

*FDA efficacy requirements may do more medical harm than good.*

# Who Certifies Off-Label?

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**F**EDERAL LAW FORBIDS A NEW DRUG from being sold in the United States unless it has passed tests approved by the Food and Drug Administration examining the drug's safety and efficacy in a specified use. The specified use is called the "on-label" use and is what the FDA officially recognizes as the drug's intended purpose.

It often happens that, after the drug is permitted, physicians and researchers discover that it has other uses. Physicians are perfectly free to prescribe a permitted drug for such "off-label" uses, and the FDA plays no role in certifying those uses.

Viagra, for example, was initially intended to treat angina, but when older men reported its unusual side-effect it became a blockbuster treatment for erectile dysfunction. Since being approved for that use, Viagra has also been found to be useful in the treatment of pulmonary hypertension. Strange as it may seem, premature babies have been prescribed Viagra to help them breathe, with apparently good success. Viagra's off-label uses have not been proven effective to the same degree as its on-label uses. But the safety profile is good, and because doctors have few other treatment options for pulmonary hypertension and small trials suggest Viagra's effectiveness, doctors are taking what appears to be the best course of action for their patients.

## **OFF-LABEL IS PERVASIVE AND VITAL**

Off-label prescribing is very common in all areas of medicine, and it is not unusual for a drug to be prescribed off-label more often

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than on-label. Thalidomide, for example, is an on-label treatment for leprosy but is used much more often in the treatment of some forms of cancer and aspects of AIDS. In fact, most cancer and AIDS patients are given drugs that are not FDA-certified for the prescribed use. In a large number of fields, a majority of patients are prescribed at least one drug off-label, and in some cases the off-label prescription is the "gold-standard" treatment.

Physicians prescribe off-label because medical knowledge advances at a faster rate than the FDA. The *U.S. Pharmacopeia Drug Information* is a standard reference work that uses expert committees to compile and evaluate the dosing, indications, interactions, pharmacology/pharmacokinetics, and side/adverse effects of drugs for both labeled and off-label uses. Researcher J. Howard Beales found that off-label uses that later came to be recognized by the FDA appeared in the *Pharmacopoeia* on average 2.5 years before FDA recognition. For drugs that are off-patent, many uses that appear in the *Pharmacopoeia* will never receive official FDA recognition.

Off-label prescribing also gives physicians and patients more options when standard treatments fail. Patients are heterogeneous, and what works for one person may not work for another. If physicians were limited to labeled uses, they would in many cases have no therapies to employ at all. Off-label prescribing is more common when standard treatment regimes do not exist or fail.

Finally, when all has failed — as it often does — it is not irrational for patients to demand experimental treatments. Off-label prescribing has few costs in this context and, in addition to providing hope, it may generate important new knowledge.

## **HOW DOES THE PRACTICE OF OFF-LABEL PRESCRIBING DEVELOP?**

The research that goes into approving a drug typically provides good information about how the drug works, at least in the test population. Challenged by diseases without good treatments

or by patients for whom standard therapies have failed, researchers and physicians may try new approaches that have some theoretical basis.

Viagra, for example, is known to help dilate smooth-muscle blood vessels by boosting the production of the signaling compound nitric oxide. Pulmonary hypertension is a rare blood vessel disorder in which the lungs cannot distribute adequate oxygen to the rest of the body. Few treatments exist for babies born with this condition but, knowing that lack of nitric oxide was one of the causes, physicians made inhalation of nitric oxide a standard treatment. Inhaled nitric oxide, however, is expensive and impractical for long-term use. Thus, pediatricians have prescribed Viagra in the hope that it may provide a better, longer-term solution. In a news story about a case involving two babies, Dr. Thomas Doyle of Vanderbilt Children's Hospital indicated why he had prescribed Viagra: "Both babies were very ill and had few options. Neither had tolerated conventional therapy well." The body is complex and a little theory does not mean a guarantee of success, but early results on treating infant pulmonary hypertension with Viagra have been promising.

