Legal Backgrounder

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FDA AND DRUG ADVERTISING: NO ATTENTION DEFICIT ON NEED FOR "SUBSTANTIAL EVIDENCE"

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In Warning Letters to two companies, and in Untitled Letters to three, the U.S. Food and Drug Administration's (FDA's) Division of Drug Marketing, Advertising, and Communications (DDMAC) on September 25, 2008, alleged that promotional material for certain products intended for use in treating attention deficit hyperactivity disorder (ADHD) made implied claims about an effect on ADHD "outcomes" that were not supported by "substantial evidence," as that latter term is used in statutory parlance. DDMAC's interpretation of the promotional material as making implied ADHD outcomes claims that must be supported by substantial evidence raises policy and legal questions that deserve consideration. At the same time, no matter what their own view of the correctness of DDMAC's position, prescription drug marketers that wish to avoid a government challenge are advised to review their advertising and promotional materials in all therapeutic categories to determine whether they make implied outcomes claims of the kind alleged here by DDMAC and, if so, to ensure they are supported by substantial evidence.

Background

On September 25, 2008, DDMAC simultaneously initiated five compliance actions involving advertising and promotion of prescription drugs intended to treat ADHD. For more information, *see* "Warning Letters and Untitled Letters to Pharmaceutical Companies" (September 2008). In two cases (*Adderall XR*® and *Straterra*®), DDMAC issued a Warning Letter, and in three (*Concerta*®, *Focalin XR*® and *Methylin*®), it sent a so-called Untitled Letter. A Warning Letter is sometimes said to represent a promise on FDA's part to sue if corrective action is not taken. However, FDA does not invariably initiate a lawsuit when there is unremediated (alleged) violative behavior, sometimes even in the face of multiple Warning Letters to the same firm on the same subject. What is true is that under current agency practice, all Warning Letters are required to be reviewed and approved by FDA's Office of Chief Counsel (OCC), which means that the agency's lawyers believe the allegations are factually and legally supportable if litigation became necessary. Even though DDMAC Untitled Letters ask for corrective action and although OCC reviews them beforehand, they are generally understood to be mere notice that FDA believes there is a violation of law but is not in itself considered to be a promise to sue. At the same time, a company can take little comfort in this as issuance of an Untitled Letter in lieu of a Warning Letter is by no means a guarantee that FDA will refrain from initiating a lawsuit. While it is not entirely apparent why in this instance

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Warning Letters were issued to two companies and Untitled Letters to three, it may well have to do with the fact that DDMAC issued prior advertising compliance correspondence in connection with both *Adderall*® (November 2000) and *Strattera*® (July 2005), although the issues are not identical. Alternatively, DDMAC may view the underlying violations in these two cases as more serious than in the cases where it sent Untitled Letters.

Discussion

The message that emerges from these Warning and Untitled Letters taken as a whole is the agency's consistent legal position that what it views as representations about specific outcomes in a particular disease state must be supported by substantial evidence, *i.e.*, evidence that meets the statutory substantial evidence standard for drug approval under §505(d) of the Federal Food, Drug, and Cosmetic Act, which FDA, by regulation, 21 CFR §202.1(e)(4)(ii)(b), has imported into the advertising substantiation realm. For more information, *see* Arnold I. Friede "Recent Warning Letters for Ads Reflect FDA's Fixation on 'Substantial Evidence'" Washington Legal Foundation LEGAL BACKGROUNDER (Aug. 10, 2007), available at http://www.wlf.org/upload/08-10-07friede.pdf.

In *Adderall XR*®, DDMAC focused on a web page for the product that described the "difficulties" caused by ADHD in adolescents, the "consequences" of untreated ADHD in that population and the resultant "impact" of treatment with the product. The promotional material contained representations, the factual accuracy of which FDA did not challenge, that ADHD: (1) has a "negative impact" on "job success" and "social emotional development;" (2) has a serious negative impact on "schooling," including failing a grade and dropping out of high school; (3) causes "impulsive behavior" and is associated with "conduct disorder" such as "bullying, physical cruelty, [and] use of weapons;" (4) is associated with an increased rate of sexually transmitted disease and out-of-wedlock pregnancy; and (5) results in a higher rate of motor vehicle accidents and serious injuries generally. These statements about the "difficulties" and "consequences" of ADHD were immediately followed by the representation: "However, ADHD may be successfully treated. Today's ADHD medications, like ADDERALL XR, have come a long way in providing symptom control."

