SMOOTHING THE WRINKLES OF OFF-LABEL PROMOTION

Allergan’s Preemptive Strike Against the FDA
I. Introduction

Off-label drug use, the practice of prescribing a drug for a purpose other than the use approved by the FDA, is not an insignificant aspect of medical treatment or the revenue generated by pharmaceutical companies. Approximately 20% of all prescriptions written in the United States are for off-label indications.\(^1\) Off-label sales account for approximately $44 billion in revenues in the United States alone.\(^2\) The penalties for violating the FDA’s current regulations prohibiting off-label promotion are significant. In September 2009, Pfizer paid an unprecedented $2.3 billion to settle FDA charges that it allegedly encouraged its salespeople to promote one of its drugs for an off-label purpose.\(^3\)

The risk-reward balance in off-label use can literally mean billions of dollars in either revenue or fines, depending on the facts. Because the FDA permits physicians to use drugs as they deem medically necessary, drug companies are left in a quandary concerning precisely what information they are permitted to communicate to doctors, and in what form that communication can be made. Often, pharmaceutical companies must navigate the foggy shore-line between the requirement to provide “adequate information” about the uses for their drugs while avoiding the impression that they are “promoting” their drug for off-label uses.

In its lawsuit against the FDA, Allergan is using the First Amendment protection of free speech as a beacon and attempting to chart a course that other drug companies may be able to follow. The result of this lawsuit may have long standing consequences for how both drug and medical device manufacturers can communicate information about their products in the future.

II. FDA Authority and Regulation

Over the last 70 years, Congress and the FDA have developed a regulatory scheme that has been interpreted from time to time by courts to ensure safe and effective drugs reach consumers. This scheme attempts to balance the benefit to society from a wide variety of drugs used to medically treat ailments, while reducing the potential harm that drugs can cause either from adverse side effects or from unwarranted claims of effectiveness. Regulation of the information that accompanies a drug plays a central role in this balancing of safety and effectiveness.

A company may not market a drug without FDA approval and every drug must have a label. The FDA has extensive authority over drug manufacturers’ advertising and marketing, mandating certain communications while prohibiting others.\(^4\) All drug labeling must provide adequate directions for use.\(^5\) If the drug is dispensed with a prescription, then the label must provide adequate information for its use.\(^6\) The difference relates to the method by which the drug is dispensed – if it is sold directly to consumers it must have sufficient information so that consumers can use it safely; if it is a prescription drug, the information must provide the patient’s doctor with adequate information to make an informed medical decision with respect to prescribing and/or using the drug.

The information that is required to accompany a drug must be contained within the drug’s label. The Food, Drug and Cosmetic Act (“Act”) defines “label” as the written material that accompanies the drug, but FDA regulations have expanded the definition of “label” to include brochures, mailings, catalogs, motion pictures, sound recordings, literature and essentially any tangible thing that refers to the drug.\(^7\)
The information that the FDA requires manufacturers to include on the label must refer to the drug’s uses. The “uses” are those approved by the FDA, and, as expanded by the FDA’s regulations, the uses objectively intended by the manufacturer. The FDA regulations state that a manufacturer’s oral or written statements, or even the manufacturer’s knowledge of an off-label use, can be evidence of the manufacturer’s “intended use” of a drug.  

A pharmaceutical company is not permitted to advertise or promote a use of a drug or device that is not approved by the FDA. Advocating off-label uses carries criminal and civil sanctions, often amounting to multi-million dollar fines. Yet, when a manufacturer becomes aware that doctors are using its drug for a use not approved by the FDA, that knowledge may trigger an obligation to provide additional information in the product’s label.

Labeling is a difficult issue for a drug manufacturer. A manufacturer must provide label information concerning all uses of the product, but may not advertise or promote the drug for a use not approved by the FDA. When the manufacturer becomes aware of off-label uses of its drug, it has an obligation to provide adequate information about the use (dosing regimens, administration techniques, side effects, adverse outcomes, etc). However, providing information to doctors about an off-label use may result in:

- The FDA prosecuting the manufacturer for illegal off-label promotion;
- The FDA determining that the drug is mislabeled (containing information related to an unapproved use); or
- The FDA considering that the drug is a “new drug,” and requiring the manufacturer to begin the long and expensive New Drug Application process.

