

**Comments of the
Prescription Project, Community Catalyst,
National Physicians Alliance,
Prescription Access Litigation, Community Catalyst and
US PIRG**

Concerning

**The United States Food and Drug Administration
Draft Guidance for Industry
“Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or
Scientific Reference Publications on Unapproved New Uses of Approved Drugs and
Approved or Cleared Medical Devices”**

Docket No. FDA-2008.D.0053

April 21, 2008

The Prescription Project of Community Catalyst, Inc., a non-profit health care advocacy organization based in Boston (www.prescriptionproject.org); the National Physicians Alliance, a multi-specialty medical organization representing approximately ten thousand physicians (www.npalliance.org); Prescription Access Litigation LLC, a coalition of over 130 organizations representing consumers, health care advocates, seniors, labor union members, legal services organizations, and others (www.prescriptionaccess.org); and US PIRG, the federation of state Public Interest Research Groups (www.uspirg.org), strongly urge the Food and Drug Administration (“FDA”) not to adopt the proposed draft guidance, entitled “Draft Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices; Availability.”ⁱ

The Draft Guidance presupposes that “the public health may be advanced by healthcare professionals' receipt of medical journal articles and medical or scientific reference publications on unapproved or new uses of approved or cleared medical products that are truthful and not misleading.” For the reasons outlined below, the Prescription Project and other organizations listed above, disagree that such promotion advances the public health, and we therefore oppose the recommendations.

We also agree with the comments submitted by The Patient and Consumer Coalition and with those of the New York State Department of Health. The NYSDH urges that the FDA “leave the language of the Food, Drug and Cosmetic Act to speak for itself, or to impose meaningful restrictions on the nature and validity of the articles that manufacturers may disseminate without fear of running afoul of legal limits” and goes on to specify such reasonable restrictions.ⁱⁱ

Prescription drugs are frequently prescribed for uses that have not been approved by the FDA (“off-label” indications). Off-label use is often medically appropriate, but should be undertaken only when a clinician has carefully evaluated the medical evidence. Distribution of single studies by pharmaceutical representatives is not an effective way to facilitate evidence-based decision making and thus does not prioritize patient safety or public health. Specifically:

- Early evidence is often contradicted.
- Single trials can be misleading and may not adequately assess drug effectiveness or safety.ⁱⁱⁱ
- Statistically, any individual study has a good chance of coming to the wrong conclusion.
- Trials stopped early for benefit are found to be less striking on further review.^{iv}

This Draft Guidance lowers the threshold for the promotion of off-label uses through the distribution of published studies, thereby reducing industry incentive to conduct more conclusive trials.

- Currently, FDA approval is a major incentive for companies to test and evaluate their products. Once a medication is approved for any use, drug companies have incentive to study that product for use in additional indications.
- Creating a pathway to more off-label marketing reduces the incentive to obtain FDA approval for new indications.
- Under the Draft Guidance, a company would be able to disseminate a trial that finds positive data for any unapproved use, thus reducing the incentive to conduct more detailed research that might contradict the initial finding.

The FDA drug approval process requires review of all data regarding a drug, both published and unpublished. In contrast, the editorial review processes employed by peer-reviewed journals do not. Journal review processes vary widely and publication in a peer-reviewed journal is not in and of itself a guarantee of quality.

- FDA approval requires access to full data.
- Journal reviewers only have access to what has previously been published.
- Published studies may lack appropriate controls, design or statistical analysis.
- Industry has the potential to fund and publish individual studies with substantial bias.
- Industry-funded trials and reviews are more likely than independent evaluations to be favorable toward the sponsor’s drug.^v
- Publication bias means negative studies are less likely to be known by reviewers.
- Industry, motivated to sell more product, could selectively choose to distribute studies that show its products in a favorable light.
- Industry has frequently been shown to play an invisible role in funding and even “ghost writing” published studies that are published under the names of academic physicians.^{vi}
- FDA lacks resources to review all distributed studies and ensure they meet a high standard

This Draft Guidance would encourage pharmaceutical sales representatives (“detailers”) to further obscure their marketing goals by allowing them to characterize their interactions as “physician education”, while allowing them to disseminate materials for which there would be no meaningful standards to require fair balance. However, sales representatives are not qualified educators and should not be involved in the promotion of off-label uses—including the dissemination of published studies—for the following reasons:

- Drug detailers are incentivized by measurements of sales, not by the education they provide physicians. This goal is often incompatible with the promotion of appropriate prescribing.^{vii}
- Drug detailers are not required to have medical or scientific training and thus cannot be a reliable source of information for physicians on non-approved uses of medication.

There is enormous potential for off-label marketing to harm patients.