Critics of off-label prescribing argue that the practice should not be allowed because the drugs have not been through the same randomized clinical trials for those uses as on-label uses. This criticism misunderstands the nature of much drug discovery. Several small-scale trials for Viagra in infants have already been completed and larger trials are underway. The only reason the trials are occurring is because physicians and patients with few other options tried Viagra and were encouraged by the results. Clinical practice often precedes, rather than follows, clinical trials.

Each newly permitted drug projects a wide range of theoretically related and possibly effective off-label indications, and the promise of each gradually diminishes the further (in terms of current medico-pharmacological understanding) such prospective indications are from the on-label indications. Medical science explores possible related uses and, if they appear to pan out, it tends to adopt them.

### CERTIFICATION WITHOUT THE FDA

Physicians learn of off-label uses from medical research and experience conveyed by peer-reviewed publications, newsletters, lecture presentations, conferences, and conversations with trusted colleagues. The new learning comes from many sources: utilization and outcome reviews, clinical and epidemiological studies, new theories advanced by scientists, new judgments made by professional and scientific bodies, and new results reported by pharmaceutical companies. As the enterprise of medical science proceeds, the new learning flows back and forth between medical researchers and practitioners, albeit in fits and starts.

The off-label experience testifies to the fact that much knowledge about efficacy and safety is produced outside the FDA regulatory apparatus. The *Pharmacopoeia's* recognition of off-label indications years ahead of the FDA demonstrates that physicians and scientists have certified thousands of drug indications quite independently of the FDA, even when those indications are not very closely related to the original indications. In addition to the *Pharmacopoeia*, there are several other forms of professional certification, including the *American Hospital Formulary Service Drug*

*Information*, HMO formularies, and a wide array of specialist professional periodicals and information services. NIH studies, clinical results and determinations from other countries, and other professional, science-based judgments are examples of nongovernmental, non-mandatory certification.

Note that we use the term "certification" broadly. When a reputable medical researcher publishes compelling results in an esteemed journal and presents the knowledge at a professional conference, he is not issuing a formal certification the way a notary public does. Yet he is endorsing or approving of certain understandings about the drug and how it might help people in serious need. "Certification" is as subtle and particularistic as medicine itself. Indeed, one might see the entire enterprise of medicine and the health sciences as a system of certifications.

In the final analysis, it is that system of certifications, not FDA approval per se, that doctors actually rely on.

**DOCTORS' COMMENTS** In a recent study, we engaged nearly 500 doctors in an online survey about these matters. Some of their remarks about the practice of off-label prescribing were especially interesting, including:

"Often, efficacy information is already available from studies done outside the USA."

"There is often data from Europe or in peer review journals. FDA efficacy trials are important, but they are not the only measure (except legally in terms of company marketing) of a product's efficacy for a certain condition."

"Off label use is very often based on valid smaller studies concerning other than the index medical condition; those studies may not be large enough or the pharmaceutical company may not want to spend the [money] it takes to get FDA approval."

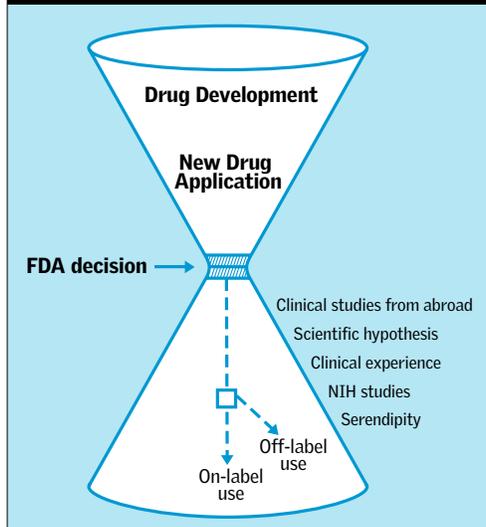
"FDA approval on efficacy lags behind peer-reviewed data that may suggest efficacy."

