



Vol. 22 No. 31

August 10, 2007

# RECENT WARNING LETTERS FOR ADS REFLECT FDA'S FIXATION ON "SUBSTANTIAL EVIDENCE"

by

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Many of us in the world of pharmaceuticals – and their promotion – are avid readers of the compliance correspondence from FDA's Division of Drug Marketing, Advertising, and Communications ("DDMAC") to pharmaceutical companies.<sup>1</sup> We also avidly read the constitutional, Administrative Procedures Act ("APA"), and other legal and policy criticisms leveled against much of this correspondence by the Washington Legal Foundation ("WLF").<sup>2</sup> As a practical matter, it may not matter all that much that FDA is in violation of the APA when it announces policy through compliance correspondence instead of through notice-and-comment rulemaking. The fact remains that unless and until a court holds that the agency has exceeded its statutory or constitutional authority, DDMAC Warning Letters, Notices of Violation, and Untitled Letters represent the best and most authoritative statement of FDA's own views on the law. For this reason, and whether one agrees or disagrees with the government's assertions, they deserve careful study by anyone engaged in advertising and promoting prescription drugs or counseling clients who do. Moreover, and while the letters do not say so expressly, DDMAC compliance correspondence also reflects, and must be understood in the context of, the broader drug safety debate that will soon culminate in new drug safety legislation from Congress, including new provisions that directly implicate prescription drug advertising. Finally, they represent a mirror for many of the criticisms of the industry that abound in the generally toxic external political and public policy environments.

Several recent DDMAC letters over the last few months clearly indicate that FDA insists on

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<sup>1</sup>See <http://www.fda.gov/cder/warn/warn2007.htm>.

<sup>2</sup>See WLF "DDMAC Watch", <http://www.wlf.org/Resources/DDMAC/default.asp>

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“substantial evidence” to support all advertising claims, including, notably, comparative claims (but not limited to comparisons).<sup>3</sup> And when the agency talks about “substantial evidence,” it uses that term in its statutory and regulatory sense, and not merely in the sense that “substantial” might mean “a lot of evidence” or “a lot of persuasive evidence” or “competent and reliable evidence” or in any other sense that the term “substantial evidence” might be understood. It is using the term in the technical sense set forth in the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 331, *et seq.*, and FDA’s implementing regulations. In this respect, FDA is largely avoiding any discussion of the potential application of the decision in *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir.), *reh’g en banc denied*, 172 F.3d 72 (D.C. Cir. 1999) There, the United States Court of Appeals for the D.C. Circuit held that the First Amendment compelled FDA to permit promotional health claims for dietary supplements that failed to meet the statute’s “significant scientific agreement” standard if these representations were otherwise truthful and not misleading and were accompanied by appropriate disclaimers about the nature and extent of the supporting evidence and the fact that the claims lacked express FDA approval.

It is true, of course, that in *Pearson v. Shalala*, the D.C. Circuit said the government did not assert that the products threatened health and safety in any way, 172 F.3d at 656, and on this basis distinguished drug claims: “Drugs, on the other hand, appear to be in an entirely different category – the potential harm presumably is much greater.” *Id.* at n. 6. But this presumptive distinction was not the subject of any further discussion or analysis by the court and for this reason does not deserve categorical deference. In particular, the D.C. Circuit in *Pearson v. Shalala* did not address why the “rule” in the dietary supplement context, where the statute expressly provides a standard for the approvability of promotional claims, should be inapplicable, despite the ostensible health and safety difference in the case of drugs, where the underlying statute does not expressly provide for a “substantial evidence” standard for promotional claims for drugs and where that standard has been engrafted by FDA from the approval context to the advertising substantiation context.<sup>4</sup> But whatever the argument for application of *Pearson v. Shalala* in other contexts, FDA has quite clearly taken the position, at least by implication, that prescription drug advertising is different and that strict adherence to the statutory “substantial evidence” standard is required.

The Act defines “substantial evidence” as:

[E]vidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

Although, as noted, the statute literally applies the “substantial evidence” criterion only to approval of

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<sup>3</sup>See, e.g., DDMAC Compliance Correspondence re: *Abelcet*® (May 21, 2007), *Acular LS*® (May 25, 2007), and *Clindesse*® (May 17, 2007)), *Flonase*® (May 7, 2007) and *Nasonex*® (May 7, 2007).

