

COMMENTS OF THE
NEW YORK STATE DEPARTMENT OF HEALTH

concerning

The UNITED STATES FOOD AND DRUG ADMINISTRATION's
Draft Guidance for Industry, Good Reprint Practices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 (Feb. 13, 2008)

April 8, 2008

The New York State Department of Health (“Department”) submits these comments to the federal Food and Drug Administration (“FDA”) concerning the FDA’s Draft Guidance for Industry, Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses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 (Feb. 13, 2008) (“Guidance”). These comments describe the backdrop against which the adequacy of the Guidance’s provisions should be evaluated and the ways in which the Guidance conflicts with established federal policy.

The Department will not reiterate the factual background and legal history set out in the Guidance document. Instead, it will concentrate on: (1) the latitude FDA has to articulate standards for acceptable and unacceptable conduct in a Guidance for Industry, (2) the evidence that the pharmaceutical industry has a history of improper off-label marketing its prescription drugs to practitioners, and (3) other announcements of federal policy that bear on the adequacy and appropriateness of the Guidance. In light of these factors, the Guidance constitutes a signal of FDA’s unwarranted increasing tolerance for conduct that could amount to illegal off-label promotion.

The Department urges FDA either not to promulgate a Guidance for Industry concerning “good reprint practices,” leaving the language of the Food, Drug and Cosmetic Act to speak for itself, or impose meaningful restrictions on the nature and validity of the articles that manufacturers may disseminate without fear of running afoul of legal limits. Specifically, to qualify for protection under the Guidance, a journal article that discusses a drug’s off-label use that the drug’s manufacturer wishes to disseminate to physicians and other practitioners should, at minimum, meet the following requirements as well as those currently contained in the draft Guidance: be published in a peer-reviewed journal that is designated by FDA as acceptable for this purpose or is at least national in scope and reputation and indexed in the Index Medicus of the National Library of Medicine; meet specific criteria similar to those spelled out in FDA’s advertising regulations and the FDA Amendments Act of 2007 for the expanded clinical trial results data bank that are indicia of quality and scientific and clinical validity for reports of the outcome of clinical investigations; not be written, edited or significantly influenced by the manufacturer of the drug, except perhaps where the principal investigator identified in any pre-patient-enrollment registration of the trial was the manufacturer’s employee, and that fact is emblazoned on the front of the reprint; and not be provided to the practitioner during the same detailing or marketing call with any promotional material for the drug.

THE NATURE OF THE GUIDANCE AND LIMITS ON ITS PROSCRIPTIVE AUTHORITY.

The Guidance only creates a safe harbor and does not prohibit any conduct or establish any enforceable rights. Thus, conduct that falls outside the safe harbor may or may not be permitted under the Food, Drug and Cosmetic Act. It is, therefore, essential that the safe harbor

be clearly delineated so that any conduct that might cross the line into misbranding, adulteration or improper promotion of a “new (unapproved) use” be unquestionably outside the protection of the Guidance. Ambiguity in the scope of the safe harbor only increases the likelihood that manufacturers will, in fact, cross that line, whether honestly or disingenuously.

Possible First Amendment concerns, moreover, do not justify the current ambiguity of the Guidance or its unnecessarily expansive safe harbor for dissemination of journal articles discussing off-label uses. It appears that even the most committed proponents of commercial free speech would agree that, as long as the Guidance is only a safe harbor, no First Amendment claim would lie even if arguably protected speech is not within the safe harbor’s protection.¹

There is an overarching concern with the general reach of the Guidance. The Guidance does not require that, to be within the protection of the safe harbor, dissemination of an article must be approved by individuals within the company who would have reason to know the fact at issue, such as whether the company had paid compensation to an author. Without such a requirement, individual detailers could decide to provide articles to the practitioners in their sales territory and could legitimately claim they did not have the knowledge that must be disclosed under the Guidance. In this situation, the company could claim that it did not know the article had been disseminated without the proper disclosure. This loophole must be plugged.