"Almost all cancer chemotherapy is off-label. There is no way two or three drug companies can expend the effort to get a combination regimen approved."

FIGURE 1

## The FDA Bottleneck

The drug-approval process excludes several useful sources of information.



Oncologists use the peer-reviewed literature to decide therapy. Almost always decisions are based on randomized clinical trials.”

“Plaquenil was developed and FDA-approved as a malarial drug. Later it was found to relieve rheumatoid arthritis symptoms in the patients taking it for malaria. Studies show that it worked and was efficacious but should we wait for the FDA to prolong the relief of pain and suffering for several years while the necessary drug company/FDA studies are done or just use common sense? Often there is no financial incentive for a drug company to pursue off-label indications for conditions that wouldn’t generate sufficient income to offset the cost of FDA approved trials. But university-based, double-blind, highly powered studies show benefits that outweigh risks.”

### OFF-LABEL AS A NATURAL EXPERIMENT IN LAISSEZ FAIRE

In his 2000 article “Assessing the FDA via the Anomaly of Off-Patent Drug Prescribing,” Alexander Tabarrok argued that off-label usage provides a “natural experiment.” In a sense, off-label uses are regulated according to the pre-1962 rules, under which the FDA held new drugs only to safety requirements, whereas on-label uses are regulated according to the post-1962 rules. Thus, the same medical institutions — in the same country at the same time — are operating under dual systems of drug regulation. Off-label prescribing tells us something about how the world might look if the FDA were restricted to safety-testing alone. If we evaluate off-label prescribing positively, then this provides some support for FDA reform; a negative evaluation supports the current system and suggests FDA control of off-label prescribing might be in order.

One piece of evidence in favor of off-label prescribing is the opinion of physicians. Do physicians clamor for the assurance of the FDA when it comes to off-label prescriptions? Or do they regard as valuable the freedom to prescribe drugs that have not been FDA-certified for the prescribed use?

In an online survey, we asked nearly 500 doctors whether the FDA should hold off-label uses to proof-of-efficacy requirements; the doctors responded with a resounding no. Fully 94 percent opposed the requirements, and many wrote strongly worded objections that described the requirements as “clearly naïve,” “stupid and unethical,” “dangerous,” “disastrous,” and claimed “medicine would grind to a halt.”

**DO DOCTORS FAVOR LIBERALIZATION?** Doctors oppose adding restrictions to off-label uses, but do they favor dropping efficacy requirements on initial use? In our survey, we asked doctors that question and 27 percent said yes, FDA efficacy standards should be made voluntary. The anti-liberalizers, however, outnumbered the liberalizers by slightly more than two to one (58 percent said no, 15 percent were not sure). Most doctors supported the status quo, namely efficacy requirements on initial uses but not subsequent uses.

Support for the status quo among doctors is in one way curious. As explained, doctors get on quite well prescribing

off-label without the FDA, so why do they not have more confidence in enjoying the wider range of new drugs that would come forth if we dropped efficacy requirements on initial uses? Indeed, there seems to be a logical inconsistency in favoring off-label prescribing but requiring proof of efficacy for the drug’s initial use. Physicians are against FDA-required efficacy tests on new uses of old drugs, but many favor such tests on new uses of new drugs. Why the difference?

In our online survey, after asking the respondents’ opinion on the two policy reform questions — adding efficacy requirements for subsequent uses, and dropping efficacy requirements on initial uses — we “challenged” those who were against restrictions on off-label prescribing but in favor of restrictions on initial prescribing. Were their choices consistent?

Their responses fell into a number of basic arguments. Pondering the responses better taught us that there are significant differences between on- and off-label uses, but on the whole we felt that none of the responses successfully deflected the basic force of the consistency argument for liberalization. Below, we briefly state the four central responses and provide our own brief rebuttal. (Our 2004 paper takes up these issues in greater depth.)