<sup>4</sup>*Cf.* § 505(d) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(d), defining “substantial evidence” for purposes of approving new drug applications in the first instance, *with* 21 CFR (e)(4)(ii)(b), applying the same “substantial evidence” standard to the quantum of substantiation necessary to support advertising claims for already approved prescription drugs.

new drugs, FDA's own regulations apply these same standards to substantiation for advertising claims for already approved products. 21 CFR (e)(4)(ii)(b). And the specific characteristics for determining when a study is "adequate and well controlled" in order even potentially to qualify as "substantial evidence" under FDA's regime are defined by the agency in considerable detail in its regulations. 21 CFR 314.126(b).

We can see absolute strict application by DDMAC of its interpretation of "substantial evidence" in the recent compliance correspondence. For example, in *Nasonex* and *Flonase*, DDMAC was troubled among other things by the lack of "substantial evidence" to support claims of specific effectiveness in "congestion." In *Clindesse*, DDMAC was troubled among other things by the absence of "substantial evidence" to support the comparison between the advertised clindamycin-containing product and competing products containing metronidazole, and particularly the absence of any specific head-to-head comparative trials. In *Acular LS*, DDMAC interpreted the data cited in the advertising as amounting to a representation that the advertised product was indicated for the use studied in data relating to the competing product, and then faulted the implied comparison as being unsupported by data that conforms to the "substantial evidence" standard. And in *Abelcet*, the absence of comparative head-to-head testing was likewise cited as a key reason why the claims lacked "substantial evidence" to support them.

So, it seems important, particularly now, given the generally toxic external political and regulatory climate that pharmaceutical companies find themselves in, to reinforce the message that FDA requires all claims to have "substantial evidence" to support them. Sometimes, this is "easy" because the proposed claims are already in the approved labeling for a product which, by definition, means that FDA has found them to be supported by "substantial evidence." Other times, however, the advertising claims are not derived directly from claims approved in labeling. Sometimes, the proffered substantiation for these claims is in retrospective analysis of data and not in analysis based on pre-determined, protocol-specified endpoints. No matter how robust these analyses, DDMAC is likely to have a problem with them.<sup>5</sup> Other times, the proffered substantiation is in finding new data subsets that, while perhaps yielding scientifically relevant and persuasive information, may have "substantial evidence" limitations. Even other times, the proffered substantiation might be based on a single study, and not two "adequate and well-controlled investigations," which is the general requirement for "substantial evidence". And comparative claims might be based on proffered substantiation, such as label-to-label comparisons, but fail to include evidence from direct head-to-head trials. Time-and-again, FDA has said that such head-to-head trials are, in its view, the absolute *sine qua non* for "substantial evidence" to support comparative claims.

The recent DDMAC compliance correspondence should be studied closely by companies and practitioners to provide a first hand sense of how FDA applies the "substantial evidence" standard to specific advertising and promotional claims for prescription drugs. But the overall message is simple and relatively straightforward: If you want to avoid problems with DDMAC, insure that claims in prescription drug advertising and promotion are supported by "substantial evidence," no matter how competent and reliable the supporting evidence might otherwise be to the company and to leading experts in the field. To put it bluntly, DDMAC doesn't really care. What DDMAC cares about is like

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<sup>5</sup>*Cf. Procter & Gamble Pharmaceuticals, Inc. v. Hoffmann-LaRoche Inc.*, 2006 WL 2588002 at \*7 fn. 23 (S.D.N.Y. Sep 06, 2006) (NO. 06 CIV. 0034 (PAC)) ("Subgroup analyses are not *per se* disfavored in the scientific community.")

“location,” “location,” “location” in the real estate purchase context. It’s about “substantial evidence,” “substantial evidence,” “substantial evidence”.

So whether we like it or not, or whether we think it is unconstitutional or violates the APA or is otherwise illegal or not, for those who seek to avoid an unpleasant compliance confrontation with DDMAC, “substantial evidence” should be the watchword.

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