THE PHARMACEUTICAL INDUSTRY’S HISTORY OF OFF-LABEL PROMOTION

Off-label promotion of drugs is common. The federal government and the states have recovered criminal and civil penalties of over \$3.3 billion in 13 settlements of investigations involving off-label marketing allegations, and another settlement estimated at \$1 billion is considered imminent.²

In 2007 testimony before the Committee on Oversight and Government Reform of the US House of Representatives, an Associate Deputy Attorney General, speaking for the Department of Justice (“DOJ”), noted that recently the “most active” area for investigation concerning drug and device manufacturers involved allegations of “violations of the Food, Drug and Cosmetic Act, including off-label marketing and unlawful promotional activities.”³ Recognizing that “dissemination of reprints of peer reviewed medical journal articles” can benefit health care practitioners and patients, DOJ’s investigations revealed that:

certain companies may seek to vastly increase their market share by promoting their products for off-label purposes, by disseminating false and misleading evidence to support those unapproved uses Clearly, the law does not give drug manufacturers carte blanche to promote drugs for off-label uses by any means. Nor does the law create vast exceptions that render the Food Drug and Cosmetic Act or the Antikickback statute inapplicable to pharmaceutical manufacturers.⁴

The ambiguity of the Guidance appears to stake out such vast exceptions to the general prohibition of off-label promotion.

The DOJ testimony also cited the promotion of “compromised science” as a way “manufacturers are subverting a healthcare system that necessarily relies on the objective medical judgment of practitioners, and . . . may also harm the public health.”⁵ Publicly accessible documents from DOJ’s case alleging off-label marketing of Neurontin (gabapentin) against the Parke-Davis division of Warner Lambert (subsequently acquired by Pfizer, Inc.) provides a unique view into the pharmaceutical industry’s promotion of compromised science through the misuse of peer-reviewed journals. The state and federal settlements in this case yielded \$450 million in criminal and civil penalties.

At the time the alleged conduct occurred, Neurontin was approved only for adjunctive or supplemental anti-seizure use by epilepsy patients. Parke-Davis determined it would not be economically feasible to seek FDA approval for other possible indications.⁶ Instead, the company developed a strategy to use peer-reviewed journal articles to promote a variety of off-label uses for Neurontin. By 2002, it was estimated that 94 percent of all Neurontin sales were for off-label uses,⁷ and in 2003, its sales exceeded \$2.7 billion.⁸

In an August 2006 article published in the *Annals of Internal Medicine*, Steinman, et al., provided a cogent and succinct description of this strategy, which is set out below⁹ (the article’s references are included in endnote 9):

Parke-Davis employed a “publication strategy,” the goal of which was to use research not as a means to gain FDA approval for new indications but “to disseminate the information as widely as possible through the world’s medical literature” (77), generating excitement in the market and stimulating off-label prescribing despite the lack of FDA approval (78, 79). This strategy focused primarily on expanding gabapentin use in neuropathic pain and bipolar disorders, for which detailed decision analyses projected the greatest revenue potential (80–83).

The success of this strategy depended in part on publications being favorable to gabapentin. Some employees of Parke-Davis felt an obligation to publish studies with unfavorable results (80, 84), and in a number of instances such results were published (85– 87). However, management expressed concern that negative results could harm promotional efforts (88), and several documents indicate the intention to publish and publicize results only if they reflected favorably on gabapentin (78, 79). As stated in a marketing assessment, “The results of the recommended exploratory trials in neuropathic pain, if positive, will be publicized in medical congresses and published” (*italics added*) (78). Similarly, in discussing 2 nearly identical trials that yielded conflicting results on gabapentin as seizure monotherapy, the “core marketing team” concluded that “the results of [the negative trial] will not be published” (89). (The positive trial was published [90], but we could not locate the negative trial on a PubMed search.)

Beyond publishing its own clinical trials, Parke-Davis expanded the literature on gabapentin by contracting with medical education companies to develop review papers, original articles, and letters to the editor about gabapentin

for \$13,375 to \$18,000 per article, including a \$1000 honorarium for the physician or pharmacist author (91–98). For example, one “grant request” from a medical education company to Parke-Davis proposed a series of 12 articles, each with a prespecified topic, target journal, title, and list of potential authors (to be “chosen at the discretion of Parke-Davis”) (96). This proposal noted that “all articles submitted will include a consistent message . . . with particular interest in proper dosing and titration as well as emerging [off-label] uses,” mirroring Parke-Davis promotional goals for the drug (96). In this case Parke-Davis requested that authors prepare articles and submit them for peer review (92, 96). However, in another instance the medical education company offered substantial assistance in the development of manuscripts, reporting in a status report that “at [the author’s] request, we did an extensive literature search and submitted selected articles to him for reference We have offered him help in identifying and collecting his appropriate cases, analyzing data, writing a manuscript, or whatever he needs” (91). Among 7 published articles that we matched to sponsorship by a medical education company, 4 had favorable conclusions about gabapentin (99 –102), and the other 3 adopted a neutral tone (103–105). Article sponsorship was often not disclosed, with 6 of 7 articles not acknowledging receipt of an honorarium from the medical education company (although 1 of these acknowledged support from Parke- Davis) (99 –105). In 5 of 7 articles, the author identified by the medical education company had received funds from Parke-Davis for speaking engagements, consultants meetings, or other activities (11). (Ellipses in original.)

