

# STARING INTO THE ABYSS

## Intolerable Ambiguity in the Law Governing the Promotion of Prescription Pharmaceuticals and Medical Devices

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*When you stare into the abyss, the abyss stares back at you.* Friedrich Nietzsche.

Over the past decade, drug and device companies have faced widespread investigations of their business practices, particularly as they relate to the marketing and promotion of their products, including physician education programs. There are now hundreds of ongoing civil and criminal investigations under way involving the U.S. Department of Justice and units of the U.S. Department of Health and Human Services, as well as dozens of associated investigations run by state Attorneys General.<sup>1</sup> Billions of dollars in civil and criminal penalties have been paid to date for alleged wrongdoing, and many billions more will surely be paid in the coming years, not considering the costs of the investigation itself nor the potential liability that may stem from related private class actions brought by plaintiffs' counsel.

These developments might be seen as a natural consequence of the anachronistic character of the business of discovering, developing, manufacturing and selling medicine and medical technology. Companies operating in this segment of our economy are, on the one hand, engaged in a supremely risky high-wire act requiring that vast amounts of private capital be deployed in an endeavor where things can – and usually do – go wrong at virtually every stage of the process. On the other hand, the extent of government involvement with, and oversight of, life sciences firms is so comprehensive that the industry in some ways resembles more a public utility. The tension between naked capitalism and extensive government regulatory control has broad implications for public policy, and is readily apparent in the context of commercialization. Once a product is approved for sale and distribution, a drug or device company must do all that it can – within the bounds of the law and ethical business practices – to maximize their stockholders' return on investment by bringing the product to market in the most effective manner. Nevertheless, there is deep suspicion (approaching disgust in some quarters) among many government officials, consumer advocates, and even physicians, that customary commercial tactics are somehow vaguely beneath the dignity that ought to accompany the introduction and consideration of the use of medicine.

This is perhaps most evident when drug and device companies communicate scientific and medical information that goes beyond the four corners of the approved labeling, known as “off-label” information. Off-label information may relate to new indications or uses for a product, new potential side effects or safety concerns, new dosing regimens to enhance efficacy in certain circumstances, or any other product related information that was not known or fully developed and appreciated at the time of product approval. While the labeling may well be amended in time to include this information, there will invariably be occasions in which the company that has developed

the drug or device, and is charged with monitoring strictly its performance in the marketplace, is in possession of truthful, non-misleading scientific and medical information that will not be described in the approved labeling for some time.

The U.S. Food and Drug Administration (FDA) generally interprets its various regulations to prohibit any communication to physicians or other health care providers by a drug or device company of information that is not “consistent with” the approved product labeling.<sup>2</sup> Their interpretation is based upon a construct of several regulations that some view as strained, but in summary it is as follows: the agency approves products for a specific intended use; if there is to be a new intended use or if the intended use otherwise changes, then a manufacturer must demonstrate safety and efficacy for that new intended use and obtain FDA approval for modified labeling that properly reflects this new intended use; if a manufacturer provides information to physicians or other health care providers that is not consistent with the existing, approved product labeling, then the manufacturer has established a new intended use without obtaining said FDA approval;<sup>3</sup> this, in turn, “misbrands” the product in violation of the Federal Food, Drug and Cosmetic Act (FDCA).<sup>4</sup> When one considers that the government interprets “labeling” under the regulations to mean everything and anything that a company or its employees say (in writing or otherwise) about a product, it becomes clear that the scope of scrutiny is very broad indeed.

In the 2004 case involving the Parke-Davis unit of Warner Lambert, and its drug Neurontin® (gabapentin) for seizures, the government effectively announced its intention to focus on off-label promotion as a separate, actionable violation of the FDCA in addition to various kinds of financial impropriety. Since that time, subsequent settlements and public pronouncements have made clear that prosecutors will continue to focus even more on the off-label promotion issue, with cases such as the 2005 settlement involving Eli Lilly and its drug Evista® for osteoporosis based exclusively on off-label promotion. Early in 2008, press reports indicated that Eli Lilly was again in late stage discussions with government prosecutors in an effort to settle an investigation related to the marketing of its antipsychotic drug Zyprexa®, and that the amount of the settlement payment would likely exceed \$1 billion.<sup>5</sup> With this breathtaking level of financial penalty, as well as potential individual executive strict liability, and the underlying threat of exclusion from federal reimbursement programs at stake, the laws and regulations applicable to the promotion and marketing of drugs and devices ought to be pretty clear. But they are not.

### **The Public Policy Ideal and the Law, Such As It Is**

Transparency, clarity and consistency surely are among the most important, admirable goals in the formulation of public policy. Although courts have acknowledged that agencies have broad discretion to engage in *ad hoc* enforcement actions rather than rulemaking in effecting policy, they have emphasized the benefits of transparency, clarity and consistency inherent in a rulemaking approach. Specifically, rulemaking is preferred as being consistent with due process and rule of law principles, and provides more effective notice to the regulated industry in question.<sup>6</sup>

In my view, those charged with developing and issuing the applicable rules and regulations that define the bounds within which companies seek to fulfill their obligations should diligently clarify, to the extent humanly possible, precisely what is – and is not— to be allowed. Those who review and approve product marketing applications and associated labeling, as well as amendments, should be consistent in their statements to companies with respect to the prospects for regulatory approval and the concerns that are raised by an application. Still others should be presented regularly with cases and that raise genuine legal and policy questions as to whether companies have crossed the occasionally fuzzy line into commercial excess so that the rules can be even better expressed over time. In essence, those with the authority to regulate have the responsibility of clarifying, and applying consistently, the rules of the game. More specifically, our public policy should foster an environment in which companies can fulfill with confidence their ethical and legal obligations to inform physicians as to all truthful, non-misleading scientific and medical information relevant to the prescription and administration of their products.<sup>7</sup> We are far from this ideal.

