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Re: Draft Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved Uses of Approved Drugs or Approved or Cleared Medical Devices, Notice of Availability, 34 Fed. Reg. 9342 (Feb. 20, 2008)

Docket No.:FDA-2008-D-0053

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These comments are in response to FDA's request for comments on this Draft Guidance. These comments deal with the distribution by drug manufacturers to physicians of medical reprints about an unapproved use for their drug.¹

A. Overview on Basis for Policy Position. 1. Problematic Purpose and FDA's Statutory Role. Before dealing with the specific difficulties raised by the Draft Guidance, its underlying premise needs to be addressed. The Draft Guidance starts by recognizing that the F D&C Act generally prohibits manufacturers from distributing products in interstate commerce for any intended use that has not been approved by the agency. The Guidance then states that "FDA does, however, recognize the important policy reasons for allowing manufacturers to disseminate truthful and non-misleading medical journals articles...on unapproved uses of approved drugs...to health care professionals and health care entities." P. 3.

There have been some court decisions that have recognized that constitutional

¹ While these comments discuss drugs, the same points seem applicable in principle to the other distributions covered by the FDA Draft Guidance. See my article on Drug Review and the Constitution after *Western States*, 37 Univ. Of Richmond L. Rev. 901, 923-30 (2003).

commercial speech protections apply when manufacturers distribute medical journals, accompanied by disclaimers, to physicians, but this litigation ended without resolving the merits and with vacated decisions. *Washington Legal Foundation v. Henney*, 202 F.3d 331 (D.C. Cir. 2000) and 128 F. Supp.2d 11 (D.D.C. 2000) The agency's rationale for the Draft Guidance does not, though, relate to the constitutional grounds, and that basis is not discussed here. Instead the agency as a **policy matter** has found that "the public health can be served" by the manufacturer's distribution of reprints about unapproved uses and that agency will not regard distributions made in accordance with the Draft Guidance to be "evidence of intent" that the product can be used for an unapproved use. P.6 The agency's justification for issuing the Draft Guidance is that the "safe harbor" for the distribution of reprints provided for in FDAMA ceased to be effective in 2007. FDAMA, however, provided for several safeguards before that safe harbor applied, but the agency has not included them in its Draft Guidance or discussed why they are not needed.

2. Policy Impact and Statutory Standards. The Draft Guidance states that the public health can be promoted by the distribution of reprints on unapproved uses but the Draft does not explain the basis for this determination and the scope of its policy. For example, will the policy apply to all new uses or only those that relate to unmet medical needs for life-threatening conditions?

The agency also failed to discuss or take into account the ways in which the distribution of reprints by manufacturers on unapproved uses can undercut the agency's important role in ensuring that drugs are safe and effective. If the policy in the Draft Guidance is adopted, there is a risk that drug manufacturers will obtain approval for a new drug for a short-term or other limited use based on studies that are similarly limited in scope. Later, manufacturers may fund studies by researchers about more significant uses involving longer-term use by a wider population that may present a wider potential for safety risks, and closer questions about the efficacy of the new use. These difficulties are especially important when the funding for the study in the reprint distributed by the manufacturer comes from the manufacturer of the drug. The Draft Guidance did not discuss the potential to undercut the agency's statutory role, but it needs to do so.

Another core problem is that the agency has failed to address how its policy position can be reconciled with the statute. Before a drug manufacturer can promote a drug for a new use, the manufacturer needs to file a new drug application to show that the new use is safe and effective.² The Draft Guidance states an enforcement policy³ that the agency "does not intend to use" the manufacturer's distribution of reprints that meet the guidance as "evidence of an intent" by the manufacturer that the drug is to be used for an unapproved use. P. 5 The Draft Guidance relies on disclosures as the means to prevent deception and to make manufacturer-initiated distributions acceptable. Disclosures, though, have their limits as a protection.

B. Differences between Reliance on Reprints and FDA Review, and the Adequacy of Disclosures. The FDA position is questionable because of the differences that can exist between the extent of the support for manufacturer-distributed reprints in contrast to that needed for FDA approval.

1. Scope of Review for Reprints and by FDA. The peer-reviewers for medical journals may, in practice, have limited access to the protocols for the study or the underlying raw data. FDA reviewers automatically have this access which permits a more thorough assessment. Even if the manufacturer were to make a disclosure about the limited access of reviewers to this information, it would be difficult for physicians to assess the significance of the risks that might have been found if the reviewer had this additional information. There also are reports that peer-reviewers for journals spend a limited amount of time doing their reviews. See Letter to Commissioner von Eisenbach from Congressman Henry Waxman, p. 4 (Nov. 30, 2007). In contrast, FDA medical reviewers work full-time in this field.