Another lawsuit, brought by the New York Attorney General, alleged that in connection with one marginally successful and several negative studies of Paxil (paroxetine) to treat Major Depressive Disorder in children and adolescents, the drug’s manufacturer GlaxoSmithKline, plc planned “[t]o effectively manage the dissemination of these data in order to minimise any potential negative commercial impact” by preparing and placing for publication an article only on the successful clinical trial.”¹⁰ This is, in fact, what occurred. The settlement required GSK to post the results of virtually all of its clinical studies on a publicly accessible Web site.¹¹ A similar outcome was obtained in an investigation by a number of state Attorneys General against Bayer concerning Baycol.¹² Congress subsequently enacted the FDA Amendments Act of 2007, which requires all manufacturers to post the results of their clinical studies on marketed, and possibly unmarketed, drugs.¹³

The Neurontin and Paxil cases demonstrate the well-documented fact of publication bias toward trials with favorable outcomes¹⁴ and, of greatest importance here, manufacturers’ responsibility for this bias. Publication bias necessarily undercuts even the possibility that, after receiving a reprint of a favorable published journal article concerning an off-label use, a physician would be able to obtain from a literature search a fairly balanced view of that use.

As noted in the DOJ testimony quoted above, manufacturers’ misuse of the medical literature to promote off-label use can have a direct and profound effect on patient care. It impacts a practitioner’s evaluation of the risk-benefit balance in prescribing a particular drug to treat a patient with a specific disease or condition. In the Neruontin case, DOJ cited clinical study findings that this drug was no more effective than placebo in treating bipolar disorder.¹⁵

The two concealed Paxil studies also showed that placebo was equal to or superior to Paxil in treating Major Depressive Disorder in a pediatric patient. If these facts had been known, physicians would certainly have taken them into account in deciding which drug to prescribe to treat the serious, even life-threatening disorders of depression and bipolar disorder.

General, ambiguous criteria for distinguishing between acceptable and unacceptable conduct may be appropriate for some industries. It is not the case for pharmaceutical manufacturers.

THE GUIDANCE CONFLICTS WITH ESTABLISHED FEDERAL POLICY

Federal Policy Favors Explicit Standards for Reporting Outcomes from Clinical Trials.

The draft Guidance relies primarily on the fact that an article was published in a peer-reviewed journal to establish its bona fides. Other than this objective requirement, the Guidance requires only that disseminated articles address adequate and well-controlled clinical investigations that are considered scientifically sound” by experts – not necessarily persons unconnected with the manufacturer – with the background to evaluate the drug or device’s safety and efficacy; (2) not be false or misleading; and (3) not pose a significant risk to the public health. The remaining provisions pertain to disclosures of potential conflicts of interest, the type of journal in which an article must appear and how it is to be distributed to practitioners.

As reflected in the Guidance, FDA apparently – and erroneously – assumes that any concern about the validity of a study, the adequacy of the reporting and an author’s independence is adequately addressed if the article is published in a peer-reviewed journal. There is, however, significant variability in the rigor of peer reviews, and a substantial number of journals that would meet the draft Guidance’s criteria for acceptable publications do not instruct their authors to comply with the standards promulgated by recognized medical journal organizations.¹⁶

There is, moreover, ample evidence that manufacturers have arranged for articles in such peer-reviewed journals to be ghostwritten, to have honorary authors and to disclose only partial data from a reported study.¹⁷ This conduct has undercut reliance on publication in a peer-reviewed journal as an assurance the reported data and conclusions are valid. Additionally, substituting a journal’s internal peer-review standards for explicit requirements that must be met to qualify for the Guidance’s safe harbor is in stark contrast to other expressions of federal policy for identifying outcome data from clinical trials that are sufficiently valid to constitute science, not promotion.

