' report on the health effects of direct-to-consumer advertising." *Health Affairs*. Published online 26 February 2003. Available at: www.healthaffairs.org. Accessed 14 December 2005.
- Weissman (2), Joel S. et al. "Physicians Report on Patient Encounters Involving Direct-to-Consumer Advertising." *Health Affairs*, 23, No. 3 (May/June 2004): 292.
- Wilkes, Michael. Congressional Testimony Before the Committee on Government Reform, 4 May 2005.
- Zipkin, Daniella A, Michael A. Steinman. "Interactions Between Pharmaceutical Representatives and Doctors in Training." *J Gen Intern Med*, 20 (2005): 777-786.