November 30, 2007

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane, Room 15-47
Rockville, MD 20857

Dear Dr. von Eschenbach:

I have obtained a copy of an October 2007 internal draft of new FDA guidance that would allow drug companies to use journal articles to promote potentially dangerous uses of drugs and medical devices without prior FDA review and approval. It is my understanding that the FDA intends to issue this guidance without significant changes in the very near future. I urge you to refrain from going forward with this ill-advised guidance.

A fundamental tenet of our drug and device laws is that a manufacturer cannot market a drug or device for a therapeutic use without FDA approval. The draft guidance would carve a large loophole in the law and create a pathway by which drug and device manufacturers can promote unapproved (off-label) uses of their products without first obtaining FDA approval by passing out journal articles about the off-label use to physicians. Published reports of company-funded studies can be biased in favor of the company's product. Allowing drug and device companies to freely disseminate these articles can result in doctors using questionable study results to guide their prescribing habits. In addition, allowing marketing through journal articles can reduce the incentive for drug and device companies to conduct the rigorous studies needed to win full FDA review and approval, leaving physicians and patients without definitive data on the benefits and risks of medical products.

The draft guidance that I have obtained would, in effect, allow drug and device companies to short-circuit FDA review and approval by sponsoring drug trials that are carefully constructed to deliver positive results and then using the results to influence prescribing patterns. This undercuts the prohibition on marketing of unapproved uses of drugs and devices and puts the public at risk for ineffective and dangerous uses of drugs.

I recognize this area of the law is complex and that FDA needs to respect the First Amendment rights of drug and device companies to communicate truthful and non-misleading

information to doctors and patients. But the draft guidance is not the answer. It would open the door to abusive marketing practices that will jeopardize safety, undermine public health, and lead to an increase in unapproved uses of powerful drugs.

The Committee will be examining the draft guidance and the process that led to their development. Before taking any further steps to issue this draft guidance, I hope you will cooperate with this inquiry.

The Draft Guidance

The Federal Food, Drug, and Cosmetic Act (FDCA) prohibits the marketing of drugs and devices for uses that have not been approved (or, for certain devices, cleared) by FDA.[1] This prohibition on marketing "off-label use" is one of the cornerstones of the FDCA and was reinforced in the Kefauver-Harris Drug Amendments of 1962. Senator Estes Kefauver at the time warned that if promotion of unapproved uses was allowed, "the expectation would be that the initial claim would tend to be quite limited, which, of course, would expedite approval of the new drug application. Thereafter, 'the sky would be the limit,' and extreme claims of any kind could be made."[2]

FDA has traditionally interpreted the FDCA to give it authority to consider a company's dissemination of reprints of articles about unapproved uses of the company's product as evidence that the company was engaged in illegal marketing.[3]

The draft guidance I have obtained would undercut the basic prohibition against marketing drugs and devices for unapproved uses. Under the draft guidance, a company would be able to disseminate scientific articles on unapproved uses as long as they are:

1. Published in peer-reviewed journals, not including supplements or other publications paid for by the manufacturer;
2. Not false or misleading;
3. Not abridged or summarized by the manufacturer;

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[1] See discussion of this prohibition in FDA's Federal Register notice entitled "Decision in Washington Legal Foundation v. Henney," 65 FR 14286, 14286-7 (Mar. 16, 2000), citing 21 U.S.C. 331(a), (c), (d), and (k), 351(f), 352(f), and 355(a), (b), (d), and (j).

[2] As quoted in a keynote address by the Senior Associate Commissioner of FDA. (FDA, *Remarks as Prepared for Delivery by Senior Associate Commissioner Linda Suydam as the Keynote Address for the FDLI Conf. on Advertising and Promotion in the New Millenium* (Sept. 13, 1999)).

[3] 59 Fed Reg. 59820, 59823 (Nov. 18, 1994).

4. Accompanied by approved labeling for product, by a bibliography of previously published studies of the unapproved use, and if the article has been called into question by other articles, a representative article reaching different conclusions;
5. Distributed separately from promotional materials; and
6. Accompanied by a number of disclaimers and disclosures.