Further complicating the issue, the FDA occasionally requires pharmaceutical manufacturers to respond to FDA-issued Risk Evaluation and Mitigation Strategies (REMS). The FDA issues REMS in response to reports of unexpected outcomes or adverse side effects. Although the FDA may require a REMS concerning an off-label use of a drug, a manufacturer is still prohibited from promoting the off-label use of a drug when responding to a REMS.  

Even in situations where a manufacturer believes specific scientific information pertaining to an off-label use would be helpful to physicians, the manufacturer can only provide the specific information permitted by the FDA.

### III. Allergan Enters the Off-Label Fray

Founded in 1950, Allergan, Inc. is a global, technology-driven health care company based in California. Allergan has discovered, developed and commercialized diverse pharmaceutical treatments. It employs more than 8,000 people worldwide and operates competitive research facilities and manufacturing plants in numerous countries. In addition to its discovery-to-development research organization, Allergan actively markets its products in more than 100 countries. During the last reporting period, Allergan's total product net sales were $1,206.5 million. During 2008, total product net sales totaled $4.3 billion, a 12 percent increase over 2007. Allergan increased R&D spending 13 percent in 2008, to approximately $729 million.

Over 20 years, Allergan spent nearly $800 million in research and development of Botox®, which is derived from the Botulinum toxin and declared “one of the World’s most versatile medicines.” The Botulinum toxin, a purified protein
derived from the bacterium *Clostridium botulinum*, has been approved in approximately 80 countries for 21 different indications including: eye muscle disorders (first received approval in December 1989); cosmetic uses such as wrinkle repair; excessive underarm sweating; and upper limb spasticity (which received approval in March of 2010). Generally, Botox® is administered by small injections, and has the effect of reducing specific muscle activity and blocking nerve impulses that trigger excessive muscle contractions or glandular activity.

In addition to these FDA-approved uses, physicians have prescribed Botox® for the off-label treatment of post-stroke spasticity, migraines, spasmodic dysphonia, neuropathic pain, and juvenile Cerebral Palsy. However, despite the wide use of Botox® for a variety of off-label treatments, Allergan is restricted from communicating about Botox® for these unapproved uses. Allergan is also limited in its ability to provide information it has learned from studies of unapproved uses, except where a doctor solicits that specific information or where the FDA has compelled Allergan to communicate certain information.

In April 2009, the FDA informed Allergan that it required revisions to the Botox® packaging and instructions, in the form of a boxed warning, to ensure safe use of Botox® products. This warning also applied to off-label indications, thus putting Allergan in the difficult position of facing prosecution for abiding by the FDA’s mandate. The FDA required these revisions through a REMS under § 505-1 of the Act, “to ensure that the benefits of the products outweigh their risks.” The FDA informed Allergan that it needed to provide on-label and off-label users the following information:

- A MedGuide (paper handouts that accompany drugs and are meant to help patients avoid serious adverse effects);
- A Communication Plan, including a “Dear Health Care Provider” letter; and
- A timetable for assessments.

The FDA found that the MedGuide was necessary because “botulinum toxin products pose serious and significant public health concerns and that these risks could affect a patient’s decision to use, or continue to use, the products.” The FDA required Allergan to prepare a Dear Health Care Professional letter to be sent to neurologists, dermatologists, and other relevant specialists and professional staff describing the risks of botulinum toxin effects spreading from the injection site. Additionally, the FDA expected the new information for the Botox® products to include a “Boxed Warning,” highlighting the risks associated with the known uses of Botox® (approved and off-label uses), including the potential spread of toxins from the area of injection which may cause symptoms similar to those of botulism.

In September 2009, the FDA instructed Allergan to implement the above-described REMS for all Botox® products and uses, including for certain off-label uses of Botox®. By way of the REMS, the FDA permitted Allergan to communicate some of the off-label information Allergan understood was important to provide to the medical community. However, the REMS failed to address all outstanding safety issues. In the FDA approved REMS, Allergan could not include information that Allergan believes is essential for the safe use of Botox®. For example, Allergan considers that it is vital to also provide physicians with information related to:

- Amount of dosing at injection sites;
- Total dose exposure;
- Frequency of dosing;
- Frequency of administration;
- Injection techniques; and
- Existing patient debilities and relevant co-morbidities.
Absent this information, Allergan believes that its response to the REMS would be incomplete. However, to include such information, Allergan faces civil and criminal penalties because the FDA could consider its inclusion of the additional information as prohibited off-label promotion.