Principal among these statements of policy are FDA’s own advertising regulations, which explicitly do not apply to a manufacturer’s provision of a journal article reprint to a prescriber.¹⁸ On-label advertising cannot: selectively report side effect data to inflate the drug’s safety profile; pool data from insignificant or dissimilar studies, report side effects under general terms rather than specific ones, rely on a study that is inadequate in design, scope or conduct to support the claims; use the concept of “statistical significance” to support a claim that has not been demonstrated to have clinical significance or validity; use post-hoc analysis to establish findings not soundly supported by the study; or use statistical analyses or interpretations that do not

comply with established principles of statistical theory, methodology, applied practice or inference.¹⁹ These or equivalent criteria are completely absent from the Guidance.

The expanded clinical trials results data bank created by the FDA Amendments Act of 2007 similarly imposes criteria for the reporting of these outcomes that are sufficiently explicit and objective that they leave little room for manipulation or promotion. Congress has mandated, in some cases subject to modification through National Institutes of Health (“NIH”) regulations, that, among other things, manufacturers include the results for the primary and secondary outcome measures reported to the registry at the outset of the trial, the number of patients who dropped out of the trial or were excluded from the analysis, all of the serious adverse events, all adverse events with a frequency in excess of five percent in any arm of the trial, and whether there is any agreement that restricts in any way the principal investigator’s publication of the results in a scientific or academic journal, presumably including limitations on the author’s full and unfettered access to, and right to publish, all the data from the entire study.²⁰ Congress also requires NIH to evaluate whether a manufacturer’s ostensibly objective, apparently scientific report is slanted to accomplish a promotional interest.²¹

In at least one area, the Centers for Medicare and Medicaid Services (“CMS”) do not accept most peer-reviewed journals’ decision to publish an article as sufficient evidence of the quality of the study or the completeness with which the study and its outcomes were reported. To support a reimbursement claim under Medicare Part B for an off-label use of an oncology drug based on a clinical investigation, the study must appear in one of the journals CMS specifically designates as acceptable.²² CMS imposes this protective restriction although approximately half of anticancer chemotherapy drugs are used off-label.²³ The lapsed regulations FDA promulgated under the Food and Drug Administration Modernization Act (“FDAMA”) similarly required that disseminated articles on off-label uses be published in peer-reviewed journals that were recognized as national in scope and reputation and were indexed in the Index Medicus of the National Library of Medicine.²⁴

These elements from the FDA Amendments Act of 2007 and the FDA’s advertising regulations, as well as the CMS journal list and FDAMA journal requirements, lie at the heart of promoting the use of valid processes to obtain, analyze and report the outcomes of clinical trials, information that is likely to influence treatment decisions. The draft Guidance, in contrast, leaves that responsibility to medical journals and provides, at best, ambiguous “guidance” to the industry about what is, and what is not, permitted.

The Guidance, for example, directs manufacturers not to distribute “false or misleading” materials, but the agency’s regulations that explicate what “false or misleading” means in the context of reporting the results from clinical studies is specifically made inapplicable to this very activity. In a similarly ambiguous vein, the Guidance directs manufacturers to disclose their financial relationships with the “authors” of the disseminated articles, but fails to indicate whether this pertains to individuals who wrote or made significant contributions to the article but are not listed in the byline (ghostwriters). The Guidance, as the FDAMA regulations before it, requires journals in which disseminated articles appear to be published by organizations with editorial boards that use experts to review and comment on submitted articles, adhere to a policy of full disclosure of conflicts of interests and publish articles in accordance with its peer-review

procedures. But unlike the FDAMA regulations, the Guidance does not require that these journals be national in scope and reputation and be indexed in the Index Medicus.

There does not appear to be any barrier to including in the definition of the Guidance's safe harbor many of the specific standards and guidelines described above that are set out in the FDA false advertising regulations, the clinical trial results data bank provisions or the CMS and FDAMA minimum journal requirements. A manufacturer would not be foreclosed from disseminating an article that did not meet these more explicit standards, but could distribute it at its own risk in the event the dissemination is deemed to be false, misleading or the promotion of a new use. This is the situation that presently obtains in the absence of a safe harbor.

Additionally, the Guidance is internally inconsistent about whether the safe harbor encompasses the dissemination of published materials on an off-label use when the manufacturer has had substantial influence over or involvement in their development. The Guidance protects reference texts only when such influence is absent, but is silent on manufacturers' involvement in or influence over journal articles. Although the Guidance does require disclosure of both reference text and article authors' financial relationships with the manufacturer, this does not substitute for restrictions on the influence and direct involvement of the manufacturer in the preparation of the manuscript.