- The off-label use of atypical antipsychotic medications in patients with dementia illustrates these risks. Eli Lilly is reported to have heavily promoted Zyprexa for this off-label indication, despite an FDA warning that the drug can increase the risk of death in older patients with dementia-related psychosis.^{viii}
- An AHRQ review found an absence of evidence for many off-label uses of antipsychotic drugs, including use in the treatment of depression and obsessive compulsive disorder. For dementia, there is an increase in the risk of death, weight gain, stroke and neurological problems such as stroke and tremor.^{ix}
- According to US Department of Justice findings, Warner Lambert (now Pfizer) promoted Neurontin for off-label indications “even when scientific studies had shown it was not effective.”
 - For example, the company promoted Neurontin as effective for use as the sole drug (monotherapy) for epileptic seizures, even after solo use had been specifically rejected by the FDA. Similarly, the pharmaceutical company falsely promoted Neurontin as effective for treating bipolar disease, even when a scientific study demonstrated that a placebo worked as well or better than the drug.^x
 - The manufacturer settled the complaint for \$430m.^{xi}
- Patients may suffer economic harm as well as clinical harm from off-label promotion of expensive brand-name medications.^{xii}

As noted recently in the *New England Journal of Medicine*, the FDA acts in essence as a “learned intermediary,” scrutinizing clinical and preclinical data on behalf of prescribing physicians. Few individual prescribers have time or expertise to independently assess the quality of studies disseminated by industry sales representatives. The Draft Guidance would allow industry to distribute large quantities of materials to promote off-label indications not well supported by the balance of scientific evidence. While any individual study “might be technically

non fraudulent... the body of material could be chosen selectively to create an appearance of safety or efficacy that would not meet FDA standards.”^{xiii}

In conclusion, the Prescription Project and other organizations listed above urge the FDA not to issue the Draft Guidance in its current form, which would encourage the pharmaceutical industry to expand marketing practices which have been found to be illegal by government fraud investigations and successful litigation by government and consumers. We urge the FDA to hold public hearings to consider under what circumstances, if any, the industry should be allowed to market products for off-label indications.

In order to protect the interests of patients and the public, physicians and other prescribers should be informed by an unbiased synthesis of the best available information, not by ad hoc distribution of materials that are intended to promote off-label use of particular products.

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s.Allan Coukell, BSc (Pharmacy)
Director of Policy, The Prescription Project
Community Catalyst
30 Winter St., Boston, MA

s.Jean Silver-Isenstadt, MD
Executive Director
National Physicians Alliance
1902 Association Dr, Suite 200, Reston, VA

s.Alex Sugerman-Brozan, JD
Director, Prescription Access Litigation
Community Catalyst
30 Winter St., Boston, MA

s.Steve Blackledge
Senior Policy Analyst
U.S. PIRG, Federation of State PIRGs
1107 9th Street Ste 601, Sacramento CA

ⁱ [Fed. Reg. February 15, 2008. \(Docket No. FDA-2008-D-0053, OC 2007268\)](#)

ⁱⁱ Comments of the NY State Department of Health, April 8, 2008, concerning Docket No. FDA-2008-D-0053 (Feb. 13, 2008)

ⁱⁱⁱ Wilson P, Petticrew M. Why promote the findings of single research studies? *BMJ* 2008;336:722, doi:10.1136/bmj.39525.447361.94

^{iv} Montori VM, Devereaux PJ, Adhikari NKJ, et al. Randomized Trials Stopped Early for Benefit: A Systematic Review *JAMA*. 2005;294(17):2203-2209.

^v Jørgensen AW, et al. Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review *BMJ* 2006;333:782; and Lexchin Jet al. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;326: 1167-70; and Bekelman JE, et al. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA* 2003;289: 454-65

^{vi} Ross, J.S.et al. "Guest Authorship and Ghostwriting in Publications Related to Rofecoxib," *JAMA* 2008; 299(15): 1800-1812; and Steinman et al. "Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents," *Ann Intern Med.* 2006;145:284-293.

^{vii} ["Amgen documents on Enbrel marketing subpoenaed" Reuters Thu Jan 17, 2008](#)

^{viii} Berenson A. Drug Files Show Maker Promoted Unapproved Uses. *New York Times* (Dec 18, 2006)

<http://www.nytimes.com/2006/12/18/business/18drug.html>

^{ix} <http://www.ahrq.gov/news/press/pr2007/antipsypr.htm>

^x http://www.usdoj.gov/opa/pr/2004/May/04_civ_322.htm

^{xi} Steinman et al. "Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents," *Ann Intern Med.* 2006;145:284-293.

^{xii} Armstrong, David. "Pfizer Is Sued Over Lipitor Marketing ," *Wall Street Journal*, December 20, 2007; Page B5.

^{xiii} Kesselheim AS, Avorn J. Pharmaceutical promotion to physicians and first amendment rights. *New Engl J Med* 2008; 358: 1727-1732