

PROMOTION OF OFF-LABEL USE: IN FAVOR OF A REGULATORY RETREAT

*Byron Stier**

The title of my talk is *Promotion of Off-Label Use: In Favor of a Regulatory Retreat*, and by that I mean that the FDA's background prohibition on off-label promotion should recede and just go away. In the gap should step in the tort claims that co-panelist Eric Chaffin has today been talking about: fraud, negligence, and duty to warn. And those tort claims should step in only where that promotion is either fraudulent or careless in some way.

My argument proceeds in four parts. First, as I said, the FDA's general prohibition on promoting off-label use is counterproductive because it curtails the dissemination of useful information that doctors need to make informed judgments. Useful information can also come from sales representatives; such information is not automatically tainted by bad influence. And doctors need reliable information on off-label uses because they are in the best position to determine appropriate treatments and appropriate prescriptions. Second, I would argue that a better approach would be to eliminate this general ban on discussing off-label uses, and instead resort to these general tort remedies of fraud, negligence and failure to warn. These tort claims could be brought by patients who claim that as a result of some mis-promotion that lead to a mis-prescription they have actually been injured. Third, I would argue that my approach is broadly consonant with the *Wyeth v. Levine* decision, 129 S. Ct. 1187, because the *Wyeth* case recognized the limits of the FDA as an arbiter of public health information and placed the burden

* Irving D. and Florence Rosenberg Professor of Law, Southwestern Law School. I thank my fellow symposium panelists Eric T. Chaffin, Raul Tabora, and Mollie Hertel, as well as moderator Alicia Ouellette, all of whom participated in the Albany Law School symposium on off-label drugs. In addition, I am thankful for the general research support provided by Southwestern Law School.

squarely on manufacturers to be responsible in tort for the information disseminated by them about their products. Lastly, I would argue that mass tort litigation is a potent counterweight to the kinds of abuses that we are here concerned about. Genuine abuses stem from fraud or carelessness, not merely the presentation of any information. Mass tort litigation, which can be of far-reaching scope, provides a tremendous threat to pharmaceutical companies and industries to make sure that they are presenting accurate information. This litigation can lead to huge settlements that not only compensate plaintiffs, but also have the effect of deterring future misconduct—we can be confident that plaintiffs' lawyers will hold their feet to the fire.

So into the argument with greater detail, first with regard to the FDA's counterproductive ban on off-label promotion. Generally, a drug may not be prescribed legally at all in the United States unless it has been approved by the FDA as safe and effective for some use. Obtaining FDA approval requires several levels of clinical testing that can take years and cost millions of dollars. Once a drug is approved, however, doctors in their clinical judgment may then lawfully prescribe that drug for other uses that are not FDA-approved—so-called off-label uses. Both the FDA and the medical community recognize that these off-label uses are important, appropriate methods of developing medicine. And off-label prescription is rampant: a remarkable 20 to 60% of prescriptions are off-label. Moreover, in certain areas of medicine, such as cancer and AIDS, there is even higher off-label usage of medications.

Yet the FDA generally prohibits manufacturers from promoting what so many doctors are doing and providing information about it. Why is the FDA stopping the transfer of information? First, the FDA is appropriately concerned that the information provided by the manufacturers might be incomplete, misleading, or untruthful. Second, the FDA wants to push manufacturers into filing new drug applications to test the new use. The problem with that latter reason is that, as I have noted, obtaining approval for a new use is time-consuming and expensive, and the approval of those uses is so specific that repeated requests for approval may be necessary. As a result, additional applications for approval are often not filed, while doctors continue to prescribe off-label. And manufacturers are generally gagged from discussing those off-label uses with the doctors, even though the manufacturers are likely the most

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efficient gatherers and disseminators of all this information, which they can then give out to doctors.

In recent years, the FDA has increasingly understood that its position may have hurt public health by depriving doctors of information about the drugs they are making decisions to prescribe or not. For example, in a January 2009 FDA notice entitled “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,” the FDA stated that it

does recognize, however, the important public health and policy justification supporting dissemination of truthful and non-misleading medical journal articles, and medical or scientific reference publications on unapproved uses of approved drugs to health care professionals and health care entities. Once a drug has been approved or cleared by the FDA, generally health care professionals may lawfully use or prescribe that drug for uses or treatment regimens that are not included in the approved labeling. These off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care.

