

On-Label vs. Off-Label Drug Prescribing

FDA approval of drugs is based on what they are going to be used to treat, cure or prevent. But physicians regularly prescribe medicines for conditions not specified on the label, and while that may come with some risks, in many cases, it provides patients with better care.

By Heather Claverie

When patients are prescribed a drug to treat an ailment, most assume the drug has been approved for that use. However, one-fifth of drugs prescribed in the U.S. are for a use not approved by the U.S. Food and Drug Administration (FDA), which is known as an “off-label” prescription.¹ Yet, while off-label use of a drug such as immune globulin (IG) may cause concern for some, it is both legal and, in most instances, beneficial.

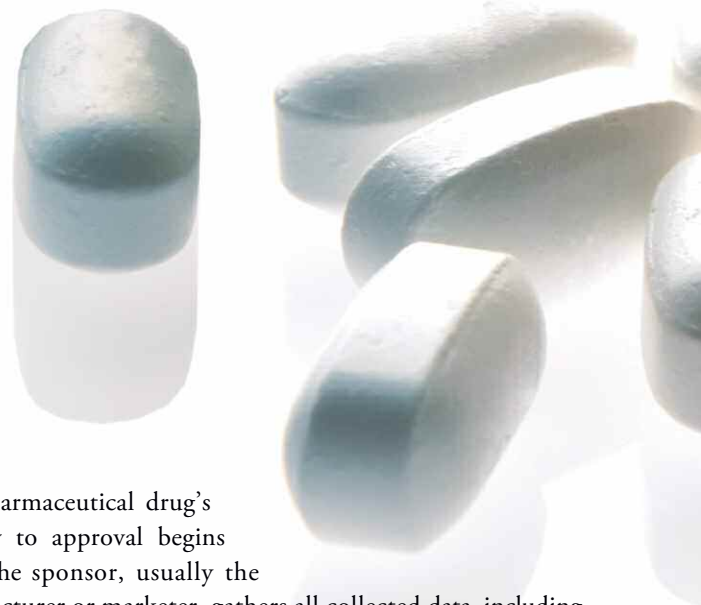
FDA Approval Process: How a Drug Is Designated On-Label