When I suggest that the law is unclear, I do not mean that it is entirely unclear. Certain aspects of the law are fairly clear, and all ethically responsible companies accept these strictures. For example, the FDCA states unambiguously that you may not “sell, purchase, or trade or offer to sell, purchase, or trade” any drug sample.<sup>8</sup> It is equally clear that advertisements and other promotional statements must be truthful and not misleading; you cannot instruct your sales representatives to tell doctors that your approved drug is good for a particular condition, unless there is valid scientific and medical information that makes clear it really is, in fact, good for that condition. Over the years, the FDA has expressed the view that efficacy claims are truthful and not misleading only if they are found to be such by the agency and are then included in the approved labeling.<sup>9</sup>

When I suggest that the law is unclear, I do mean that it is simply not clear where the line is drawn between impermissible off-label promotion, and the permissible exchange of scientific information. The industry and their legal counsel have long relied upon the understanding that the FDA has established certain “safe harbors” that allow companies to communicate certain off-label information under certain circumstances that constitute scientific exchange. For example, companies may respond to an unsolicited request for information on off-label uses from a health care professional, so long as the response is non-promotional, truthful, balanced, and scientific in nature. Companies may exchange scientific information, such as in connection with the issuance of a press release announcing the results of a recently completed clinical study concerning a new use for an approved drug, provided that there are no definitive statements made related to safety and efficacy. Companies also may provide financial support for scientific and educational activities, provided that they do not influence the content of such activities or effectively serve to promote its product. Yet the government has never outlined its perspective in a comprehensive way. Moreover, in its recently issued draft “Guidance on Reprints” the FDA may be signaling that it does not accept one or more of these safe harbors.<sup>10</sup>

When I suggest that the law is unclear, I also mean that since the 1998 and 1999 *Washington Legal Foundation* cases,<sup>11</sup> it has never been clear as to what extent companies may properly rely on the First Amendment to the United States Constitution, and its explicit protection of free speech, in communicating truthful, non-misleading scientific and medical information. This is because it is not clear as to whether Judge Lamberth's reasoning in these cases ultimately will be adopted broadly within the Federal judiciary, or whether it will be extended to protect other forms of speech about off-label information. In 2003, U.S. District Judge Castillo of the Northern District of Illinois in *United States v. Caputo*<sup>12</sup> agreed with the underlying analysis employed by Judge Lamberth in *Washington Legal Foundation*. *Caputo* required that the court consider whether the First Amendment shielded defendants from liability for promoting a medical device in a form that had never been approved by the agency. In finding that it did not, Judge Castillo distinguished *Washington Legal Foundation* by noting that the communication at issue in that case was limited to the dissemination of peer reviewed journal articles and the sponsorship of continuing medical education programs, while accepting defendants' First Amendment argument in *Caputo* would necessarily allow much greater leeway for manufacturers to promote off-label. As Judge Castillo noted, "permitting Defendants to engage in *all* forms of truthful, non-misleading promotion of off-label uses would severely frustrate the FDA's ability to evaluate the effectiveness of off-label uses."<sup>13</sup> As another data point, in 2007 Judge Saris of the U.S. District Court in Boston had occasion to express her views at a hearing in which the drug manufacturer Schering-Plough Corporation was sentenced for violating the FDCA for, among other things, promoting off-label and misleading the FDA. In contrast to Judge Castillo, Judge Saris did not suggest any level of support for *Washington Legal Foundation* principles. "I do not accept that there is a First Amendment right to market something that does not get FDA approval," she said.<sup>14</sup>

So where does this leave us? If the First Amendment insulates companies from liability so long as their speech is truthful and non-misleading, then the extent of the disagreement over company activities will have been narrowed considerably. Companies could choose, whether individually or collectively, to adopt standards under which they only would disseminate truthful, non-misleading scientific and medical information if they determined that there was substantial, credible (however those terms might come to be defined) evidence as to safety and efficacy. Moreover, companies could work with the FDA in an effort to compromise around the edges so that they could exercise their freedom to speak without completely vitiating the vital FDA role in reviewing and approving drugs.<sup>15</sup> But that is not where we are today.

### **How Wide is the Gulf?**

To put this into some perspective, let's say that going forward companies will not offer any financial inducements or enter into any inappropriate financial relationships with physicians or other health care providers, nor will they allow any overt, off-label promotional messages to be provided by their sales representatives or any other field-based personnel having commercial objectives. For the sake of this discussion, the government would specify that no company or individual employee will face any liability

for the mere dissemination of peer reviewed journal articles containing truthful, non-misleading information about off-label uses of drugs or devices. Would the understandings established in this hypothetical resolve the problem of ambiguity in the law and allow industry to move forward with a well founded sense of the expectations of government officials?

Unfortunately, I don't think that they would, and I don't think that my former colleagues serving as executives and chief counsels of drug and device companies would expect that they would either. There are two distinct reasons for the legitimate anxiety that would surely linger, even if the understandings described in my hypothetical situation are accepted by all concerned. First, there is the not insignificant problem of the substantial difference of opinion and general lack of good feeling that presently separates industry and government officials. It has been my experience that Justice Department prosecutors are so skeptical of the industry, including its history, its profit and revenue motivations and its commercial practices, that it is difficult to imagine how to reconcile this world view with that of a for profit, publicly-traded drug or device company. The apparent standards to which companies are being held in order to avoid suspicion, investigation and (at the very least) preliminary allegations are such that they essentially must somehow cleanse their corporate culture of any expectation of off-label sales, whether legitimate or not. If there is any perspective or policy that has the lingering aroma of commercial ambition, it may well prove to be fatal, or at least terribly expensive and time consuming to defend.