The FDA admits there that the state of the art for a particular medical treatment may actually be what the FDA has not specifically approved—the off-label prescription of drugs. The FDA concludes that “[a]ccordingly, the public health may be advanced by health care professionals’ receipt of medical journal articles and medical or scientific reference publications on unapproved new uses of approved or cleared medical products that are truthful and not misleading.”

Based on such concerns, the FDA had moved to loosen some of these restrictions under §401 of the FDA Modernization Act of 1997. Manufacturers were allowed certain ways to disseminate medical and scientific information on unapproved uses of drugs. Then, in 2000, the FDA published a notice clarifying application of §401 on implementing regulations. In that notice, the FDA created a safe harbor before and while disseminating journal articles and reference articles about unapproved uses, if various conditions are followed. But the FDA said that if a manufacturer distributes information without following these conditions, then even though it would not constitute an independent violation of law, the violation could be used as evidence of impermissible intent that the product be used for an unapproved use. In effect, the FDA told manufacturers what they should do to avoid

liability. In September 2006, however, §401 ceased to be applicable under a sunset provision in the statute.

As I mentioned, after the sunset of §401, the FDA then promulgated the notice, updated as of January 2009, allowing further distribution of medical journal articles on unapproved uses. Under this notice, only certain types of articles may be distributed to the doctors. Such articles must be peer reviewed. In addition, they cannot have a special supplement or publication funded by the manufacturers. Moreover, they cannot be primarily distributed by the manufacturer, but instead must be generally available. Furthermore, such articles cannot be edited, written, or significantly influenced by the manufacturer. The studies must also be well-controlled clinical investigations. And again, the articles cannot be false or misleading, nor may their promotion pose a significant risk to public health if they are relied on—essentially a negligence approach. As a result of these restrictions, various standard ways of conveying medical information are not permitted. For example, the manufacturer could not provide a letter to the editor written by a doctor, an abstract of a publication, or reference publications that do not include discussion of the investigation or the underlying data.

The FDA also limits the way this information is distributed. It has to be an unabridged reprint, and may not be marked, highlighted, summarized, or characterized by the manufacturer. In addition, it must be distributed separately from promotional information and not in promotional exhibit halls or during promotional speaker presentations. Moreover, the information must be accompanied by the approved labeling for the drug, as well as a comprehensive bibliography of publications and, interestingly, one representative publication of a contrary conclusion. So it is sort of a gift basket of materials that goes as determined by the FDA. Furthermore, other approaches to disseminating information may run afoul of the requirements of no off-label use. As a result—whether or not the manufacturer also engages in conduct in conformance with these recommendations—if the manufacturer does anything else than what the FDA provides, such other conduct may result in an enforcement action for inappropriate discussion of information. In addition to all these rules, other rules govern the manufacturer's involvement in continuing medical education programs, which I will not go into because obviously there is a lot of detail here.

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The problem is that the FDA's current approach still prevents much of the dissemination of useful information to the doctors. Sales agents are not permitted to discuss or comment on the peer-reviewed articles. In addition, sales agents are not allowed to answer questions from doctors in a back-and-forth, or provide other internally gathered data from the manufacturers. And manufacturer-prepared summaries of studies or reference publications are prohibited, even though they could well be useful based on the manufacturer's interest in supplying accurate information to doctors to make their decisions. That is counterproductive. We want good information being provided in many flexible ways to the doctors so that they can make decisions.

