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Cancer Patients Deserve Faster Access to Life-Saving Drugs

Companies should be able to promote all uses of their drugs that are reliably shown to be effective.

By [RICHARD A. EPSTEIN](#)

As President Barack Obama's new Food and Drug Administration team of Margaret Hamburg and Joshua Sharfstein take the reins, they must decide what to do with off-label uses of FDA-approved drugs. Right now these drugs provide immense life-saving opportunities for many sick patients, particularly those threatened by cancer. The FDA and Congress should protect physicians' and patients' right to off-label uses -- and for the first time allow drug makers to promote off-label uses that prove beneficial.

At present, no drug can reach the market without FDA approval. That approval is explicitly limited to the specific indications that have been subjected to exhaustive clinical tests, which usually take around seven years to complete, typically at the cost of hundreds of millions of dollars. Yet once a drug reaches the market, the FDA has no statutory power to "limit or interfere with the authority of a health-care practitioner to prescribe" how physicians use that drug to treat their patients.

Thus drugs licensed by FDA for one purpose are deployed for a second "off label" use on which clinical trials have not been run or, if run, not completed. These uses are neither fragmentary nor episodic. In 2008, Mark Ratner and Trisha Gura reported in *Nature* that estimates for off-label use of cancer drugs run from 50% to 70% of total usage, and perhaps higher.

There is ample reason for this extensive off-label use. Cancer patients are often in desperate straits. And when existing treatments fail, patients and physicians alike can rationally conclude that they lose nothing by rolling the dice.

Clinical trials sometimes give way to educated guesses that a drug approved for one kind of tumor might treat a second. In many instances the result is failure. But when early results from clinical trials suggest favorable results on which the FDA is unwilling to act, off-label use begins in earnest.

The drug Avastin, for example, already had FDA approval for treating lung and colorectal cancer when early clinical trials suggested in 2005 that adding Avastin to breast cancer treatments retarded tumor spread. Oncologists pounced on these results long before Avastatin ultimately

received FDA approval for breast cancer in 2008. It was a case where bottom-up markets did an end-run around top-down regulation.

Any reliable information about what drugs work has the potential to save lives -- but the FDA's slow and ponderous system can't respond in real time to new data. Yet the gap between the FDA and the ordinary physician is being filled by the National Comprehensive Cancer Network (NCCN), a nonprofit alliance of 21 leading cancer centers, which gathers and evaluates information on off-label uses, much of which it publishes in its own journal.

This information is regarded as sufficiently reliable that -- after some initial hesitation -- Medicare now reimburses physicians and hospitals for off-label uses at much considerable cost to its own budgets. Moreover, the NCCN guidelines are commonly accepted in practice as setting the standard of care in medical malpractice cases.

The FDA is a bystander to this process. But it makes sure to raise its administrative sword against any drug company that dares promote the off-label uses of its products. For example, Pfizer was fined \$430 million for the off-label promotion of Neurontin for migraine headaches. Serono Labs ponied up over \$700 million to settle charges of the illegal promotion of its synthetic growth hormone, Serostim, used to combat AIDS-related wasting.

This absurd situation calls into question the entire FDA approval system for cancer drugs.

As matters now stand, no off-label use is possible for any drug that has not been certified for some particular on-label use. That necessarily reduces the number of drugs available on the market for off-label experimentation.

Sometimes the results are quite perverse. A promising drug fails its clinical tests, for example, because the data collection at a particular site may not have been properly monitored. Physicians following the trial could easily conclude that some related drug currently on the market might be suitable for the same purpose. So that drug is used off-label, while the newer one, which could easily be superior, remains on the shelf, perhaps forever. Such may be the fate of Pharmacyclic's Xcytrin, which was tested for treating the brain metastases of lung cancer in a \$300 million-plus clinical trial that went awry on data collection at one site. The FDA has demanded new clinical trials that may be too expensive to complete. So physicians resort to the off-label use of Temodar (temozolamide), for which the evidence of clinical efficacy is much weaker.

Remember, recruiting subjects for the ever greater number of clinical trials required for drug approval is no easy task. The number of patients required per trial increased from around 1,600 in the late 1970s to around 4,200 in the mid-1990s and more since then. Patients are not available in the U.S. in endless numbers, and many will rightly stay out of clinical trials for untested drugs if they think that some off-label use of an existing drug is more promising.

In order to speed up its approval process for cancer drugs, the FDA introduced its Critical Path initiative in 2004. But its expedited processes have become bogged down, as the FDA has turned cautious after the negative publicity from the withdrawals of drugs like Rezulin and Vioxx. This threatens further contraction in the universe of new cancer drugs.

So what should be done? No one thinks that unapproved cancer drugs should be freely available to patients in the over-the-counter market. Yet once a drug passes Phase I clinical trials -- which test for high toxicity -- why not make it available for general distribution through the NCCN, which has far superior access to specialized medical expertise than the FDA? The blunt fact is that no matter how able FDA scientists and physicians are, none of them have the years of experience dealing with particular tumors and particular drugs that specialist scientists and physicians can bring to this project.

This may sound radical. But when lives are at stake, we should consider drastic measures.

Mr. Epstein is a professor of law at the University of Chicago and a senior fellow at Stanford University's Hoover Institution.