Rather than risk unfair generalization, I refer to a 2007 presentation made by First Assistant United States Attorney Michael K. Loucks of the U.S. Attorney's Office for the District of Massachusetts.<sup>16</sup> In it, Mr. Loucks summarized the "relevant factors" that he examines in determining whether a prospective case brought to the attention of his office might be worth further inquiry. These factors include (i) the extent of the total product market for FDA approved use(s); (ii) whether sales representatives promote the product to physicians who do not treat patients having the FDA approved condition, or whether the company otherwise "targets" such doctors by paying bonuses to sales representatives that take into account sales outside of the FDA approved use(s), or whether such sales are included in company annual objectives; (iii) whether the company sought FDA approval for these uses and failed to receive it; (iv) whether the company declined to seek FDA approval for these uses, and if so, whether it was due to concerns presented by prospective generic entry or due to the absence of clinical data; (v) whether the company uses product marketing literature that claims safety and efficacy for the unapproved use; (vi) whether it engages consultants to boost off-label prescribing; and (vii) whether it provides incentives to physicians to prescribe off-label?

With the exception of items v and vii, which fairly imply direct promotional impropriety in the first case, or some level of financial impropriety in the second, the factors on Mr. Loucks' list could all be present even under my favorable hypothetical, and thereby would expose a company to liability or at least the burden of a multi-year investigation. In summary, Mr. Loucks is asking whether a company has business policies and practices that, taken together, suggest it expects to have, or would enjoy

having, physicians prescribe its product(s) for uses that are not yet approved by the FDA? Of course a company would enjoy having the benefit of off-label prescriptions, so long as physicians make proper, independent medical judgments for the benefit of their patients. But Mr. Loucks' criteria indicates a willingness to inquire further into the corollary circumstances that are present if there happens to be substantial, though legitimate, off-label prescribing. Rather than describing acts that clearly violate the law, Mr. Loucks has presented indicia that evince a metaphysical quest to look into the soul of a company and divine whether it is black, white, or a hue in between.

Please tell me that this is not the legal standard that is being used to determine whether to subject healthcare firms to millions of dollars in defense costs and thousands of hours of time expended. To my knowledge, there is nothing in the law, including FDA regulations, that in any way proscribes the ambition and expectation that may underlie these indicia. While I appreciate that FDA regulations examine evidence of objective intent in ascertaining whether a company has "misbranded" a product, I read the applicable language as being focused on the precise circumstances of the company's promotion and advertising effort.<sup>17</sup> In contrast, the broad commercial and financial intent that may fairly be evident from the factors set forth by Mr. Loucks goes to whether the company in question has the intent to fulfill its fiduciary duty to stockholders.

Perhaps with this in mind, a leading healthcare lawyer recently declared, "I don't think that a company that has legitimate off-label sales has a safe harbor anymore."<sup>18</sup> This leads directly to the second reason why these understandings will not clear up all of the ambiguity in the law. Quite simply, it is because that aside from outright financial impropriety and peer reviewed journal article dissemination, there will continue to be significant ambiguity in the law. And, as the above comment indicates, it will continue to be especially difficult to manage risk and liability, and to provide sound legal and regulatory advice, if you happen to have a product that has legitimate off-label sales.

### **Bringing It Down to Earth: A Few Product Related Scenarios**

In *Caputo*, the court evaluated the defendants' assertions under the *Central Hudson* commercial speech balancing test,<sup>19</sup> but in the end determined that the facts were materially different from those presented in *Washington Legal Foundation*, and therefore reached a different outcome. Since the FDA had not approved the form of the marketed product in *Caputo*, protecting the off-label speech here would completely undermine the FDA's authority to consider and approve medical devices. Disseminating reprints that elucidate some additional benefit or aspect of an approved product is (perhaps) not so threatening to the FDA's authority, but allowing a full fledged marketing campaign for an unapproved device is quite threatening – and not just to the FDA's authority but perhaps even to the public health. Does this distinction help to reconcile the tension in this area?

Based upon the different outcomes in these two cases, we might begin to think in terms of identifying the relative degree to which the off-label speech is more or less consistent with the approved labeling, or more or less incrementally different from that

information already contained in the approved labeling, rather than merely trying to ascertain if the context of the speech is primarily promotional or primarily scientific exchange. An important distinction may lie between information that is not included in the current labeling, but would logically and properly fall within the existing, FDA-approved use, and information that pertains to a therapeutic use considerably broader than, or even entirely different from, the use for which the drug or device was originally approved. The circumstances surrounding off-label information in connection with three different companies, are relevant to this distinction.

### **Gilead Sciences' Viread® (tenovir disoproxil fumarate)**

In 2001, the FDA approved Viread®<sup>20</sup> for “the treatment of HIV infection in adults” based upon its review of a study of treatment-experienced adults infected with HIV. Two years later, the FDA added clinical data to the labeling from a second study, which examined treatment-naïve patients and their experience with the drug. From 2003, Gilead has continued to run ongoing clinical trials in order to accumulate additional patient experience data from long-term observation; publication of these results serves to advance the science and, more importantly, enable the medical community to better understand the safety and efficacy profile after years of patient exposure.

This is critically important clinical work, as those who suffer from HIV and associated health problems will likely remain on Viread® for many years, at least as long as the drug continues to be effective and reasonably tolerable, or until a superior treatment is developed and approved. As such, each public release of new long-term clinical data is eagerly anticipated and received at prominent medical conferences by physicians who treat patients with HIV. With each release of new clinical data, there is a pattern of information migration that runs from the company to conference attendees, to publication in peer reviewed medical journals in the United States and abroad, to submission by the company to various regulatory authorities around the world. When the data finally is approved by the FDA and other agencies for inclusion in the product labeling, it has taken at least ten months, and usually far longer.

During the interim period, between first presentation of the data to physicians at a medical conference and the eventual approval by regulatory authorities of modification of the product labeling, there are those who believe that Gilead should not have any role in disseminating this truthful, non-misleading and extremely relevant clinical information. Many more would have it that, at the very least, Gilead should not permit its field based sales representatives or medical liaisons to discuss this data with physicians. If this view prevails, the only physicians who will become aware of the new clinical data would be those who were involved directly in the Gilead clinical study or otherwise obtain it through their own independent efforts. Indeed, a good many physicians would not likely become aware of the new data, and would not take the data into consideration in their treatment of HIV patients. Does this affect our public policy preference? Does it matter that the data is at least arguably “consistent with” the existing labeling since we are considering follow-on clinical studies of the same kinds of patients suffering from the

same illness and being treated with the same drug? Needless to say, there are no such distinctions in the law at this time.