The tension between the FDA’s required response to the REMS and Allergan’s belief that it is obligated to provide safety information to physicians related to all uses of Botox placed Allergan in a quandary. In the end, rather than leave physicians without the information it believed was necessary for patient safety, Allergan filed a lawsuit against the FDA on October 1, 2009, in the United States District Court for the District of Columbia.12

IV. Allergan Takes Action, Seeking Injunctive and Declaratory Relief from FDA Regulations

Allergan’s lawsuit seeks injunctive and declaratory relief from the FDA’s labeling regulations. The Complaint describes the reasons the court should preclude the FDA’s enforcement of its off-label marketing regulations. Allergan claims that the FDA’s restriction on its ability to proactively share truthful, medically accurate information about its products with physicians constitutes an unconstitutional restraint on its First Amendment right of free speech.

Unless a government body can demonstrate that a restriction on speech is narrowly tailored to protect a compelling state interest, the restriction is unconstitutional and cannot be enforced.13 According to the United States Supreme Court, First Amendment protections encompass commercial speech, which “assists consumers and furthers the societal interest in the fullest possible dissemination of information.”14 “The commercial market place, like other spheres of our social and cultural life, provides a forum where ideas and information flourish. Some of the ideas and information are vital, some of slight worth. But the general rule is that the speaker and the audience, not the government, assess the value of the information presented.”15

Following a traditional approach to First Amendment rights, the Vice President of Allergan, Douglas S. Ingram has stated, “[i]f the ultimate goal is to get an accurate view of a drug's uses and quality, the answer is not to restrict that dialogue but to encourage it.”16 The speech Allergan seeks to share with medical professionals is scientific speech, not commercial speech, which, Allergan contends, is entitled to the highest protections afforded under the Constitution.

Allergan contends that the FDA’s broad prohibition on off-label speech fails the Supreme Court’s test of government limitation on speech. Allergan characterizes the FDA’s position as a total suppression of truthful speech, which is not justified to protect the public health. Regardless of whether the FDA can handle truthful information, Allergan argues that its prohibition on speech deprives doctors and their patients from receiving medically significant off-label information regarding dosing, injection protocols, and the potential risks of the drug’s uses. Allergan also relies on the fact that the FDA has already acknowledged that truthful off-label information provides a clear benefit to the medical community and may even constitute a medically recognized standard of care.

V. The Empire Strikes Back

The FDA’s initial defense is that this matter is not ripe for adjudication because Allergan has not yet said anything that could potentially violate the off-label regulations. Although the FDA appears to be saying that Allergan must first violate the law before it has an actual dispute for the Court to decide, the “ripeness” argument is procedural in nature and the
FDA must raise at this stage of the litigation or the argument would be waived. To the extent the FDA fully approves the use of Botox® for spasticity in the treatment of pediatric patients and adults during the litigation (some uses related to spasticity were approved in March 2010 after the lawsuit was filed), all outstanding issues in dispute as raised in Allergan’s complaint may indeed be resolved. If one party or the other appeals the district court’s ruling, this ripeness issue may ultimately be dispositive.

In its papers, the FDA repeatedly points out that drug and device manufacturers are permitted to engage in a wide range of speech including:

- Promotion of a drug’s approved applications;
- Warnings related to the risks associated with approved and off-label uses of the drug; and
- Dissemination of requests for published study reports.

In practice, the FDA argues that it usually does not treat “an unapproved use as an ‘intended use’ solely because the manufacturer knows that the unapproved use is taking place.” Furthermore, the FDA argues that its regulations do not constitute a “prior restraint” on speech because the regulations do not prohibit speech before it happens. As the FDA has briefed the issue, it appears to create an ambiguity in the manner in which it enforces its regulations, leaving inadequate breathing room for constitutionally protected truthful speech concerning off-label uses. Allergan’s response is that this ambiguity and fear of prosecution creates a chilling affect on its right to provide truthful, scientific speech to physicians regarding all uses of Botox®.

Even if the speech at issue is truthful and non-misleading as Allergan contends, the FDA claims that its regulations are narrowly tailored and “directly advance the compelling government interest in drug safety and public health, by means in proportion to the interest served.” That interest is to ensure safe medical treatments, but “drug manufacturers, when left to their own devices, frequently make untruthful claims about new uses.” Therefore, the speech is limited and the public protected “from promotional claims that are unsubstantiated at best and false at worst.” Therefore, the FDA’s regulations are directed toward “encouraging manufacturers to evaluate and demonstrate the safety and effectiveness of their drugs before marketing them for new uses.”