In a pre-FDAMA Guidance, FDA also applied the no-manufacturer-influence standard only to reference texts, but that was because this earlier Guidance was limited to peer-reviewed journal articles reporting one of the adequate and well-controlled trials the manufacturer submitted to FDA for approval of the indication discussed in the disseminated article.²⁵ FDA's acceptance of the study guaranteed that all of the data from the underlying study had been rigorously and independently reviewed. Peer-reviewers do not routinely have access to these data.

It is far from a novel concept to expect drug manufacturers to meet specific criteria that guard against the dissemination of information from clinical studies about off-label uses that is false, misleading or the promotion of a "new use." The justification for articulating such standards is fully supported by the industry's history of manipulating this type of information, even when it appears in peer-reviewed journals. As written, the Guidance creates an inappropriately lenient safe harbor that protects only the drug industry, not prescribers or their patients. It would be better for FDA not to describe a safe harbor than to create one that will invite manufacturers to market their drugs for off-label purposes through the medical literature.

Federal Policy Favors Fair Balance in the Information Disseminated about Prescription Drugs.

FDA's false advertising regulations explicitly require fair balance in an advertisement's presentation of information about a prescription drug. Similarly, the principle underlying the clinical trial results data bank is that, in order to make good treatment decisions, prescribers and patients need to have access to the outcomes from all clinical investigations of a particular drug to treat a specific disease or condition, regardless of whether the results were favorable or unfavorable to the drug. In other words, there needs to be fair balance in the available information about potential treatment options.

The Guidance, however, falls far short of the mark in this area. It provides that “where conclusions in an article or text to be disseminated have been *specifically* called into question by another article(s) or text(s), [it] must be disseminated with a representative publication that reaches contrary or different conclusions regarding the unapproved use.” (Emphasis added.) Manufacturers can be expected to interpret this to mean they are safe as long as the conflicting article does not actually reference the disseminated article in its discussion of contrary conclusions. Such a limited obligation does not provide fair balance.

Additionally, the FDAMA regulations did not require such a close linkage, but provided that disseminated peer-reviewed journal articles could be false or misleading when the material included only favorable publications although unfavorable publications existed.²⁶ This approach is far more in keeping with the educational purpose FDA advances for the dissemination to prescribers of journal articles about off-label uses. There is no barrier to constructing the Guidance’s safe harbor so it promotes fair balance, instead of suggesting to manufacturers that they may withhold information that genuinely educates practitioners about all the potential risks and benefits of a use that has not undergone rigorous FDA review, simply because it is unfavorable to the manufacturer’s product.

The example the Guidance provides for identifying when the failure to provide countervailing authority could be false or misleading creates a loophole ready-made for small, industry-sponsored clinical investigations of questionable value. According to the Guidance, dissemination of an article without including contrary authority could be false or misleading when the disseminated article is “inconsistent with the weight of credible evidence derived from adequate and well-controlled clinical investigations (*e.g.*, where a significant number of other studies contradict the article or reference text’s conclusions)” The Guidance does not suggest what is meant by the “weight” of authority or a “significant” number of contradictory studies. Again, a manufacturer might conclude from the language of the Guidance that it would be safe to disseminate a small, manufacturer-sponsored, short-term favorable study without including a very large, publicly funded, much longer duration or more rigorous study with contradictory results.²⁷ The Guidance, after all, is cast in terms of a “significant” number of conflicting studies. Yet, any fair reading of “false or misleading” would encompass such a one-sided dissemination. The Guidance virtually invites manufacturers to test this boundary.

This leniency, or at best ambiguity, concerning when contradictory articles must be disseminated with ones favoring an off-label use is not cured by the Guidance’s requirement that a manufacturer provide a comprehensive bibliography of published articles concerning adequate and well-controlled investigations that reached contradictory results to those reflected in the disseminated article. It is highly questionable whether practitioners would have ready access to the articles listed on such a bibliography.