Viread® also appears to be effective in treating patients with chronic hepatitis B infection (CHB).<sup>21</sup> Gilead scientists discovered this as the company reviewed data from its ongoing HIV clinical trials that included subsets of patients who were co-infected with HIV and CHB. If one concludes that the additional HIV patient data is “consistent with” the existing labeling, it would not appear that data related to an entirely new prospective use would be covered by this broad standard. Does that make the case for disseminating information to physicians any less sympathetic from a medical treatment perspective?

### **Cephalon’s Provigil® (modafinil)**

Provigil®<sup>22</sup> was approved by the FDA in late 1998 for the treatment of “excessive daytime sleepiness (EDS) associated with narcolepsy” after being discovered and first marketed in France for the same condition in the early 1990s. Although the precise mechanism of action is not fully understood, it appears to work by affecting the area of the brain that regulates wakefulness. The active ingredient, modafinil, is not an amphetamine but a mild stimulant, so patients generally do not experience the jitteriness or other negative symptoms associated with the use of amphetamines and are able to return to a normal sleep pattern shortly after they stop using the drug. Furthermore, all clinical and anecdotal evidence demonstrates that it keeps patients awake and alert regardless of why they might be sleepy or tired.<sup>23</sup>

With this in mind, Cephalon had extensive discussions with the FDA about the drug’s potential utility in conditions other than narcolepsy, even before the drug was first approved. Initially, the agency advised the company to pursue a series of placebo-controlled clinical studies with distinct groups of patients, with each such group selected to represent a recognized model of underlying sleep disorder or other medical condition. If the company demonstrated efficacy and safety in each of these distinct models of sleepiness, the FDA division staff indicated that it would be prepared to recommend a broad label for the treatment of EDS associated with any underlying medical condition. The company decided to study patients who were sleepy due to one of three conditions: narcolepsy, obstructive sleep apnea, or a disturbed circadian rhythm pattern due to extended periods of shift work known as “shift work-sleep disorder.” Cephalon completed the additional studies, which all demonstrated efficacy and were consistent with earlier studies in terms of a limited number of relatively minor adverse events. However, after the additional clinical data was submitted to the agency, the FDA in 2003 convened an advisory committee which recommended against approving the broad label in favor of a pseudo-specific label for use in EDS associated with each condition evaluated in the studies; the FDA accepted this recommendation in approving the expanded label, thereby ensuring continued significant levels of off-label use. It was evident at the FDA advisory panel that at least some of the panel members were concerned as to whether approving the broader label would result in unwarranted prescribing for patients who did not suffer from any underlying medical disorder, but simply wished to have a “replacement for the normal amount of nighttime sleep.”<sup>24</sup>

Indeed, many physicians had already become aware of the product as the additional clinical studies were conducted, as data was presented at medical meetings, and as the mainstream news media began to write about the incredible “wonder drug”<sup>25</sup> that was being prescribed to pilots, college students and others who may not have had any underlying medical condition, but simply were sleepy or tired during the day.<sup>26</sup> This awareness was boosted by studies conducted by those outside of the company. For example, there were a number of clinical studies conducted by the U.S. military that examined aviator performance and pilot sustained alertness while taking Provigil®.<sup>27</sup> At the advisory panel itself, Dr. Robert Temple of the FDA suggested that he was not necessarily troubled by off-label use of Provigil® in the case of truck drivers or others who might be driving while sleepy, noting that “[i]f they’re driving next to me, I think I’d prefer they be on it.”<sup>28</sup>

Two things are evident here. First, there are a host of factors outside the control and influence of the company that may well affect significantly the extent of off-label prescribing, including government sponsored activities. Second, Provigil® is a case of a company developing clinical data with registration and non-registration studies in contemplation of a pending label expansion into related therapeutic areas in which the underlying medical cause may differ, but the condition being treated is the same or very similar. With this in mind, is the additional clinical data, all related to efficacy in treating excessive daytime sleepiness or EDS, “consistent with” the labeling first approved by the FDA for EDS associated with narcolepsy?

### **Genentech’s Avastin® (bevacizumab) and Lucentis® (ranibizumab injection)**

The saga of these two biological products, each a therapeutic monoclonal antibody designed to bind to and inhibit so-called VEGF (human vascular endothelial growth factor), has received substantial press coverage and generated controversy in the medical and patient community.<sup>29</sup> Avastin®<sup>30</sup> was the first angiogenesis therapy approved in the United States. The FDA approved it in February 2004 for the first-line treatment of patients with metastatic carcinoma of the colon or rectum, and in 2006 approved it for second-line treatment of colon or rectal cancer, as well as first-line treatment of non-small cell lung cancer. Lucentis®,<sup>31</sup> is a smaller molecule, or fragment version, of the same molecule found in Avastin®, and was approved by the FDA in 2007 for the treatment of neovascular (wet) age-related macular degeneration (AMD), a severe disorder of the retina that is the leading cause of vision loss in persons over age 60. Prior to the approval of Lucentis®, a retinal specialist in Miami was reported to have been the first to experiment with off-label use of Avastin® to treat AMD.<sup>32</sup> Since then, Genentech has been struggling to address a number of difficult issues, including drug access, distribution, pharmacy compounding, safety and price. There also are interesting questions of off-label communication presented in this case.