**“Off-label uses are often related to the on-label use.”** Many off-label uses are related to the on-label use, but “related” does not guarantee effectiveness. The off-label uses actually practiced are a fraction of all possible related uses, so we see medicine working to discover effective therapies and to weed out ineffective ones, regardless of how related they may be. Moreover, many off-label uses are not related to the on-label use. It is surprising that Viagra works for pulmonary hypertension as well as erectile dysfunction (surprising but not unexplainable). Finally, some uses come to be understood as related only because of demonstrated results of off-label usage. After all, “relatedness” is a function of the current state of pharmino-medical understanding.

**“Efficacy requirements on initial uses are good, but because of patent life expiration it would be crazy to impose them on subsequent uses.”** It is correct that dwindling patent life helps explain why it would be harmful to impose new requirements on subsequent uses. But this argument does not justify the initial efficacy requirements. This response explains why the respondent rejects the consistently restrictive position, not why he rejects the consistently liberal position.

**“Initial efficacy requirements are desirable because they enhance knowledge of safety.”** Efficacy requirements do enhance knowledge of safety, but if stronger safety testing is the goal, it ought to be pursued and justified in those terms.

**“Without efficacy requirements, new useless drugs would flood the market.”** That might be true, but to what extent—for how long—would physicians prescribe and patients take inferior drugs instead of the drugs that would really help them? The medical marketplace is far from perfect, but patients and physicians are willing to

pay more for medicines that work and this demand provides an incentive to produce quality assurance.

### **ERROR IS INERADICABLE, BUT . . .**

Doctors who disagree with liberalization remind us of valid points. For decades, women were prescribed hormone replacement therapy. But we now know from the Women's Health Initiative studies that, contrary to what was expected, such therapy resulted in increased risk of heart attacks, strokes, blood clots, breast cancer, and dementia for which the reduced risk of fractures and colorectal cancer do not appear justifiable. Hormone replacement therapy was largely prescribed off-label (the on-label use is short-term prevention of hot flashes, sleep difficulties, and other problems of menopause). It is clear, therefore, that off-label use can be harmful.

Of course, on-label use can also be harmful. Perhaps even more harmful than on- or off-label usage is the non-usage or suppression of would-be beneficial drugs because of excessive FDA regulation and costs. Sam Peltzman and Steven Wiggins have each estimated that increased FDA regulation in the 1960s and 1970s reduced the number of new drugs by 60 percent. Even a few suppressed or long-delayed drugs could account for tens of thousands of excess deaths.

Rather than seeking a tally of mortality and morbidity, we can perhaps understand some of those costs better by recognizing that progress depends on discovery and discovery on experimentation. Experimentation always involves false steps.

Eliminate false steps and you eliminate progress. False steps can be made less costly, however, if they are corrected quickly. Thus, it is valuable to compare error correction in the two cases of allowing a bad drug and withholding a good drug. In the first case, the error can be corrected with experience, but it is much more difficult to gain experience about a non-approved good drug and impossible to do so if the drug is never researched and developed. Error correction tends to be rapid in decentralized systems and rather slow in centralized, bureaucratic systems.

A more error-prone system is not necessarily worse than a less error-prone system, if the errors are corrected more quickly in the former than in the latter. That point is familiar from the debate over central planning. In capitalist systems, entrepreneurs make a lot of mistakes, but error correction is swift. In centrally planned systems, error correction is very poor. It is now widely recognized that progress is more rapid in the capitalist systems. The same may be true with respect to the regulation of pharmaceuticals.

### **CONCLUSION**

Off-label usage provides a window onto how a less-regulated drug certification system would operate. An extensive but little-studied system of drug certification exists outside the control of the FDA. The experience with off-label prescribing and the experience of pre-1962 America suggest that initial efficacy requirements may do more harm than good. Dropping efficacy requirements is a proposal that should be taken seriously. **R**

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