DDMAC had little difficulty in reaching a conclusion about what are the "implied" claims in this advertising. It alleged that the advertising implies that use of *Adderall XR*® "reduces the likelihood or severity of the 'difficulties' and 'consequences' of 'untreated ADHD.'" However, according to DDMAC, these outcomes in ADHD are not supported by substantial evidence. On the contrary, DDMAC said, the effect of *Adderall XR*® on ADHD was measured in the supporting clinical trials using an evaluative instrument that considered the reduction of symptoms such as "fidgeting, not listening, and talking excessively." But the results on this scale, DDMAC contended, do not constitute substantial evidence for the implied claims about the effect of *Aderall XR*® on outcomes, such as the consequences of untreated ADHD, as represented in the web page advertisement. Nor did DDMAC view any of the references cited as even potentially amounting to substantial evidence of the drug's effect on the outcomes of ADHD allegedly implied by the advertising. On the contrary, DDMAC largely discounted these because, while they provided an overview of ADHD and its management and studied academic and social outcomes in young adults diagnosed with ADHD, and one even evaluated symptom improvement in adolescents treated with *Adderall XR*®, none of them, according to the agency, studied the effect on treatment outcomes such as those impliedly claimed in the advertising (*e.g.*, job success and social emotional development).

It is important to observe that in interpreting the advertising for *Adderall XR*®, DDMAC offered only its own opinion about what the implied claims are. It offered no empirical evidence establishing what it asserts are the specific implications from the juxtaposition of the representations about ADHD generally and use of *Adderall XR*® in particular. In arguably related contexts, FDA has said that "surveys, copy tests, and other reliable evidence of consumer interpretation can be helpful in assessing the particular message that FDA believes constitutes an implied claim;" at the same time, of course, the agency has asserted that "the

act does not require FDA to have survey evidence or other data before the agency is entitled to proceed under [the misbranding provision]." For more information, *see* "Guidance for Industry: Qualified Health Claims in the Labeling of Conventional Foods and Dietary Supplements," 67 Fed. Reg. 78002, 78003 n. 1 (Dec. 20, 2002). Here there is no evidence, other than DDMAC's own interpretation, about what the implied outcomes claims are. And even if FDA is correct that the Act itself does not require that the agency have consumer survey evidence to prove the meaning of an advertising claim, its position, at least with respect to implied claims, raises serious First Amendment questions. For more information, *see* George W. Evans and Arnold I. Friede, "Mixed Results for Free Speech In FDA Health Claims Guidance," Washington Legal Foundation LEGAL OPINION LETTER at 1, (Jan. 17, 2003), available at http://www.wlf.org/upload/011703LOLEvans%20.pdf (" . . . the First Amendment demands that FDA adopt transparent and neutral evaluation procedures" that "should include the use, as appropriate, of empirical methodologies (*e.g.* consumer surveys) for determining what message is communicated by a particular advertising claim.")

Likewise, in *Strattera*®, DDMAC construed a promotional sales aid intended for use in physician detailing as making implied claims that the product would correct the negative outcomes associated with ADHD. Whereas in *Adderall XR*® the representations about the difficulties and consequences of ADHD were immediately followed by a claim that specifically mentions use of the product, this was not the case in *Strattera*®. In fact, the representations about ADHD itself were separate and distinct from those that mention the product. Nevertheless, DDMAC had little difficulty, again *without* empirical evidence, in reaching the following conclusion: "While these presentations do not directly assert that Strattera will correct the negative outcomes associated with ADHD, *the implication created by placing these presentations in a piece promoting Strattera for treatment of ADHD* is that treating ADHD patients with Strattera will reduce the likelihood or severity of the negative outcomes associated with ADHD." (Warning Letter at 3, emphasis supplied). In the absence of substantial evidence to support these allegedly implied representations, DDMAC asserted that the claims are misleading and hence violative.