In early 2006, Genentech’s position was that, while it appreciated that the retinal physician community was acting “with noble intent, which is to help patients who are going blind as we speak . . . there have been no safety and toxicity studies conducted on

Avastin® as an ophthalmic drug.”<sup>33</sup> Dr. Charles Johnson, Genentech’s Vice President of Biotherapeutics, also noted that the off-label use was increasing “because of advice generated by the medical community.”<sup>34</sup> What did Genentech do about communicating with physicians on the off-label use? “We make educational material available to the doctors but we don’t take a position,” said Dr. Johnson.<sup>35</sup>

Although the two products were quite similar and intravitreal use of Avastin® was possible for those who purchased Avastin® through a compounding pharmacy that would then dilute the potency of the formulation, it was not the preferred method of treatment. Specifically, the company raised questions about the maintenance of sterility in the process of dividing the Avastin® dose due to a lack of preservatives in that drug’s formulation; it also cited a warning letter issued by the FDA to a compounding pharmacy to that effect.<sup>36</sup> Subsequently, Genentech caused a firestorm by pricing Lucentis® at approximately \$2,000 per dose and announcing that it would no longer allow compounding pharmacies to purchase Avastin® from its wholesalers; the compounding method had resulted in an effective price of \$50 per dose. Shortly thereafter, following the announcement by U.S. Senator Herbert Kohl (D-Wisconsin) that his Senate Committee on Aging would launch an investigation into Genentech’s decision to limit Avastin® availability,<sup>37</sup> the company announced that it had reached agreement to continue to allow retina specialists and ophthalmologists access to Avastin® under certain circumstances. The company emphasized that although it continued to believe that Lucentis® was “the most appropriate treatment for patients with wet [AMD] because it was specifically designed, formally studied, approved by the [FDA] and manufactured for intraocular delivery . . . [it] does not interfere with physicians’ prescribing choices.”<sup>38</sup>

Leaving aside the pricing controversy, and the contradictions inherent in government officials effectively encouraging off-label use of an untested product, Genentech was in an awkward position during the period 2004 to 2007 as interest in off-label use of Avastin® intensified. Although the company could freely reiterate and emphasize any statements made by the FDA, it is not clear that it could lawfully communicate directly to physicians any safety information that related to an off-label use. This alternate use, which is completely unrelated to the approved cancer indications and which use, by the company’s own admission, raised concerns of eye infections, could not possibly be said to be “consistent with” the FDA approved labeling. From a public policy perspective, it would be preferable to permit companies to act in an ethically responsible manner and to share fully any concerns about prevailing physician practice, rather than to limit communication to a brief press statement and the dissemination of peer reviewed journal articles.

### **The Practical Challenge of Counseling Companies**

In regarding this tangled legal and regulatory landscape, how is one reasonably to counsel a drug or device company in this area? To be sure, lawyers are highly educated, well trained professionals, and must become accustomed to providing sophisticated, nuanced advice to business clients when the law is murky or else they will not last long in

a challenging environment such as this one. While I do not expect a reader to be unduly sympathetic to the plight of successful corporate lawyers nor to the multinational companies they advise, it is useful to consider the issues that arise virtually on a daily basis in a pharmaceutical or medical device company of any significance.

Here is a summary of various commercial and educational activities commonly employed by drug and device companies, together with some of the relevant questions that are not clearly or adequately addressed by current law, regulation or guidance.

### **Marketing Strategy**

How ambitious about the prospect for unapproved uses for an approved product may a company dare admit to being, lest it be accused of embracing an off-label marketing strategy? Should it support non-registration physician studies to determine what range of additional indications might be feasible? Should the company think about, and express itself in terms of, a return on investment in the context of off-label use? Does it matter if the hoped for return on investment reflects a reasonable expectation that the FDA will approve a new use for the product in question on the basis of ongoing, placebo-controlled studies? Should the company establish annual revenue targets that include or presume some level of off-label sales? Should the company establish bonus eligibility for sales and other commercial organization personnel that include or presume some level of off-label sales?

### **Promotion by Sales Representatives**

If you are going to send your sales representatives out into the world to speak to physicians, they must limit their discourse to information that is “consistent with” the approved labeling. What exactly does that mean? What if there is information that is simply not addressed by the label? Does it matter if it is important, or if it relates directly to safety and efficacy? For example, can a sales representative discuss the mechanism of action of the active compound? Perhaps company scientists have done some good work on this question, and they are reasonably confident that they have identified the likely mechanism, suggesting there may be some similarities with other approved products on the market; perhaps a patent application has been filed disclosing this important finding. Or what if the company is in the process of completing post-marketing, registration studies that it hopes will lead to a new indication, can representative talk about any of the data that has been released publicly and presented at medical meetings? To whom can the sales representatives speak? May they address any physician or health care provider, so long as their message is consistent with the approved labeling? If not, to whom can they speak, and whom should they avoid? Does it matter if the physician does not prescribe for on label use at all, or is there a certain threshold or propensity to proscribe that is sufficient? What if he or she says they might prescribe on label, but have not done so in several years? Should a representative come back in a few months and see whether they have changed their prescribing habits? Are there any reasonable limits as to how many times a sales representative may attempt to see a particular physician or group? What may representatives do to respond to questions from physicians about off-label use?

What may representatives do to respond to questions about dosing or the manner of administration if the question asked, and fairly answered, would logically take one outside the approved labeling? Most companies require that representatives refer many of these kinds of questions to their internal medical affairs group to respond appropriately, and that may well be good policy but it is worth noting that this leads to many awkward conversations and can be very difficult as a practical matter to enforce strictly.

### **Continuing Medical Education and Other Physician Programs**

**Independent CME.** As far as I can tell, most companies continue to operate under the premise that the FDA safe harbor for bona fide, independent CME programs remains in place, and that it is therefore permissible to provide financial support to outside organizations so long as a company does not influence the content of the program. There are detailed guidelines for these programs that have been established by the Accreditation Council for Continuing Medical Education, but following these rules does not mean that the program will be regarded as appropriate by all who scrutinize it. Indeed, U.S. Senator Charles Grassley (R-Iowa), ranking member of the Senate Finance Committee, has been a frequent critic.<sup>39</sup> In the ideal circumstance, an outside firm would approach the company entirely on its own initiative. The outside firm would have completed an analysis of whether a program would be useful by reviewing the precedents, and by speaking to physicians practicing in the relevant, on-label therapeutic area. None of the physicians consulted by the outside firm would have any financial or other relationship with the company, and ideally would not prescribe the drug very much, if at all, outside of the approved on-label use. The outside firm would recommend that the program be held, develop the agenda topics to be presented, identify and engage the physician speakers to speak, and invite the prospective participants, all without any influence by the company. The company would have no role whatsoever in this process, other than to negotiate with the outside firm the precise amount of a grant to cover a portion of the meeting expenses. As suggested by this “ideal” (which may well not be practical in many cases), any deviation that increases the extent of company involvement, or involvement by physicians who may be seen to have some sort of vested interest in supporting the off-label use, may well be challenged as inappropriate.