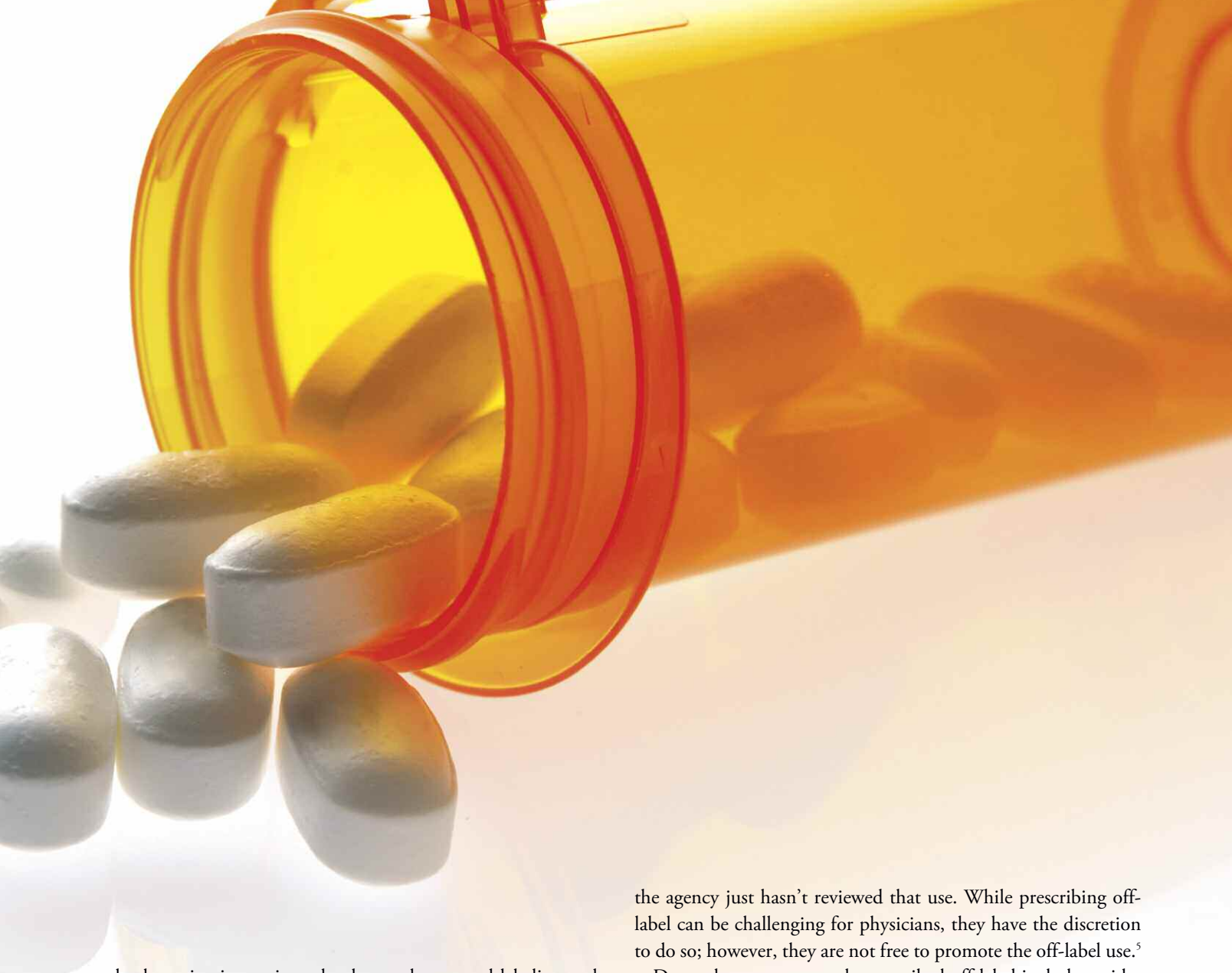
FDA was established by the Federal Food, Drug and Cosmetic Act of 1938 to tighten controls over drugs and food, protect consumers against unlawful cosmetics and medical devices and enhance the government’s ability to enforce the law.² FDA’s authority was further expanded when President Kennedy signed the Kefauver-Harris Drug Amendment into law in 1962 to strengthen the drug provisions of the Federal Food, Drug and Cosmetic Act.³ Thanks to those pieces of legislation, all over-the-counter and prescription medications sold in the U.S. must undergo a rigorous approval process overseen by FDA.

A pharmaceutical drug’s journey to approval begins when the sponsor, usually the manufacturer or marketer, gathers all collected data, including the results of animal tests and proposed labeling, and submits a new drug application or biologics license application to FDA. The results of the animal and toxicology studies must show that the drug is reasonably safe before it can be tested on humans. The manufacturing and labeling information must illustrate that the company will be able to adequately produce the drug. And, the application must include proposed clinical studies.

Before beginning any trials, a 30-day waiting period is instigated. During that time, FDA reviews the application for any safety issues and ensures individuals participating in the trials aren’t subject to unreasonable risk. Once approved, the company may begin clinical trials. If FDA runs into any issues concerning the drug, it may interrupt clinical trials or delay investigation into the proposed medication.

When the company has completed testing, it sends all data to FDA’s Center for Drug Evaluation and Research (CDER). A team of CDER physicians, statisticians, chemists, pharmacologists





and other scientists reviews the data and proposed labeling and then decides if the drug is safe and effective in its proposed use and if its benefits outweigh its known risks. If all boxes are checked, FDA will approve the drug, and the company may begin marketing it to the public.⁴

Off-Label Prescribing

FDA's role is to ensure the quality of products in the U.S. marketplace so that physicians and patients can rely on them to treat a given indication. Once a drug is approved and released into the market, FDA doesn't play a part in defining the drug's standard of care or how it is prescribed. For patients, that means a drug approved to treat depression may end up being prescribed to treat chronic pain. A physician prescribing a drug exactly as approved by FDA is doing so on-label. When a physician veers from that path, he or she is prescribing a drug off-label.