Concerns Raised by the Draft Guidance

The draft guidance poses multiple risks. First, it appears to be based on the premise that peer-reviewed reports provide accurate, validated information and that even if individual articles are biased, the published literature as a whole can provide balance. Regrettably, recent experience shows that this is not always the case. There have been a number of high-profile instances in recent years where journal articles provided a distorted picture of a drug's safety or effectiveness. This has been in particular a problem in the case of journal articles based on studies funded by drug companies.[4]

The danger to patient health should be readily apparent from the examples of journal article abuses described in the addendum, including anti-depressants, Vioxx, Celebrex, anti-arrhythmics, Neurontin, and other False Claims Act settlements. Drug and device companies can manipulate and selectively distribute studies in order to make their products appear safer and more effective than they truly are. Where the unapproved uses are actually ineffective, patients have been denied other, more effective treatments and have been unnecessarily exposed to the ineffective products' known side effects. Even worse, patients have suffered serious harm due to unanticipated and serious side effects of unapproved uses.

Second, the draft guidance may create a disincentive for drug and device manufacturers to seek approval for unapproved uses. It is certainly more profitable to be able to promote a use without undergoing rigorous FDA review, but it will be at the cost of exposing patients to more unsafe and ineffective uses of medicines and devices. The new guidance would allow companies to sidestep the FDA review process, and could transform the stream of high-profile problems listed in the addendum into a torrent.

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[4] R. Smith, *Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies*, PLoS Medicine (2005). There is abundant evidence that industry-funded published studies are overwhelmingly more likely to show favorable results than independently-funded studies. (J. Lexchin et al., *Pharmaceutical industry sponsorship and research outcome and quality*, BMJ (2003)). In addition, the great majority of studies published in major journals are industry-funded. (M. Egger et al., *Are randomised controlled trials in the BMJ different*? BMJ (2001)).

Until the Bush Administration, these risks of permitting dissemination of journal articles on off-label uses were recognized by FDA. FDA repeatedly expressed grave concern that allowing this practice would create a powerful disincentive to conduct definitive studies and seek approval from FDA.[5] According to FDA, this would likely result in companies seeking approval of very narrow uses to get on the market, and then promoting other, more lucrative uses through preliminary scientific data.[6]

FDA also repeatedly raised concerns about the risks associated with promotion of unapproved uses, citing examples of unapproved uses that were thought by the medical community to be safe and effective, but were later proven to be ineffective or dangerous.[7] FDA appropriately took the position that peer-reviewed articles could not be relied on as a substitute for FDA review of new uses of drugs and devices:

> Regardless of the rigor, there are severe limitations inherent in the peer review process that make it inappropriate to rely solely on a peer-reviewed journal article for efficacy determinations. For example, peer reviewers almost never receive the study protocol. They cannot tell what the initial hypothesis was or whether the final analysis represents the planned analysis or an analysis crafted with the results in hand. Peer reviewers do not have access to the underlying data. The peer reviewers must rely on the data and facts as they are presented by the author. FDA, on the other hand, does have access to the data and can verify the critical statistical outcomes and the conclusions of a study. Moreover, peer reviewers do not necessarily have the time or the expertise in all aspects of the subject matter to adequately review the information. In fact, a survey reveals that a peer reviewer spends on average less than three hours reviewing a prospective article. The peer review process cannot guarantee the correctness or authenticity of the article, nor can it detect fraudulent or flawed research.
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> The data and information supporting off label uses that appear in reference textbook chapters, which could highlight off label uses of particular drugs or devices, CME materials, and materials related to third party coverage and reimbursement are even less likely to be validated than that in peer-reviewed

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[5] FDA, *Remarks as Prepared for Delivery by Senior Associate Commissioner Linda Suydam as the Keynote Address for the FDLI Conf. on Advertising and Promotion in the New Millenium* (Sept. 13, 1999); Senate Committee on Labor and Human Resources, Testimony of Deputy Commissioner For Policy, Food And Drug Administration William B. Schultz, *Hearing on Unapproved Uses of Prescription Drugs and Medical Devices*, 105th Cong. (Feb. 22, 1996).

[6] *Id.*

[7] See, e.g., 59 Fed. Reg. 59820.