**Company Promotional Programs.** Companies frequently hold programs at which they pay a physician to speak to their colleagues about a product. In 2002, the Pharmaceutical Research and Manufacturers Association (PhRMA) trade industry organization adopted an expanded version of its “Code on Interactions with Healthcare Professionals;” the Code allows companies to provide “modest” meals in connection with presentations if it is conducive to the exchange of information.<sup>40</sup> In addition, it is quite clear that this kind of event is promotional in nature, and therefore must comport with FDA regulations that restrict off-label promotion. As such, the speaking physician may not speak about any off-label use, even if it reflects his own experience and deeply held views about the efficacy of the product for the off-label use. The company, ideally, would review any written material that the speaking physician intends to present and would make clear that he or she cannot speak about any off-label use(s). Many, if not

most, companies allow the speaking physician to respond to questions from the other attending physicians about off-label prescribing of the product, in reliance on the safe harbor provision referred to above and in consideration of their professional status as a medical doctor with experience in the field. This general overview as to how a company might approach an event of this sort would seem to be reasonable, so long as the meal is not unduly expensive. But questions remain. How much money may a company spend per person on a dinner presentation? May the company pay for wine with the meal, or should it be served at all? How many physicians should attend; is there a minimum or maximum number that is permissible or advisable? What level of expertise should the speaking physician have with respect to the product or their area of practice? The PhRMA Code has not persuaded prosecutors of the propriety of these types of events, as they regard them with a high degree of cynicism (doctors are treated to “ritzy resort and lavish meals”). Others suggest that a presentation by a physician who is paid by the company may turn the event into “white coat promotion,”<sup>41</sup> and it is just as inappropriate for them to respond to a question related to off-label use as it would be for a field sales representative to do so.

### **Items of Value**

Whether at a dinner event or otherwise, there are innumerable questions that arise related to the practice of offering items of relatively modest value to physicians or other health care providers. The anti-kickback statute does not specify a de minimus amount below which the provisions of the law will not apply; strictly interpreted, the law requires that a physician declare to be a discount or otherwise disclose any item of any value whatsoever.<sup>42</sup> On the other hand, it is widespread practice for drug and device company sales representatives to provide lunch for physicians and their staffs on a daily basis. In fact, it is widely believed that most physicians will not speak to sales representatives unless they bring lunch with them, and it is even common to see job listings for nurses and physician office administrative staff as offering “free lunch provided daily.” One prominent outside counsel to healthcare companies refers to the unwritten “fruit basket exception” to the anti-kickback statute, meaning of course that no company ought to be concerned with violating the law for offering a gratuity that does not exceed the value of a fruit basket, such as a coffee mug or a logo pen or a sandwich. Nevertheless, this seemingly reasonable approach is small comfort these days in light of the strict statutory language and the penalties associated with any such violations.

### **Consulting and Advisory Agreements**

Complicated, heavily regulated, science and technology-based businesses tend to rely on consultants and advisors for various purposes. For example, life sciences companies generally will establish scientific and medical advisory boards for purposes of obtaining the perspective of experts in the relevant fields. Do these engagements support the reputation of the firm, and introduce the firm to potential customers who might prescribe products down the road? Of course they do. But there is nothing unethical or illegitimate about them so long as the compensation is fair, and there is meaningful time expended and real work produced by the consultant or advisor. How should these

arrangements be handled? Clearly, there must be a written agreement that is negotiated with the consultant or advisor, and the duties to be performed should be specified in detail. The difficulty arises when companies must establish a fair market value to compensate a physician who is advising them; how to do that? The OIG guidelines speak of fair market value in concept, but do not offer assistance otherwise.<sup>43</sup> Should physicians be paid a rate that attempts to keep them whole in comparison with the amount of money they would earn in their private medical practice? Or by attempting to estimate fairly the potential worth of the advisory services to the company? Must the company demand to see written proof of the physician's compensation to establish fair market value? Should a company simply establish an estimated "going rate" for a physician in a particular specialty and insist on paying that specified rate for each of its advisors? Should a company establish a maximum amount per annum for its physician consultants, regardless of the amount of legitimate work that they might undertake for the company?

### **Reimbursement and Coverage Related Information**

Reimbursement for off-label prescriptions of a product often depends on the submission of information related to the off-label use. The industry uniformly acknowledges that sales representatives should not provide specific diagnosis codes to physicians. But beyond that, how should a company attempt to support payment for its products? Specifically, what may a company do to provide information to CMS or to a state pharmacy and therapeutics committee? May the company engage a physician to present information? May the company offer training to physician office staff on reimbursement generally, or specifically as it relates to one of its products? May the company have its medical affairs group write letters of medical necessity in support of a reimbursement request, or should the physician write the letter with advice from the company? May the company offer advice at all, whether through its medical affairs group, or through a third party service?

### **Web Site Construction and Hypertext Link Issues**

Like all companies, drug and device firms have embraced the internet as an effective means of communication and presentation of information. Specifically, companies have established branded product sites for promotional purposes, and separate, unbranded sites that present information on the underlying disease or medical condition without recommending product treatment options. Companies understand that these websites must be maintained independently, and that branded, promotional information may not be included in a broader, informational site that offers scientific and medical information about the underlying illness or condition. But how distant must these websites be without running afoul of the off-label promotion strictures? Are two or three or four hypertext clicks sufficiently remote? Are there any graphic or textual guidelines that companies should use to maintain the kind of separation that would be seen as appropriate by government regulators?