The Guidance requires the manufacturer to include with the disseminated articles a number of types of information that were required by the FDAMA regulations, such as the absence of FDA approval of the use described in the article, the manufacturer’s interest in the drug, any financial relationships between the manufacturer and the authors of the article, the study’s funders and any known safety risks or concerns with the described use of the drug. It does not, however, adopt the FDAMA regulation’s standard that the manufacturer give to the

practitioner receiving the off-label article a notice identifying other drugs approved for the treatment of the disease or condition discussed in the disseminated article. Again, there is no apparent reason FDA could not include this provision in the description of the safe harbor, and it should be included. This is of special concern when the control in the disseminated article is placebo rather than a drug approved to treat the condition.

Excluded from the safe harbor defined by the Guidance are editorials, letters and similar types of articles published in peer-reviewed journals. As a general rule, the Department agrees with this position, but raises one caveat. When editorials or articles, published in the same journal as the disseminated article, raise questions about the validity of the underlying study or the analysis or conclusions reported in the article, or raise ethical concerns about the study or the authors' involvement in the study or development of the article, those materials should be disseminated with the off-label article. Indeed, dissemination of these materials should not only be permitted, it should be mandatory to qualify for the safe harbor.

The Guidance unnecessarily retreats from the very clear FDAMA prohibition against providing a published article or reference text concerning an off-label use with any promotional material.²⁸ The Guidance merely requires that the off-label journal article and promotional material not be fastened together. Even if the detailer complies with the Guidance's admonition that the off-label material not be discussed, providing the off-label "educational" and on-label promotional materials together in fact acts to promote the off-label use.

The absence of meaningful standards for providing fair balance when a manufacturer disseminates journal articles describing an off-label use of a drug raises serious doubts about whether the safe harbor is designed to promote the exchange of information that can validly inform a prescriber's judgment. Because the Guidance creates a safe harbor, rather than proscribing conduct outside its boundaries, FDA should be punctilious about ensuring that all conduct that arguably falls within the safe harbor is permitted under the Food, Drug and Cosmetics Act. Allowing dissemination of off-label information without providing contrary information that has at least equal scientific and clinical significance does not meet this standard of care and, in fact, undermines the purported educational purpose of the dissemination. The act of providing only one side of the available information about a product fairly defines promotional activity, not education.

Federal Policy Favors FDA Review of the Efficacy and Safety of Drugs

The ambiguity and apparent expansiveness of the safe harbor envisioned by the Guidance virtually invites manufacturers to market their drugs off-label through published journal articles without subjecting what amounts to a new indication to rigorous and independent FDA review. This is at odds with both FDA's and Congress' recent attempts to strengthen the initial and ongoing validity of FDA's approval process.

FDA recently announced efforts to strengthen the Advisory Committee process, which in turn should improve FDA's review of applications for approval of new drugs and devices and new indications for approved products.²⁹ In the FDA Amendments of 2007, Congress gave FDA more authority to require (not just request) additional safety information about marketed drugs.³⁰ Yet, the Guidance eliminates any incentive for a manufacturer to seek approval of a new

indication – and risk denial under the strengthened review – except when a new indication’s potential market justifies the cost of substantial advertising. Absent the possibility of huge sales for a new indication, the company will just disseminate to practitioners journal articles on the off-label use. This perhaps unintended consequence of the Guidance would undermine FDA’s core purpose of protecting the public health through careful assessment of a drug’s safety and efficacy for a specific indication.

CONCLUSION

The New York State Department of Health urges FDA not to issue the Guidance as currently drafted. The current version ignores the pharmaceutical industry’s unrepentant and ongoing marketing of drugs for off-label uses and its documented manipulation of the medical literature to do so.

A safe harbor should only encompass that conduct which is unquestionably unobjectionable and specifically serves the purpose for which the safe harbor is being established. The safe harbor described by the Guidance casts its net so broadly that a manufacturer could argue that its conduct is protected even though it amounts to the same conduct that previously gave rise to government fraud investigations and resulted in settlements of hundreds of millions of dollars in criminal and civil penalties. The Department assumes this was not FDA’s intention, but it could certainly be the unintended consequence of this ambiguous, unacceptably tolerant Guidance document.