> journals. In fact, we have no reason to believe that such data have been reviewed or validated at all. Textbook editors do not review the data underlying information about off label uses that appear in those books. The recognition of suggested uses in texts or treatment guidelines for purposes of third-party reimbursement serve different societal purposes. The decision to include such uses is not based on the standards used by FDA to substantiate safety and efficacy. FDA has serious concerns about a provision that allows companies to use these types of unproven/unvalidated information for promotional purposes.[8]

In 1997, Congress passed legislation that allowed the temporary use of journal articles under controlled conditions. The FDA Modernization Act of 1997 (FDAMA) allowed an exception to the general rule that company-disseminated reprints on unapproved uses would be considered evidence of marketing for the use.[9] I recognize that section 401 of FDAMA and other FDA guidance on distribution of reprints have been met with legal challenges based on the First Amendment. At the close of these legal challenges, however, FDA concluded that it still retained the authority to consider distribution of reprints as evidence of marketing.[10] To my knowledge, no subsequent court has considered this question. While there may need to be a balance between First Amendment and protection of the public health, the answer is not to open the door to unrestricted dissemination of potentially questionable information about drug safety and effectiveness.

The draft guidelines appear to be an effort by FDA to displace Congress and establish by administrative fiat a new system for use of journal articles that lacks the safeguards set by

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[8] Senate Committee on Labor and Human Resources, Testimony of Deputy Commissioner For Policy, Food And Drug Administration William B. Schultz, *Hearing on Unapproved Uses of Prescription Drugs and Medical Devices*, 105th Cong. (Feb. 22, 1996) (emphasis added).

[9] Under section 401 of FDAMA, Congress provided that company dissemination of such reprints would not be considered evidence of promotion of an off-label use if, among other things, the company submitted the reprints to FDA for review 60 days before dissemination and the company had submitted an application seeking approval of the new use to FDA. These conditions addressed the policy concerns underlying the prohibition against marketing of unapproved uses. Section 401 of FDAMA was enacted as a temporary provision, with a sunset date of 2006. During the period between enactment in 1997 and 2006, a number of abuses involving journal articles occurred, including the abuses involving anti-depressants, Vioxx, Celebrex, and Neurontin described in this document. There was no effort to renew section 401 when Congress passed the FDA Amendments Act of 2007. The result is that FDA's authority over dissemination of reprints reverts to its pre-FDAMA status.

[10] 65 FR 14286, 14286-7 (Mar. 16, 2000).

Congress. The draft guidelines would permit far more dissemination of articles on unapproved uses than was sanctioned under FDAMA.

Committee Request

Before taking any further steps to issue a draft guidance on this issue, I ask that you provide the following information to the Committee:

1. Please provide a chronology of the development of the new draft guidance, specifying each of the FDA and HHS officials involved in each stage of its drafting and review, and all internal written and electronic documents relating to the guidance.

2. Please provide all documents relating to communications between FDA and other executive branch offices and nongovernmental sources concerning the new draft guidance on dissemination of reprints and textbooks.

3. Please provide cites to any federal court decisions subsequent to Washington Legal Foundation v. Henney (D.C. Cir. Feb. 11, 2000), which prohibit or restrict FDA's authority to consider dissemination of journal articles on an unapproved use as evidence of intent to market the product for that use.

4. Please explain how the draft guidance addresses the policy concerns underlying the prohibition against marketing drugs and devices for unapproved uses. Specifically, how does it provide an incentive for manufacturers to seek FDA approval of new uses, and how does it ensure adequate, independent review of the reliability of safety and effectiveness data used by manufacturers to persuade physicians to prescribe products for new uses?

5. The draft guidance gives responsibility to manufacturers to put a reprint or textbook in context, and to ensure that the physician receives balanced information. Most reprints will be disseminated by tens of thousands of drug and device representatives behind closed doors in physicians' offices. Enforcement of the draft guidance will therefore be particularly difficult. Please furnish the following data:

    a. How many FTEs does FDA estimate would be required to determine whether companies are complying with the new draft guidance?

    b. Where will the necessary FTEs come from?

    c. How will the extent of compliance/non-compliance be determined? Will FDA rely exclusively on reviewing submissions from drug and device companies?

How will FDA determine whether company representatives are in fact providing to individual physicians all of the context and balancing information specified in the draft guidance?

d. How many FTEs has FDA set aside to bring enforcement actions against companies who do not comply with the draft guidance?

The Committee on Oversight and Government Reform is the principal oversight committee in the House of Representatives and has broad oversight jurisdiction as set forth in House Rule X. Enclosed with this letter are instructions on how to respond to the Committee's document request.