But it is worse than that because in addition to limiting that information, the FDA is fueling the fires of litigation that may not always have served valid policy goals of preventing fraud and carelessness in off-label marking. That is because any violation of the FDA's very detailed off-label promotion policy, even if the information is truthful, reasonable, and helpful to doctors, could well be the basis of an FDA enforcement action or the predicate for other legal theories that the industry could be sued for just because the manufacturer violated the FDA's requirements on how this information should be presented. Indeed, there has been litigation prosecuting companies for violations of these rules. Some of the actions, as Eric Chaffin mentioned, have been based on this False Claims Act, which pertains to wrongful payments made from Medicare and Medicaid, which themselves do not generally allow reimbursement for off-label prescriptions, which seems like a questionable approach as a background rule, given widespread off-label use. Off-label promotions have also led to criminal fines based upon products being misbranded or mislabeled. Other lawsuits have sought to characterize off-label promotion as negligence per se, premising the lack of due care solely on the violation of the standard set forth by the FDA. Still other lawsuits seek to impose liability on manufacturers under RICO, by viewing off-label promotion as a form of racketeering activity, a theory originally associated with organized crime. Even accurate and helpful information might be alleged to be racketeering based on the violation of the FDA's rules.

At base, I would argue with all these legal theories though, one should ask, in the absence of proof that the promotional material is fraudulent or the off-label use is negligent or misleading, why

is the promotion bad? Why is the FDA limiting it? Indeed, to the contrary, such promotion could be good and could be something we want to encourage. In fact, we may need to get that information out as quickly as possible.

We heard from the panel this morning about patients who are in extremis—who may die very quickly—and for whom there may not be time to wait for the perfect peer-reviewed article that may be included in the FDA-condoned basket of materials. Maybe information needs to move more quickly because such clinical decisions are made day-to-day. Yet companies who provide such information outside the FDA-approved route are exposed to multi-million dollar liability, and the government attorneys prosecuting these cases expend their scarce prosecutorial resources. So if the focus should be whether there was negligent or fraudulent activity by the industry, should not the default rule be the time-tested tort claims for negligence and fraud as well as failure-to-warn products liability claims, which themselves are largely based on a negligence approach? In addition, there could be claims of contribution and indemnity against manufacturers by doctors who are sued for malpractice by their clients if the doctor makes a bad decision in clinical judgment about prescribing a drug, a lack of care. I think that approach preserves the upside of open communications about off-label uses—i.e., the dissemination of useful information about treatments—but it also ensures that unhelpful marketing and promotion that is careless or untruthful is deterred.

What we do not need is an overbroad FDA rule that eliminates truthful, non-negligent exchange of information by companies and doctors, or even a rule that unduly burdens those valid communications by seeking to micromanage them. We heard a little bit on the panel today, earlier this morning, about a question to a sales representative, who might respond, “Oh, I can’t talk to you about that, because I have to process this through several different, detailed rules.” Why can’t we just allow discussion to go forth subject to the requirement that one cannot lie, or be misleading or careless? That seems flexible.

Similar arguments have been made against these FDA off-label promotion rules in the First Amendment context. In those cases, the Washington Legal Foundation argued that the FDA’s restriction on truthful, careful speech was unconstitutional under the First Amendment. Although that constitutional litigation may continue to go on, focusing on this new January 2009 FDA

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notice, the argument that I am putting forward is not based on First Amendment constitutional law, but rather the systemic advantages of tort law and ex-post litigation rather than an ill-advised ex ante micromanaging attempt to regulate by the FDA.

What are some of the advantages of mass tort litigation over the FDA's regulatory approach? First, as I have said, the tort claims would allow truthful, careful information to be disseminated, which would further public health goals about good prescription of medications. Second, these tort claims benefit from their flexibility and their adaptability. While the FDA strains to detail, based on the information it has at any given moment, the minutia of when, how, and what of interactions between doctors and manufacturers, tort principles would sit on the shoulder of the manufacturer, always looking over and asking important questions: Are you doing the right thing? Is this inappropriate or not? Is it careless, misleading, or untruthful? Are you doing the right thing in light of all the information you have now, today, not when you filed your FDA application three years ago? Should you change what you are doing based upon something that was published last week? That flexibility assists the flow of important information on health. Why shouldn't sales agents be able to truthfully answer questions from doctors in a conversation about their products? Why shouldn't the companies be able to present letters to the editor, case reports, and other information? There is a reason they are published in the *New England Journal of Medicine* and all these other journals—doctors find them helpful to consider. Why shouldn't the companies be able to fund their own truthful materials and well-grounded analyses and provide them to doctors? Tort causes of action will let this truthful, carefully prepared information be exchanged. But tort law will still prevent negligence and fraud, especially with the prospect of punitive damages for gross misconduct.