## Conclusion

These are just a sampling of the constant refrain of questions and concerns that in-house and outside counsel to drug and device companies face on a daily basis. While I do not excuse the promotional and financial excesses of recent years, it is troubling that companies seeking to act in an ethically responsible manner will not find substantial clarity in existing law and regulations. This is not the case in other regulatory contexts. The U.S. Securities and Exchange Commission, for example, considers and issues so-called “No Action” letters in response to company and legal counsel inquiries. These letters address specific circumstances in great detail, and are published so that the guidance contained within them may be used by firms in similar situations to develop and improve their policies and practices, and to make judgments that are more likely to comply with SEC rules and regulations. Securities lawyers may still find it wanting in some respects, but this vehicle at least results in some advancement of the law on an ongoing basis. Should the FDA choose to do so, I see no reason why it could not introduce a mechanism under which it would provide similar advisory opinions. It could also develop a formal mechanism for consultation with industry on this issue, which might itself assist in the development of policy proposals and enhance industry involvement and compliance. The largely private, self-regulating systems established to regulate the promotion and advertising of drugs and medical devices in the European Union present another model that appears to better provide for incremental advancement of the law and comprehensive industry compliance.

Unfortunately, the prevailing political dynamic and our legal and regulatory systems have not provided the kind of detailed guidance that is constitutionally required for criminal culpability, and that would be ideal for companies seeking to comply with the law and meet the expectations of government officials. How will the law develop in this area? I think I can safely speak for the industry in saying that I am decidedly pessimistic as to the prospects for any prompt resolution. Companies simply cannot risk exclusion from Federal reimbursement programs by litigating in the face of government allegations. Although the FDA has taken a welcome step forward in issuing its recent guidance on the dissemination of article reprints, many believe that this draft was insufficiently sensitive to free speech concerns,<sup>44</sup> and yet at the same time it was roundly criticized by Congressman Waxman as a vehicle that “puts the public at risk for ineffective and dangerous uses of drugs.”<sup>45</sup> The net result of this apparent stalemate surely will be a continued reduction in the amount of truthful scientific and medical information that is shared by companies with physicians, and continued damage to the reputation of a vitally important, but beleaguered, industry.<sup>46</sup>

## NOTES

**\*John E. Osborn was a visiting research fellow with the Centre for Socio-Legal Studies, University of Oxford, and a senior member of Wadham College Oxford, during Trinity Term 2008. Formerly, he was executive vice president and general counsel with Cephalon, Inc. During his tenure with the company, he defended it against allegations of illegal off-label promotion; a settlement of all Federal and state Medicaid-based claims was announced in November 2007. He also serves as a member of the board of directors of Incept BioSystems, Inc., an early stage biomedical device company.**

1. Peter Keisler (then Assistant U.S. Attorney General for the Civil Division), quoted in “Cases, Fines Soar in Fraud Probe,” *Wall Street Journal* (June 7, 2005).
2. See FDA Response to Comments on Final Guidance on Industry-Supported Scientific and Educational Activities, 64 Federal Register 64074, 64085 (Dec. 3, 1997), available at <http://www.fda.gov/cber/gdlms/sciedu.pdf>. (“Under the act, the regulated industry cannot promote its products for unapproved uses, or . . . in ways not consistent with approved labeling”). See also DDMAC warning letters to Alcon, Inc. (2006), Abbott Laboratories (2005) and Kos Pharmaceuticals, Inc. (2001).
3. 21 CFR 201.128
4. 21 CFR 201. See also Sections 502(a) and (b)(1) of the FDCA.
5. Alex Berenson, “Lilly Considers \$1 Billion Fine to Settle Case,” *New York Times* (January 31, 2008).
6. See *American Mining Congress v. Mine Safety & Health Administration*, 995 F.2d 1106, 1112 (D.C. Cir. 1993)(notice and comment to affected parties of proposed rules is preferable to “ad hocery” of enforcement actions). See also *Securities and Exchange Commission v. Chenery Corporation*, 332 U.S. 194 (1947)(SEC may pursue enforcement actions, but rules allow for notice, participation and transparency); *Morton v. Ruiz*, 415 U.S. 199, 231 (1974)(“agency must, at a minimum, let the standard be generally known so as to ensure that it is being applied consistently”); *Whisenhunt v. Spradlin*, 464 U.S. 965, 969 (1983)(J. Brennan, dissenting)(Due Process Clause demands “that government articulate its aims with a reasonable degree of clarity”).
7. I hasten to add that this must be accompanied by ethically responsible behavior on the part of companies, who must adopt and enforce rigorous compliance policies and programs, and more than that, must act in a meticulous, ethically responsible manner when speaking about products for human health. They must be brutally honest with themselves and others as they evaluate clinical and medical data, they should consult with medical experts in the field and weigh their advice seriously,

and they should publish comprehensive summaries of product related information and publications on a timely basis. Above all, they must act with the highest levels of integrity in their relationships with physicians and patients so as to avoid even the appearance of impropriety.

8. See section 305 of the FDCA.
9. 21 CFR 202.1. But see *Washington Legal Foundation v. Friedman*, 13 F.Supp.2d 51 (D.D.C. 1998). “In asserting that any and all scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe.” 13 F.Supp.2d at 67.
10. See FDA 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 (February 2008).
11. See 13 F.Supp.2d 51 (D.D.C. 1998) and subsequent associated case citations.
12. 288 F.Supp.2d 912 (N.D. Illinois 2005).
13. *Id.* at 922.
14. Michael K. Loucks, “Trends in Prosecutions and So-called Off-label Promotion Issues,” (November 26, 2007). See also Denise Lavoie, “Schering to pay \$435M to settle charges,” Associated Press (January 17, 2007).
15. See “Drug Firms Want FDA Regs Allowing Journal Article Dissemination,” *Inside Washington’s FDA Week* (September 7, 2007).
16. While Mr. Loucks labels his presentation as reflecting only his personal views, his position as the driving force behind arguably the most active healthcare fraud unit in the land is such that many companies surely must consider his “personal” views as approximating official government policy. See John Simons, “Why Do Drug Companies Fear This Man?,” *Fortune* (October 27, 2003). When asked at a recent industry sponsored panel if he regards it significant that the off-label information in question is truthful, Mr. Loucks replied: “I would say this from an investigator’s or prosecutor’s perspective, I don’t know that it matters much that the off-label promotion activity might be entirely truthful and accurate, it’s still off-label.” National Pharma Audioconference: Lessons of Bristol Myers-Squibb \$515 Million Settlement (November 26, 2007).