Please submit your responses by December 21, 2007. If you have any questions about this request, please contact Stephen Cha at (202) 225-5056.

Sincerely,

Henry A. Waxman
Chairman

Enclosure

cc: Tom Davis
Ranking Minority Member

ADDENDUM ON EXAMPLES OF JOURNAL ARTICLE ABUSES

- **Manufacturers of selective serotonin re-uptake inhibitors (SSRI) systematically suppressed studies that failed to show effectiveness in children.** The Center for Science and the Public Interest analyzed published studies on selective serotonin re-uptake inhibitor (SSRI) use in children and found that 95.7% of industry-funded published studies were reported to have positive results.[11] Manufacturers of SSRIs, however, also submitted a large number of unpublished studies in children to FDA. In FDA's more comprehensive review of both published and unpublished studies, only 20% of the well-designed placebo-controlled trials were positive.[12]

- **Published studies of SSRIs in children were also distorted to make their products appear better than they are.** In this same comprehensive review of SSRIs, FDA found two industry-funded studies which FDA concluded failed to show effectiveness, but which were published as showing effectiveness. Both studies failed on their primary efficacy endpoint. One paper instead highlighted success on secondary endpoints, and the other study inappropriately pooled two studies together that had individually failed.[13] A recent review in the *British Medical Journal* also found that industry-funded published studies on antidepressant use in children frequently "exaggerated the benefits, downplayed the harms, or both."[14]

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[11] Center for Science in the Public Interest, *SSRI Use in Children: An Industry Biased Record,* 5-6 (Feb. 2004). CSPI found that only 63.3% of independently-funded published studies were positive.

[12] T. Laughren, *Background Comments for February 2, 2004 Meeting of Psychopharmacological Drugs Advisory Committee (PDAC) and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee,* 5 (Jan. 5, 2004). In some cases, the lack of published negative studies can be attributed to medical journals' lack of interest in such studies (publication bias), rather than to suppression of such studies. However, it is unlikely that medical journals would have been uninterested in publishing studies on the lack of effectiveness of anti-depressants in children.

[13] T. Laughren, *Background Comments for February 2, 2004 Meeting of Psychopharmacological Drugs Advisory Committee (PDAC) and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee* (Jan. 5, 2004).

[14] J. Jureidini, *Efficacy and Safety of Antidepressants for Children and Adolescents,* British Medical Journal, 879-883 (Apr. 10, 2004).

- **A widely distributed 2000 publication on Vioxx in the New England Journal of Medicine omitted important heart attack data.** After the Vigor study, published in 2000 by the New England Journal of Medicine, showed fewer stomach side effects for Vioxx than for a competing pain-killer, Merck purchased 929,400 reprints of the article — more than one for every doctor in this country. [15] Some raised early concerns about discrepancies in the heart attack data after examining data available on FDA's website, but the top editor at New England Journal of Medicine at the time said that "we can't be in the business of policing every bit of data we put out."[16] By 2005, however, it came to light that the article, as published, had omitted three heart attacks — all in the Vioxx group of the trial. The editors of the New England Journal of Medicine published a 2005 *Expression of Concern* rebuking the authors of this article for failing to include all relevant heart attacks.[17]

- **A 2001 study of Celebrex in the Journal of the American Medical Association (JAMA) reported only six months of data despite having collected 12 months of data.** This article also concluded that there were fewer stomach side effects for Celebrex than for a competing pain-killer in a six-month trial.[18] Only after data were submitted for an FDA advisory panel meeting did it come to light that the study had actually lasted 12 months — and the Celebrex advantage in side effects largely disappeared by 12 months. In other words, the authors simply chose to report selectively the data that were more favorable to the product. The editor of JAMA was quoted as saying that "we are functioning on a level of trust that was, perhaps, broken."[19] Based on the data from the complete trial, FDA concluded in 2001 that there was no proven safety advantage for Celebrex over older drugs. Reprints of the published "6-month" study had likely been widely distributed, however, and sales of Celebrex skyrocketed, despite the FDA

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[15] C. Bombardier, *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxyn in Patients with Rheumatoid Arthritis,* New England Journal of Medicine, 1520-1528 (Nov. 23, 2000); *How the New England Journal Missed Warning Signs on Vioxx,* Wall Street Journal (May 15, 2006).