Tort claims also have a practical limitation on litigation, which is the requirement of injury. A patient who sues in tort must have actually suffered an injury from what happened. Tort litigation would not stem from some miscommunication that may not have ever negatively affected the clinical judgment or prescription actions of a doctor. If a patient has not been proximately harmed by some mis-prescription based upon this misconduct, then perhaps it is not worth the sizeable attorneys fees and transaction costs to society to have litigation churning

forward.

Furthermore, the tort principles underscore that it is the responsibility of the manufacturer to stand behind its product and the information it presents, which brings me again to the *Wyeth* case. My argument, I think, is consonant with what the *Wyeth* opinion holds. The *Wyeth* opinion rejected the claim that the FDA's earlier approval of a label and warnings for drugs preempted all state tort lawsuits. The opinion also rejected Wyeth's claim that Wyeth could not change on its own the label of its drug. Instead, the Supreme Court said it was Wyeth's responsibility to ensure its product was adequately labeled; it was not the FDA's responsibility. Wyeth could change the label on its own and file the paperwork with the FDA later on. In addition, the *Wyeth* Court noted, remarkably, that the FDA does not have the resources to accomplish its public health mission. And so I would argue, if Wyeth can make its own decisions on labeling and is after *Wyeth v. Levine* subject to state tort lawsuits, why can't Wyeth and other pharmaceutical companies also make their own decisions on off-label promotion? Because if such companies can change the label, isn't that really in effect off-label promotion that they may be required to do to avoid tort liability? Although the *Wyeth* opinion treats preemption, the opinion suggests a model in which tort law steps forward to take up the slack from an imperfect FDA, and in fact expects manufacturers to do careful off-label promotion in appropriate instances.

My final point is that these individual lawsuits by plaintiffs in litigation, which lead to mass tort litigations, are a tenable counterpoint to the pharmaceutical industries potential abuse of off-label promotion. Although mass tort class actions for personal injuries have been largely rejected, they have been replaced by an approach where masses of lawsuits, frequently in the thousands, are filed across the country by plaintiffs' lawyers who network with each other to pool resources, share information, and coordinate strategy, utilizing the internet and databases of documents. These multiple plaintiffs' firms effectively form an ad hoc law firm. As the court in *Arch v. American Tobacco Co.* commented, actually in the tobacco litigation, it's no longer "David versus Goliath" in plaintiffs versus defendants, but instead it's "Goliath versus Goliath"—that is how organized and powerful the plaintiffs' bar can be when seriously involved in mass tort litigation.

There is every reason to think that a mass tort litigation

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approach works well. For example, the Vioxx mass tort litigation recently moved towards settlement of approximately \$5 billion. Such an approach would also work in an off-label promotion context. The result would effectively forward appropriate policy goals, and also be efficient because settlements are less costly than proceeding through trial.

It is also interesting that some of the prior off-label litigation has been successful based upon regulatory-oriented claims, like the False Claims Act, rather than based upon pure tort claims, which of course are also available. Why is that? Some of the tort claims may have foundered on proof that there was actually any effect on the doctor's decisions by the alleged off-label mis-promotion; causation could not be traced from the alleged mis-promotion to anything that actually ever hurt anyone. The doctors may have still prescribed appropriately. Perhaps any mis-promotion in many of these litigations has not actually been hurting people. That is not that surprising to me because doctors, as learned professionals, are generally able to process information from multiple sources and still safeguard the patient interest. One wonders how socially beneficial this prior litigation has been in stopping genuine misconduct involving fraud and negligence.

In conclusion, I argue that the FDA should drop its general curtailments of off-label promotions, and that it would be socially beneficial to empower and encourage dissemination of valuable medical information. Such an approach would free up scarce public prosecutorial resources to focus in litigation on real wrongdoing. But my approach would not leave without any remedy the patients who are injured by untruthful or careless marketing for off-label uses. A patient could still sue in tort the manufacturer as well as the doctor, if there is any malpractice. Moreover, the doctor could sue the manufacturer for contribution or indemnity if the doctor's decision stemmed from genuine misconduct by the manufacturer. The prospect of all those lawsuits together provides a potent alternative to the FDA's current approach.

Thank you very much.