In other words, in *Strattera*®, DDMAC appears to have staked out a position that, ironically, itself has broad ranging implications. Taken to its logical conclusion, this interpretation holds that any time a single promotional piece contains "disease awareness" representations about the consequences of a condition and simultaneously promotes a specific product, even if there is no direct proximity and juxtaposition of the two in the piece, the advertiser is necessarily making a representation about outcomes directly attributable to use of the product. This represents new and broader boundaries than FDA appears to have staked out on the subject in the past. On this logic, promotional material of this kind must be supported by substantial evidence proving the drug's direct effect on the asserted outcomes. This is a difficult evidentiary burden to meet in many cases. For more information, *see* Draft Guidance, "Guidance for Industry: Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" (Feb. 2006).

DDMAC's approach would appear to force companies to separate all "disease awareness" advertising from all product-specific promotion lest any combination of the two, no matter how separate the representations are and no matter how clear the absence of a direct linkage between the two, be deemed an unsubstantiated outcomes claim because it is not based on substantial evidence. And if the Warning Letter in *Strattera*® is correctly read to mean that any nexus between disease awareness advertising and product promotion amounts to a claim to effect outcomes, then what does this say about dissemination of different pieces that nevertheless are part of the same collection of materials? All of this seems like a dramatic extension of FDA policy on implied outcomes claims. Even FDA's draft guidance on disease awareness advertising does not go that far. For example, *see* Draft Guidance, "Guidance for Industry: 'Help Seeking' and Other Disease Awareness Communications By or on Behalf of Drug and Device Firms" (Jan. 2004). Moreover, and again, important First Amendment questions are raised by an interpretation by DDMAC, absent any empirical evidence, which conclusively holds that an implied outcomes claim is communicated any time a drug, and the consequences of a particular disease or condition, are mentioned in the same

promotional piece no matter what their proximity or linkage. This represents a significant problem for all pharmaceutical marketers given current widespread approaches to pharmaceutical advertising and promotion. Nor is there any suggestion that DDMAC would have interpreted the advertising for *Strattera*® any differently were there language conspicuously disclaiming a direct linkage between the use of the product and specific ADHD outcomes. *Cf. Pearson v. Shalala*, 164 F. 3d 650 (D.C. Cir.), *reh'g en banc denied*, 172 F. 3d 72 (D.C. Cir. 1999) (First Amendment favors disclaimers in lieu of outright speech suppression). Note that similar allegations about the absence of substantial evidence to support implied claims of an effect on the negative outcomes of ADHD are made in DDMAC's Untitled Letters on *Concerta*®, *Focalin XR*® and *Methylin*®.

While the allegations in the DDMAC compliance correspondence on ADHD drugs are directed to the absence of substantial evidence to support particular behavioral outcomes, they are somewhat analogous to the broader debate now raging about surrogate markers and their relationship to disease outcomes more generally. For example, while there might be substantial evidence to prove that a drug favorably affects a surrogate marker, such as reduction in blood pressure, there may well be a lack of substantial evidence that it affects cardiovascular disease outcomes. So the controversy over behavioral outcomes claims for ADHD drugs, and the need for substantial evidence to support them, might also be viewed in the context of this broader debate. After all, physicians do not ordinarily prescribe drugs simply because of their effect on some surrogate marker of disease.

They prescribe them because they believe the surrogate markers validly predict their effect on disease outcomes in real patients. But there seems to be something fundamentally incongruent about approving a drug to treat a specific condition, on the one hand, and, on the other, foreclosing companies from ever mentioning product use and the disease outcomes in the same breath without being able to prove an absolute correlation between the two that is supported by substantial evidence.

Conclusion

FDA's current compliance initiative on ADHD drugs should be considered by all pharmaceutical marketers as notice that the agency appears to be broadening the nexus between disease information and product statements that it will consider to establish an implied "outcomes" claim. The agency may well construe any promotional piece that mentions both the consequences of a disease or condition and use of a particular product in the same piece as making implied outcomes claims that require substantial evidence to support them. Accordingly, a careful review of a company's advertising and promotional pieces appears to be in order. Likewise, companies may wish to consider an appropriate factual situation that might be used to challenge a DDMAC policy that always requires substantial evidence to support allegedly implied outcomes claims whenever an advertising or promotional piece mentions the consequences of a disease or condition and use of a particular product. Even in today's current difficult environment, perhaps the courts or even the agency itself might be receptive to the right arguments.

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