[16] *How the New England Journal Missed Warning Signs on Vioxx,* Wall Street Journal (May 15, 2006).

[17] G. Curfman et al., *Expression of Concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxyn in Patients with Rheumatoid Arthritis," N Engl J Med 2000; 343:1520-8,* New England Journal of Medicine, 2813-2814 (Dec. 29, 2005).

[18] F. Silverstein et al., *Gastrointestinal Toxicity with Celecoxib vs Nonsteroidal Anti-inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis,* Journal of the American Medical Association, 1247-1255 (Sept. 13, 2000).

[19] *Missing Data on Celebre,* Washington Post (Aug. 5, 2001).

conclusion. Director of Medical Policy at the Center for Drug Evaluation and Research, Robert Temple, said in the *Washington Post* that "when the JAMA article comes out and confirms the hype, that probably has more impact than our labeling does."[20]

- **Whistleblower lawsuit settlements reveal that the use of publications to promote off-label uses is a concerted strategy.** False Claims Act lawsuits, often called whistleblower suits, reveal many more examples of industry promotion of unapproved uses through deliberate manipulation of published literature. Between 1994 and 1998, Parke-Davis engaged in what they called a "publication strategy" to promote unapproved uses of Neurontin.[21] The company hired marketing consultants to create studies and find willing physicians to "author" them — but only positive studies were selectively published. Off-label use of Neurontin skyrocketed. This strategy ended in 2004 when Pfizer, on behalf of Parke-Davis, paid $430 million to settle civil and criminal liability relating to off-label promotion under the False Claims Act. Additional False Claims Act settlements that involve off-label promotion have followed. The settlements for Lupron (a prostate cancer drug), Serostim (human growth hormone), and Abilify (an anti-psychotic) were respectively $875 million, $704 million, and $515 million.[22] However costly the growing number of False Claims Act settlements for off-label promotion may be, they may not pose a significant enough deterrent on their own to prevent marketing of unapproved uses. In the case of Neurontin's $430 million settlement, the annual sales for Neurontin in 2003 alone were $2.7 billion — and nearly 90% of sales were for unapproved uses at the time of the settlement.[23]

- **Off label use of antiarrhythmic drugs based on published literature was not simply ineffective, but dangerous.** Patients suffering from heart attacks often have transient arrhythmias. In the 1980s physicians began to use two antiarrhythmic drugs called encainide and flecainide in patients who were recovering from heart attacks after studies in peer-reviewed journals showed a reduction in these arrhythmias with the use of these drugs, despite the fact that the FDA-approved label carried a warning that use in this

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[20] *Missing Data on Celebrex,* Washington Post (Aug. 5, 2001).

[21] M. Steinman et al., *Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents,* Annals of Internal Medicine, 284-293 (Aug. 15, 2006).

[22] House Committee on Oversight and Government Reform, Testimony of Department of Justice Associate Deputy Attorney General Ronald J. Tenpas, *Hearings on Financial Impacts of Waste, Fraud, and Abuse in Pharmaceutical Pricing* 110th Cong. (Feb. 9, 2007); United States Department of Justice, *Bristol-Myers-Squibb to Pay More Than $515 Million to Resolve Allegations of Illegal Drug Marketing and Pricing* (Sept. 28, 2007).

[23] *Pfizer to Pay $430 Million Over Promoting Drug to Doctors*, New York Times (May 14, 2004).

group of patients was not thoroughly studied. Comprehensive studies of this question later confirmed this reduction in arrhythmias for heart attack patients, but showed a more disturbing finding: patients on these drugs had more than twice the death rate of patients on placebo.[24] It is not clear that the manufacturers of encainide and flecainide engaged in any inappropriate activity, but distribution of the early peer-reviewed journal articles could have led to many unnecessary deaths.[25]

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[24] FDA, *Remarks as Prepared for Delivery by Senior Associate Commissioner Linda Suydam as the Keynote Address for the FDLI Conf. on Advertising and Promotion in the New Millenium* (Sept. 13, 1999).

[25] Senate Committee on Labor and Human Resources, Testimony of Deputy Commissioner For Policy, Food And Drug Administration William B. Schultz, *Hearing on Unapproved Uses of Prescription Drugs and Medical Devices*, 105th Cong. (Feb. 22, 1996).