17. See 21 CFR 201.128. “The words *intended uses* . . . refer to the objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons’ expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives.”
18. Scott Bass (partner, Sidley Austin LLP), quoted in *The RPM Report* (Windhover, December 2007).
19. *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York*, 447 U.S. 557 (1980). For a review of the historical development of the legal doctrine concerning the protection of commercial speech, see Daniel E. Troy, “Advertising: Not ‘Low Value’ Speech,” *Yale Journal on Regulation* (Winter 1999).
20. Prescribing and other background information on this product may be found at <http://www.gileadhiv.com/320Viread.aspx>.
21. The press release announcing positive Phase III clinical results may be found at [http://www.gilead.com/pr\\_1012569](http://www.gilead.com/pr_1012569).
22. Prescribing and other background information on this product may be found at <http://www.provigil.com/pat/default.aspx>.
23. Joel Garreau, “The Great Awakening,” *Washington Post* (June 17, 2002).
24. Meeting of the FDA Peripheral and Central Nervous System Drugs Advisory Committee (Bethesda, Maryland, September 25, 2003), Transcript of Proceedings at page 184.
25. “The War, On Drugs,” *Esquire* (February 2003).
26. Physicians have prescribed Provigil® extensively for a number of off-label uses, but one often cited has been fatigue associated with multiple sclerosis (MS). In fact, the use of the drug is characterized as the standard of care (“medications commonly used in the treatment of MS”) by the National Multiple Sclerosis Society. See [www.nationalmssociety.org/about-multiple-sclerosis/treatments/medications/modafinil/index.aspx](http://www.nationalmssociety.org/about-multiple-sclerosis/treatments/medications/modafinil/index.aspx). The Society makes reference to two clinical studies with mixed results in its summary of the product, one study conducted over a nine-week period in 2000 by Cephalon that showed efficacy in a low dose of Provigil against placebo, and a second study conducted in 2005 by a physicians’ group in France that failed to show efficacy. However, the Society notes that the clinical experience of physicians treating patients with MS has shown “significant benefit for many patients with MS-related fatigue.”

27. See U.S. Department of the Air Force memorandum (2 December 2003)(“Modafinil, a “Go Pill”, is now approved for management of aircrew fatigue”).
28. Transcript of FDA Advisory Committee Proceedings at page 186.
29. See “Drug Maker and Eye Doctors Settle Dispute Over Avastin,” *New York Times* (December 21, 2007). See also “Ophthalmologists Concerned About AMD Patients’ Access to Avastin,” American Academy of Ophthalmology News Release, October 12, 2007.
30. Prescribing and other background information on this product may be found at [www.gene.com/gene/products/information/oncology/avastin/](http://www.gene.com/gene/products/information/oncology/avastin/).
31. Prescribing and other background information on this product may be found at [www.gene.com/gene/products/information/tgr/lucentis/](http://www.gene.com/gene/products/information/tgr/lucentis/).
32. It is interesting to compare the perspective of a retinologist, as reflected in comments posted on [www.visionassociates.net](http://www.visionassociates.net), with those of the FDA. The physician opines that although the FDA approves drugs for a specific use, “when the safety and effectiveness of medications for ‘off-label’ indications is known, it would be malpractice not to use drugs in this way.”
33. “Genentech: Avastin Not Intended for AMD; Company Cautions on Off-Label use of Cancer Drug,” *Retinal Physician* (January 2006).
34. Id.
35. Id.
36. Genentech open letter, October 29, 2007. This letter may be found at [www.gene.com/gene/features/avastin/open-letter.html](http://www.gene.com/gene/features/avastin/open-letter.html).
37. “Senator Criticizes Genentech’s Limits on a Cheaper Drug,” Bloomberg News (November 29, 2007).
38. Genentech press statement, December 20, 2007. This statement may be found at [www.gene.com/gene/features/avastin/press-statement.html](http://www.gene.com/gene/features/avastin/press-statement.html).
39. See Senate Finance Committee Report on improper drug company influence over continuing medical education programs at [www.finance.senate.gov/press/prb042507a.pdf](http://www.finance.senate.gov/press/prb042507a.pdf). The accompanying press statement acknowledged that the Accreditation Council for Continuing Medical Education has issued guidance, but that in the judgment of Senators Max Baucus (D-Montana) and Grassley, its “oversight of accredited CME providers is insufficient to guarantee the required independence.”

40. See PhRMA Code on Interactions with Healthcare Professionals.
41. See OIG Compliance Program Guidance for Pharmaceutical Manufacturers, 68 Federal Register, No. 86 (May 5, 2003).
42. See 42 U.S.C. 1320a-7b(b)(3)(A); 42 CFR 1001.952(h). The OIG Compliance Program Guidance itself refers to any remuneration that is “more than trivial” and is given “with the intent to induce or reward referrals.”
43. Id.
44. See comments on the FDA Draft Guidance for Industry on Good Reprint Practices filed by the Medical Information Working Group (April 18, 2008) and the Washington Legal Foundation (April 21, 2008).
45. Letter from Congressman Henry A. Waxman to FDA Commissioner Dr. Andrew C. von Eschenbach (November 30, 2007). See Anna Wilde Mathews, “FDA and Drug Marketing – Plan to Tell Doctors Of Off-Label Uses Is Being Crafted,” *Wall Street Journal* (December 1, 2007).
46. See *Wall Street Journal* Online/Harris Interactive Healthcare Research Poll, “U.S. Adults Ambivalent about the Risks and Benefits of Off-label Prescription Drug Use” (December 7, 2006).