The FDA also argues that the regulatory scheme is constitutional on its face and as applied. The FDA asserts that if the regulatory scheme were changed (or “rolled-back” 50 years) such that a drug company could pursue off-label marketing without limitation, those companies could take an easier route to new drug approval by applying for FDA approval regarding a drug’s least risky or controversial use and then promote the drug for more lucrative and risky off-label applications. An unregulated off-label promotion scheme would also discourage drug companies from engaging in what the FDA sees as necessary, but expensive internal studies to receive approval for other uses of an approved drug.

VI. Friends of the Court – The Amicus Briefs

In support of Allergan’s position that the FDA regulations prevent important, truthful information from being conveyed to health care professionals, several organizations have filed amicus briefs including, National Spasmodic Torticollis Association, the National Spasmodic Dysphonia Association, the Allied Educational Foundation, and Washington Legal Foundation. These groups characterize the regulations as aggressive limitations on speech by manufacturers that “can be critically important to the prescribing decisions of medical professionals, and when
such speech is truthful, accurate, and non-misleading, it deserves full First Amendment protection.” If successful, Allergan’s claim would allow it and other drug companies to bypass the federal system of pre-market safety and effectiveness review and return the nation to the days of snake-oil salesmen, when products were regularly promoted with unproved, exaggerated, or fraudulent health claims.”

Public Citizen argues that without the FDA restrictions on the promotion of off-label uses, drug companies would have no incentive to assemble evidence of the safe and effective means of using their products. According to Public Citizen’s brief, the inherent bias of drug companies creates an incentive to deceive the public and healthcare professionals as to the serious harm caused by certain pharmaceutical products and, therefore, any action to suppress FDA regulations would produce deadly results.

VII. Why the Allergan Case is Different

Other cases in which parties have raised or considered these issues have been different and the outcomes have correspondingly not favored the drug or medical device industry. Some previous cases involved bad facts arising out of the criminal prosecution of a drug or medical device company. In those situations, the FDA could typically rely on the poor conduct of the defendant company. Free speech arguments are far less effective when the record is clouded with misrepresentations or outright falsehoods.

Other cases have been pursued by free speech, civil rights or industry advocacy associations with a lack of concrete issues. In cases where the FDA does begin an investigation, large pharmaceutical companies are typically risk adverse. Rather than risk a large punitive verdict and potential exclusion from federal reimbursement programs, companies opt to settle for a fixed sum and the ability to continue to do business. Additionally, companies that rely on the FDA for approvals fear regulatory retaliation by challenging the FDA’s regulatory scheme.

By taking the offensive, Allergan is able to pick its battlefield, selecting the facts that it believes will best support its legal arguments. Here, Allergan has focused exclusively on physician off-label use of Botox® for treatment of spasticity. Allergan has not addressed the use of Botox® in the treatment of migraines, neuropathic pain or other off-label uses. By relying solely on off-label uses for the treatment of spasticities, Allergan can state that Botox® is approved to treat spasticity in over 60 countries outside of the United States, is within the medically accepted standard of care in the United States, and is reimbursable by Medicare. Thus, it is able to make the FDA’s failure to approve Botox® for the treatment of spasticity seem either unreasonable or simply bogged down in bureaucratic red tape.

This case is also different because Allergan has focused solely on its desire to communicate truthful, scientific information to doctors. Allergan has not mentioned direct-to-consumer advertising or any other kind of marketing speech. This strategy should be effective in keeping the court’s analysis focused on truthful, scientific speech and not on commercial
speech, which involves a different legal standard. Additionally, Allergan is able to make this case about its desire to provide necessary treatment information to physicians so that they can properly treat their patients for spasticity, including juvenile cerebral palsy patients. In challenging Allergan’s right to provide dosing and injection protocol information to doctors, the FDA appears to be denying medical providers the very kind of information they need to properly treat their patients – many of which are from the pediatric population.

VIII. Conclusion

The off-label storm has been brewing for years. Allergan is the first pharmaceutical company to address the conflict head-on rather than continuing to provide Botox® for off-label uses with the hope that it either will not be penalized or, if it is construed to have engaged in illegal off-label promotion, that its profits will outweigh the penalties. In some instances, pharmaceutical companies have come out ahead, realizing impressive profits on drugs that expanded into off-label areas of treatment that may not have received FDA approval for many years, if ever. However, other companies have suffered enormous penalties and negative criticism as a result of their alleged off-label promotion.