Just because an indication isn't listed on a drug's approved label doesn't mean FDA disapproves of an off-label use. Rather,

the agency just hasn't reviewed that use. While prescribing off-label can be challenging for physicians, they have the discretion to do so; however, they are not free to promote the off-label use.⁵

Drugs that are commonly prescribed off-label include antidepressants, antipsychotics, immune globulin (IG), chemotherapy and pediatric medications, among others. "Despite having many on-label drugs available, so often our patients will exhaust treatment options," said Dr. Wade Smith, medical oncologist for Breastlink Orange and Temecula Valley centers. "Sometimes, off-label use is very effective, especially in the area of cancer care where existing options may be limited. Cancer providers sometimes make clinical decisions that are not based on FDA approval so long as there exists a supporting study with necessary validation."

For instance, when Rituxan (rituximab) first came on the market in 1997, it was approved for the treatment of non-Hodgkin's lymphoma. Since then, the drug's role in treating diseases has increased to include a variety of conditions, from blood disorders such as hemophilia, chronic diseases such as Sjögren's syndrome and rheumatoid arthritis and other B-cell lymphomas.⁶ "If you had to pick one drug to say, 'Look at all the directions this biological has gone,' rituximab would be the one to choose," said

Dr. Smith. But, rituximab is just one drug among a long list of medications often prescribed to treat conditions for which they're not approved. Today, one in five prescriptions falls under these so-called off-label designated drugs.⁷

THE NUMBER OF OFF-LABEL USES FOR IVIG FAR EXCEEDS THOSE APPROVED ON-LABEL.

Many prescriptions in pediatrics are written off-label because children are less likely to be included in clinical trials. For instance, children afflicted with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) present with a whole host of symptoms, from obsessive compulsive disorder (OCD) and anxiety to tics, depression and behavioral issues. When physicians are faced with such a wide range of disorders, they will turn to studies showing that certain drugs have proven effective in treating one or more of them. Risperdal Consta (risperidone), which is approved to treat bipolar 1 disorder and schizophrenia, is one of the drugs physicians may prescribe for the tics associated with PANDAS. In addition, various antidepressants may be prescribed for OCD, and Ativan (lorazepam) may be prescribed to stabilize the mood swings that are often brought on by PANDAS.⁸

Some PANDAS patients are prescribed intravenous IG (IVIG) because studies have revealed it is effective for treatment of OCD and tics associated with the disorder.⁹ In fact, the number of off-label uses for IVIG far exceeds those approved on-label. When prescribed on-label, IVIG is approved to treat just a handful of ailments, including primary immunodeficiency, chronic lymphocytic leukemia, idiopathic thrombocytopenic purpura, Kawasaki disease, multifocal motor neuropathy and chronic inflammatory demyelinating polyneuropathy. Yet, more than 150 diseases are treated with IVIG. Some of the most common include myasthenia gravis, dermatomyositis, polymyositis, inflammatory necrotizing myopathy, pemphigus and pemphigoid.

Controversies of Off-Label Prescribing

When Terry Gross-Morton injured her foot at work, she had no idea the next six years would involve countless doctor visits

and result in a cabinet chock-full of prescription medications. Initially, physicians weren't sure what was causing the severe burning and stinging pain in her foot or why the area would turn bright reddish purple before spreading to other extremities. Although Gross-Morton wasn't suffering from fibromyalgia or shingles, she brought home prescriptions for Lyrica (pregabalin) and Neurontin (gabapentin) in an attempt to treat the unknown affliction. "I was willing to try anything that would help [that] my doctor recommended," she said.

Eventually, she was diagnosed with reflex sympathetic dystrophy (RSD), a disorder characterized by chronic arm or leg pain that develops after an injury, surgery, stroke or heart attack. These days, she treats her RSD with an extensive list of prescriptions for the pain and depression associated with it. From IVIG to Lexapro (escitalopram), OxyContin (oxycodone) and Elavil (amitriptyline), all her medications are prescribed off-label.

