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Turning a blind eye

A new proposal might allow drug makers to promote off-label uses of their products by distributing medical publications to US doctors. Stronger rules could assure that information—not propaganda—drives doctors' prescription practices.

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Doctors commonly prescribe drugs approved by the US Food and Drug Administration (FDA) for off-label medical indications. They do so in part based on published clinical studies. Although US law prohibits pharmaceutical companies from marketing drugs for unapproved uses, a draft proposal the FDA issued in October could allow companies to provide medical literature to doctors about off-label uses for their drugs. The proposal falls well short of ensuring that doctors have the right information to decide whether an off-label prescription is appropriate.

According to a study in the *Archives of Internal Medicine* (**166**, 1021–1026; 2006), 73% of off-label drug uses lack evidence of efficacy. Yet off-label prescriptions make up more than 20% of all prescriptions in the US.

Before 1997, pharmaceutical companies had to wait until the FDA approved a drug for a given indication before they could disseminate information about the drug for that indication. However, in 1997, Congress passed the FDA Modernization Act, allowing companies to distribute medical literature about off-label indications to healthcare providers if a number of conditions were met. For example, the articles had to be preapproved by the FDA. Owing to concerns that these conditions restricted free speech, a federal court revoked many of them in 1999 while maintaining that a company could distribute literature to doctors about off-label use of a drug only if the company was planning to submit an application to the FDA for approval of that new use.

The existing regulations controlling dissemination of articles lapsed in 2006, so the FDA has now drawn up a fresh proposal. Surprisingly, this new proposal relaxes restrictions that were previously in place, while also placing excessive trust in the medical literature.

First, the proposal allows for distribution of both primary research articles and medical reference books, with the assumption that both are "truthful and not misleading." However, medical textbooks are not always peer reviewed and may represent the author's opinion. It is unclear why the FDA would accept the claims in these textbooks as sufficiently "truthful" to potentially steer medical practice.

Primary research articles, which are peer reviewed, have their own problems. Unlike those who review clinical trials for the FDA, peer reviewers do not have access to all of the study protocols and data. With only a few reviewers for each paper, their opinions may not accurately represent those of the broader medical community. Referees may also be unable to detect outright fraud.

Second, the proposal calls for companies to provide a balanced view to doctors by disseminating their publications along with others that challenge it or come to a different conclusion. However, because companies may choose not to publish negative findings, the idea that a balanced view could be gleaned from the medical literature may be unrealistic. For example, The Center for Science and the Public Interest found that 96% of published studies on selective serotonin reuptake inhibitors showed efficacy in children. However, in the FDA's analysis of both published and unpublished studies, only 20% of studies demonstrated efficacy. Fortunately, a new law passed in September mandates that drug companies post all clinical trial data in a US National Institutes of Health database, which will make it more difficult to conceal negative findings.

Lastly, the proposal does not contain a key element of the previous regulations: allowing companies to distribute literature on off-label drug use only if an application is also being submitted to the FDA for that indication. Without this condition, companies could receive FDA approval of a drug for a very narrow indication. They could then dispense with the large-scale trials required for FDA approval for other indications and instead simply inform doctors about wider uses of the drug based on smaller, cheaper clinical studies. Along these lines, the proposal limits companies to distributing "adequate and well controlled clinical" studies, but does not specify whether a smaller phase 2 clinical study or a larger, more informative phase 3 trial would be necessary. For all these reasons, the proposal should be revised to ensure that companies distribute to doctors only clinical studies that are also being submitted for FDA approval.

The FDA abdicates its advisory responsibilities to the medical community and the general public if it allows recommendations from the medical literature to substitute for regulatory approval of off-label drug uses. If the FDA turns a blind eye to its mission to evaluate safety and efficacy for all the indications for which a drug is used, why do we need the FDA?