The Draft Guidance relies on disclosures as a safeguard, including full disclosure of the conflict of interest of authors, contributors or editors, and prominent affixed disclosures about the manufacturer's interest, the lack of FDA approval and any compensation provided by the manufacturer to the author. While this necessitates disclosure of funding by the drug manufacture of the study, it does not preclude it. In this setting it is especially important to have an adequate FDA review. The distribution of reprints may impact on the workload of FDA reviewers though. In the past, the workload of the medical reviewers led to delays in the review of new drugs. To deal with that lag, the law was amended to provide that drug manufacturers pay user fees for new drug applications, and supplemental applications, and these fees have been used to fund the salaries for additional reviewers. If manufacturers distribute reprints about new uses, rather than seeking FDA approval, under the Draft Guidance a supplemental application will not be needed and they will not need to pay user fees. As a result FDA may have less resources to hire FDA reviewers to examine the adequacy of the manufacturer-distributed reprint, and for FDA to bring enforcement action if necessary. The effect will seem to be to reduce the practical ability of FDA to assess the adequacy of the support for the new use described in the reprint.

2. Adequacy of Studies and Disclosures. New drugs are to be approved based on adequate and well-controlled studies, and the Supreme Court has recognized that the FDA regulations for such studies "express well-established principles of scientific investigation." *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609 (1973). The Draft Guidance provides that the distributed-articles are to "address" adequate and well-controlled studies and that the articles should not be misleading by being inconsistent with the weight of "credible evidence" derived from studies of this type. These standards are somewhat ambiguous. The manufacturer should only be able to distribute reprints about a new use if there actually are studies that are adequate and well-controlled. If the agency intends to allow manufacturers to distribute reprints that lack that level of support, the manufacturers should have to make a prominent disclosure that the study lacks such support, and the specific ways that the studies fail to meet the FDA standards. The agency's draft also seems to be influenced by the "credible evidence" test that set a lenient standard for allowing health claims on foods, with disclaimers, based on constitutional commercial speech grounds. *Whitaker v. Thompson*, 248 F. Supp. 2d 287 (D. D.C. 2002). That case seems of doubtful relevance in determining the support needed, or the benchmark for disclosures, for manufacturer-distributed reprints about new uses for drugs that relate to serious health problems.

3.. Post-Market Risks and Studies. Newly-approved drugs may often pose risks that can only be found by experience with patients or post-approval studies. A similar potential for new risks is likely to arise with the new uses for drugs described in manufacturer-distributed reprints. FDA needs to consider how the risks from the reprint use will be reported in the drug labeling, and whether the drug manufacturer will have a special obligation to notify those who received the reprint if the drug is later found to have important additional risks not described in the reprint. FDA also needs to consider whether it will have adequate authority to deal with these additional risks in view of its position, discussed earlier, that distributions that satisfy the Draft Guidance will not be regarded as establishing “evidence of intent” that the product is to be used for an unapproved use.

FDA often requires Phase IV post-approval studies to obtain further information on the safety or efficacy of an approved drug. An agency website gives the status of uncompleted studies. FDA has not addressed what steps will be taken if the new use described in a reprint is one that would ordinarily need post-market studies, and whether the manufacturer is to make disclosures about the need for and the status of the studies.

4.. Reprints and Physician Standards and Manufacturer Representations.

When a manufacturer distributes reprints, the distribution should prominently state that the reprint is for use by the physician to make an independent decision on whether the new use meets the medical professional standard of care and that the manufacturer makes no representation on that matter. A disclosure like this is needed since without it the physicians may view the distribution by the drug manufacturers as an endorsement of the new use in a way that lessen the need for scrutiny by the physician and the physician’s potential liability if problems arise. The extent to which manufacturers would face liability if they distribute reprints without adequate disclosures is a question that warrants more consideration.

C. Need for Additional Safeguards and Study. Disclosures do not seem adequate to deal with the difficulties raised above. A better approach would be to have additional safeguards including the following:

- +prior notice to the agency in advance of a planned distribution of a reprint and of the transmittal material that the manufacturer plans to provide to physicians so that the agency can provide comments on the need for additional disclosures or other measures to comply with the Guidance and the law

- +maintenance of distribution lists by the manufacturer of distribution lists in case recipients need more information about post-approval risks or other corrective information

- + an obligation by the manufacturer to submit a supplemental application and do additional studies if the agency finds that the new use described in a reprint has not been adequately shown to be effective or has the potential to impact the public health in a way that has not been adequately addressed by the study described in the reprint.

+provision of adequate resources to permit the agency to review the studies that are the subject of manufacturer-distributed reprints

These steps would seem to need Congressional action. The matter can also benefit from more study, including about the adequacy of the incentives for research on new uses. The law already provides for fast-track approval of drugs for life-threatening conditions, and incentives for orphan drugs. Congress directly funds medical research. Drug research is also protected by patents and non-patent incentives under Hatch-Waxman. FDAMA provided for an exemption from doing studies if justified by costs reasons because of the lack of exclusive marketing rights for the new use. The adequacy of the existing incentives involves complicated intellectual property issues, including the scope of the Hatch-Waxman protections, the extent to which generic drugs can be used for off-label uses and reimbursement policies for off-label uses. If the distribution of reprints is believed to be appropriate because the existing incentives are thought to be insufficient, that matter is one that should be addressed by Congress directly.

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