Dated: Albany, New York
April 8, 2008

s/Richard F. Daines, M.D.
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Commissioner, New York State
Department of Health

ENDNOTES

1. *Washington Legal Foundation v. Henney*, 477 F. Supp. 2d 202 (D.D.C. 2007), *interpreting Washington Legal Foundation v. Henney*, 202 F.3d 311 (D.C. Cir. 2000).
2. Serono S.A. (\$704 million), Purdue Pharma LP (\$634.5 million), Bristol Meyers Squibb Co. (\$499 million), Schering-Plough Corp./Schering Sales Corp. (\$435 million), Warner Lambert/Parke-Davis/Pfizer, Inc. (\$430 million), Cephalon, Inc. (\$425 million), Genentech, Inc. (\$50 million), Intermune, Inc. (\$36.9 million), Eli Lilly & Co. (\$36 million), Pfizer, Inc. (\$34.7 million), Jazz Pharmaceuticals, Inc./Orphan Medical, Inc. (\$20 million), Cell Therapeutics, Inc. (\$10.5 million), and Medicis Corp. (\$9.8 million). Berenson A. Lilly considers \$1 billion dollar fine to settle case. *The New York Times*. Jan. 31, 2008:A1. (Zyprexa).
3. Testimony of Ronald J. Tenpas, Associate Deputy Attorney General, U.S. Department of Justice, before the Committee on Oversight and Government Reform of the U.S. House of Representatives, “Allegations of Waste, Fraud and Abuse in Pharmaceutical Pricing: Financial Impacts on Federal Health Programs and the Federal Taxpayer” (February 9, 2007), at 3.
4. *Id.* at 12-13
5. *Id.* at 13.
6. U.S. Department of Justice, “Warner-Lambert to Pay \$430 Million to Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion,” Press Release (May 13, 2004). Accessed at http://www.usdoj.gov/opa/pr/2004/May/04_civ_322.htm.
7. Schmit J. Drugmaker admitted fraud, but sales flourish. *U.S.A. Today*. August 16, 2004.
8. Company News: Judge Denies Pfizer a Restraining Order against Ivax. *The New York Times*. Aug. 21, 2004.
9. Steinman MA, Bero LA, Chren MM, Landefeld, CS. Narrative review: the promotion of gabapentin: an analysis of internal industry documents. *Ann Intern Med*. 2006 145:284-93. The following are the references contained in the quoted passage:
 11. United States ex rel. Franklin v. Parke-Davis, 147 F. Supp.2d 39 (D. Mass. 2001), Exhibit 61. Payment Register.
 77. United States ex rel. Franklin v. Parke-Davis, 147 F. Supp.2d 39 (D. Mass. 2001), Exhibit 21. [Interoffice memorandum from Atul Pande to John Boris, re: “Gabapentin Approvals”, and handwritten response]; 28 March 1995:X029227.
 78. United States ex rel. Franklin v. Parke-Davis, 147 F. Supp.2d 39 (D. Mass. 2001), Exhibit 26. Marketing Assessments—Neurontin in Neuropathic Pain and Spasticity [and cover letter]; 24 July 1995:WL07520-WL07547.
 79. United States ex rel. Franklin v. Parke-Davis, 147 F. Supp.2d 39 (D. Mass. 2001), Exhibit 31. [Parke-Davis memo from John Boris to “Distribution,” re: “Marketing Assessment—Neurontin in Migraine,” and cover letter]; 31 July 1996:V082736-V082761. Review Promotion of Gabapentin 292 15 August 2006 *Annals of Internal Medicine*

