Stanford researcher criticizes FDA plans to reduce oversight of off-label drug use

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Proposed guidelines from the U.S. Food and Drug Administration would allow companies to market more drugs for unapproved uses and are a step in the wrong direction, said a researcher from the Stanford University School of Medicine.

In an editorial to be published in the April 3 issue of *The New England Journal of Medicine*, Randall Stafford, MD, PhD, associate professor of medicine at the Stanford Prevention Research Center, criticized the draft guidelines, which are subject to public comment through April 21. They curtail the FDA's already limited authority over the marketing of drugs for off-label uses, Stafford said.

While most people assume that the medicines prescribed by doctors in the United States have the FDA's stamp of approval, that's only partially true. The FDA approves drugs for specific purposes, but doctors can use drugs "off-label" for medical conditions not approved by the FDA.

Off-label prescribing for medical conditions not scrutinized during the FDA approval process is common. There's nothing illegal about off-label prescribing, and in many cases it's good medicine, said Stafford, who directs Stanford's Program on Prevention Outcomes and Practices. As long as the FDA has approved a drug for one condition, physicians are free to prescribe it for anything.

Unfortunately, what's known about the use of a drug for one situation may not apply to other clinical scenarios. Stafford pointed to the use of antidepressants in children and the use of antipsychotic medications for dementia as key examples.

"The FDA should not suddenly start telling physicians how to practice. Physician judgment is critical, especially when approved therapies have not succeeded. Off-label prescribing can be an important tool in such cases," he said. "But in other cases, off-label prescribing has become first-line therapy even in the absence of strong evidence of benefits and safety. This is problematic."

Stafford said these types of situations suggest the need for a better way to evaluate and regulate off-label drug use. Ideally, he said, a drug company would go back to the FDA with additional clinical studies and obtain supplemental approval for a new clinical use.

Off-label drug use is already common, but applications to the FDA for approval of new uses are uncommon, said Stafford. This process may be seen as irrelevant by drug manufacturers, who have strategies for expanding their off-label markets and boosting drug sales without formal FDA approval.

Although FDA regulations restrict drug manufacturers from overtly promoting their drugs for unapproved conditions, they are free to share educational materials with physicians, most often as published journal articles. According to current FDA guidelines, this practice is acceptable, but only if the manufacturer submits the articles to the FDA for review and is pursuing formal FDA approval for the new use. In reality, however, FDA enforcement is limited, said Stafford.

The new draft guidelines further pull back FDA involvement by eliminating both of these requirements. In addition, they reduce the remaining policies to non-binding recommendations.

This concerned Stafford, who wrote in the NEJM editorial: "The FDA may be conceding to drug manufacturers the responsibility for regulating their own off-label marketing practices. The agency may also believe that its limited resources can be put to better or more effective use in confronting other ongoing challenges. Nevertheless, I believe that the FDA must take an active role in fostering evidence-based practice, eliminating subversion of the

approval process, and requiring a balanced and fair presentation of the scientific evidence."

One of the proposed guidelines' major pitfalls, said Stafford, would be allowing drug manufacturers to skip obtaining approval for potentially lucrative drug uses. Instead, companies might seek approval only for a narrower use that's more easily and less expensively tested, and sponsor research on more commercially promising uses that are never evaluated by the FDA. Stafford warned that this might encourage widespread treatment of conditions with drugs never approved by the FDA for those purposes.

Off-label use is already burgeoning. In a 2006 examination of off-label prescribing of 160 common drugs, Stafford found that off-label use accounted for 21 percent of all prescriptions and 73 percent of these uses had little or no scientific support (Archives of Internal Medicine, May 8, 2006). Drugs approved for depression, schizophrenia and seizures were most likely to be used off-label without adequate support for other conditions.

Source: Stanford University