Make no mistake, this is not a David versus Goliath fight. It is better characterized as Clash of the Titans. Allergan and drug manufacturers like Allergan hope that this case will eliminate the ambiguity and contradiction in the present FDA regulations. Health care organizations also hope that a decision in this important case will lead to the creation of clear regulations at a time when legitimate off-label use is so widespread. It is undisputed that off-label prescribing is common medical practice. The question is whether manufacturers are permitted to share available research and scientific information about the benefits and risks of off-label uses to help doctors make fully informed medical decisions. This will result in safer, more effective use of off-label Botox® for many patients who may not have other treatment options available. This is often the case in specialties such as oncology, pediatrics, and HIV/AIDS.

Allergan makes clear that the lawsuit is not intended to interfere with the FDA’s right to stop companies from disseminating false or misleading information about a drug. Rather, it seeks to convey truthful information so that physicians, armed with all of the necessary facts, can make an educated choice with respect to dosing, injection techniques, and potential side effects, and can safely and effectively use or prescribe Botox® for off-label indications.

So, what happens next? The FDA may approve Allergan’s REMS program containing information on off-label uses which previously would have been considered illegal promotion of that unapproved use. The FDA may further approve pending supplemental applications for off-label uses of Botox®, rendering the remaining issues presented by the litigation moot, just as it has by its recent approval of Botox® for upper limb spasticity in March 2010. As for the Court, the issues raised present several options. It may decide to address the type of speech at issue, i.e. “core scientific speech” versus “economic speech,” and the resulting First Amendment protection afforded to that speech. Or, it may attempt to reconcile the language of the Act with the regulatory scheme created by the FDA.

Allergan may get an answer from the United States District Court for the District of Columbia, but this issue will likely become the subject of a lengthy appellate process before it is finally decided whether the FDA regulatory scheme is constitutional. Considering what is at stake, both financially and relating to the public health and welfare, the issue may not be resolved until the United States Supreme
Court provides a final answer to the important question of how much truthful information can be conveyed to doctors and patients.

It is difficult to speculate what the courts will ultimately decide. Regardless of the outcome, the potential consequences arising from the Allergan lawsuit may have far-reaching implications, perhaps resolving the parameters of off-label treatment of patients, or inundating court dockets with increased litigation in further search of answers to the issues raised by the parties here. The only thing that is clear right now is that this is a case worth watching.


4. FDA’s authority stems from the new safety labeling changes provision of the Food and Drug Administration Amendments Act of 2007 (“FDAAA”) (Section 505(o) (4) of the Federal Food, Drug, and Cosmetic Act (“Act”)) and 21 C.F.R. §§ 201.57(c) (1) and 201.80(a).


7. The definition of “labeling” under the “Act,” 21 U.S.C. §321(k), (m): labeling encompasses written, printed, or graphic matter found upon the article itself, its container or wrappers, or accompanying such article. The definition of “labeling” under the FDA’s Regulations, 21 C.F.R. § 202.1(l)(2): Brochures, Booklets, Mailing Pieces, Detailing Pieces, File Cards, Bulletins, Calendars, Price Lists, Catalogs, House Organs, Letters, Motion Picture Films, Film Strips, Lantern Slides, Sound Recordings, Exhibits, Literature and Reprints, and similar pieces of printed, audio or visual matter descriptive of a drug and reference published for use by medical practitioners, pharmacist or nurses containing drug information supplied by the manufacturer.

8. 21 C.F.R. §128.


*DVD Copy Control Association, Inc. v. Bunner*, 75 P.3d 1, 17 (Cal. 2003) (a “prior restraint is a content-based restriction on speech prior to its occurrence” (italics in original)).

Id.

Id.


Id. at 27-28. (“If the Government has concerns about, or disagrees with, the information a manufacturer provides with regard to its approved drug products, it may respond with ‘more speech, not enforced silence’), citing *Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525, 586 (2001) (Thomas, J., concurring in the judgment), quoting *Whitney v. California*, 274 U.S. 357, 377 (1927) (Brandeis, J., concurring)); *Bates v. State Bar of Ariz.*, 433 U.S. 350, 375 (“[T]he preferred remedy is more disclosure, rather than less”).


Id. at 18-21.