80. United States ex rel. Franklin v. Parke-Davis, 147 F. Supp.2d 39 (D. Mass. 2001), Exhibit 27. [Parke-Davis memo from Francie Kivel to “Distribution,” re: “Minutes from August 29, 1995 Neurontin Indications Decision Analysis Group Meeting”]; 29 August 1995:V049269-V049274.
81. United States ex rel. Franklin v. Parke-Davis, 147 F. Supp.2d 39 (D. Mass. 2001), Exhibit 29. [Parke-Davis memo from Francie Kivel to “Distribution,” re: “Neurontin Indications Publication Analysis Report”]; 26 October 1995:V053848-V053877.
82. United States ex rel. Franklin v. Parke-Davis, 147 F. Supp.2d 39 (D. Mass. 2001), Exhibit 28. Transcript of deposition of Frances J. Kivel; 20 September 2002:15-17, 92-93, 113-114, 120, 312-318, 337, 338.
83. United States ex rel. Franklin v. Parke-Davis, 147 F. Supp.2d 39 (D. Mass. 2001), Exhibit 130. 12th Core Marketing Team Meeting—Neurontin [agenda, minutes]; 19-20 March 1996:V045404-V045418.
84. United States ex rel. Franklin v. Parke-Davis, 147 F. Supp.2d 39 (D. Mass. 2001), Exhibit 1. Transcript of deposition of John Boris; 16 September 2002:11-21, 26, 29-30, 35, 79-80, 81, 86-87, 96-97, 155-160, 171, 195, 198, 219-221, 328, and 346.
85. Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. *Gabapentin Bipolar Disorder Study Group. Bipolar Disord.* 2000;2:249-55. [PMID: 11249802]
86. Gorson KC, Schott C, Herman R, Ropper AH, Rand WM. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial [Letter]. *J Neurol Neurosurg Psychiatry.* 1999;66:251-2. [PMID:10071116]
87. United States ex rel. Franklin v. Parke-Davis, 147 F. Supp.2d 39 (D. Mass. 2001), Exhibit 94. Transcript of deposition of Philip Magistro; 4 September 2002:72-73, 75-79, 85-86, 134, 153-154.
88. United States ex rel. Franklin v. Parke-Davis, 147 F. Supp.2d 39 (D. Mass. 2001), Exhibit 129. 18th Neurontin Marketing Power Hour—Minutes [and agenda for “14th Core Marketing Team Meeting,” plus cover memo]; 6 March 1997:V042365-V042371.
89. United States ex rel. Franklin v. Parke-Davis, 147 F. Supp.2d 39 (D. Mass. 2001), Exhibit 120. Neurontin 14th Core Marketing Team Meeting [agenda, conclusions, action items]; 8-9 April 1997:V047116-V047129.
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14. *E.g.*, Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent effect. *N Engl J Med*. 2008 358:252-60 (from the studies published in the medical literature, it appeared that 94 percent of the trials conducted were positive, whereas FDA’s analysis of all the studies submitted to it found only 51 percent were positive; FDA also found that 11 of 74 studies that it found had negative or questionable outcomes were reported in the literature as having had positive results); Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG, Empirical evidence of selective reporting of outcomes in randomized trials. *JAMA*. 2004 291:2457-62 (review of published articles describing studies submitted to Danish regulatory agency showed 50 percent of efficacy and 65 percent of harm outcomes per trial were incompletely reported, with significantly more unfavorable outcomes unreported; 62 percent of published studies had at least one primary endpoint that was changed, omitted or introduced; 86 percent of survey responders denied having unreported outcomes); Olson CM, Rennie D, Cook D, et al. Publication bias in editorial decision-making. *JAMA*. 2002 287:2825-8 (collects materials concerning publication bias; finds publication bias due to non-submission of articles, not editorial rejection of articles with negative outcomes); Melander H, Ahlqvist-Rastad J, Meijer G, Beerman B. Evidence based medicine – selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. *BMJ*. 2003 326:1171-3 (compares published articles to reports submitted to Swedish regulatory agency and found, among other things, that many publications did not report the intention-to-treat, but only the more favorable per-protocol analysis; studies with favorable outcomes were more likely to be published than those with unfavorable ones).
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18. 21 C.F.R. § 202.1(l)(2).
19. 21 C.F.R. § 202.1(c)(6) and (e)(7).
20. 42 U.S.C. § 282 (j)(3)(C)(ii), (j)(3)(C)(i), (j)(3)(I)(iii)(I) and (II), (j)(3)(C)(iii).
21. In addition to summaries aimed at the public, which cannot be promotional, the statute also requires manufacturers to include a summary of the trial that is technical in nature if the Secretary determines this type of summary can be included without being “misleading or promotional.” 42 U.S.C. § 282(j)(3)(D)(iii)(II).
22. CMS, Medicare Benefit Policy Manual, Ch. 15, 50.4.5; CMS, CMS Manual System, Pub. 100-02, Medicare Benefit Policy, Transmittal 78 (Sept. 27, 2007).
23. ASCO. Reimbursement for cancer treatment: coverage for off-label drug indications. *J Clin Oncol.* 2006 24:3206-8.
24. 21 U.S.C. § 360aaa-5(5).
25. “Advertising and Promotion; Guidance,” Docket No. 95D-0377, 61 F.R. 52800 (Oct. 8, 1996).
26. 21 C.F.R. § 99.101(a)(4).
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28. 21 C.F.R. § 99.101(b)(1)(v)(2).
29. FDA has stated that it is improving Advisory Committee procedures, presumably to improve approval decisions. <http://www.fda.gov/oc/advisory/default.htm> (accessed February 26, 2008); FDA, “Draft Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees,” (March 2007).
30. 21 U.S.C. § 355(o)(3).