Doctors aren't required to disclose to patients that they're prescribing a medication off-label, and some physicians aren't even aware they're doing so. Although off-label prescribing does have its place, is often effective and, in some instances, can lead to a drug's accelerated approval by FDA, especially in the area of cancer care, the practice does have its fair share of critics, according to Dr. Smith.

One of the most tragic aftermaths of off-label prescribing was in the 1960s when doctors began prescribing the sedative thalidomide to pregnant women to alleviate morning sickness. It was quickly discovered that the drug caused severe birth defects in the infants born to women who had taken thalidomide while pregnant. At the time, clinical trials in the U.S. did not require FDA approval or oversight. Therefore, thalidomide was distributed to more than 20,000 patients across the nation, approximately 207 of whom were pregnant women.¹⁰ There were 17 births of deformed infants tied to thalidomide in the U.S., according to FDA. This is the incident that led to the passage of the Kefauver-Harris Drug Amendment.

Still, even with strict guidelines now in place, there are times when off-label prescribing raises serious health concerns. In the late 1990s, doctors began prescribing patients a combination of an appetite suppressant called fenfluramine and phentermine, a type of amphetamine. The diet drug combination, coined Fen-Phen, seemed like a miracle weight-loss recipe. Yet, it didn't last long. In 1997, FDA pulled the drugs off the market after discovering that the combination caused heart valve issues.¹¹

The fact that FDA oversees the approval of a drug but not the actual prescribing once it hits the market may come as a surprise to some patients. And some may balk at the thought of taking a

medication for a disorder not listed on the drug's label. But for patients like Gross-Morton who are desperate for a treatment, the pros outweigh any possible cons. In addition to the other medications she takes, she now receives in-home infusions every three weeks, and the treatment is helping. "I felt like I've tried every other option but the drastic ones," she said. "This disease is not widely recognized."

Prescribing in the U.S.

The control and quality of prescription medications in the United States have come a long way since the early days of FDA. Today, drugs must go through a rigorous process to receive on-label approval by FDA, and those strict guidelines ensure that medications are safe and effective. Even so, physicians are legally permitted to prescribe drugs off-label, and many patients would not receive the best available care without them. ❑

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References

1. Consumer Reports. "Off-Label" Drug Use. Accessed at www.consumerreports.org/health/resources/pdf/best-buy-drugs/money-saving-guides/english/Off-Label-FINAL.pdf.
2. U.S. Food and Drug Administration. How Did the Federal Food, Drug, and Cosmetic Act Come About? Accessed at www.fda.gov/AboutFDA/Transparency/Basics/ucm214416.htm.
3. U.S. Food and Drug Administration. Kefauver-Harris Amendments Revolutionized Drug Development. Accessed at www.fda.gov/ForConsumers/ConsumerUpdates/ucm322856.htm.
4. U.S. Food and Drug Administration. How Drugs Are Developed and Approved. Accessed at www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/default.htm.
5. Dress, R, and Frader, J. Off-Label Prescribing: A Call for Heightened Professional and Government Oversight. *The Journal of Law, Medicine and Ethics*, 2009;37(3):476-396. doi:10.1111/j.1748-720X.2009.00408.x. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC2836889.
6. Mulcahy, N. FDA Approves First Drug for Neoadjuvant Breast Cancer Use. *Medscape Multispecialty*, Oct. 2, 2013. Accessed at www.medscape.com/viewarticle/811873.
7. Ipaktchian, S. 14 Drugs Identified as Most Urgently Needing Study for Off-Label Use, Stanford Professor Says. Stanford School of Medicine News Center, Nov. 24, 2008. Accessed at med.stanford.edu/news/all-news/2008/11/14-drugs-identified-as-most-urgently-needing-study-for-off-label-use-stanford-professor-says.html.
8. PANDAS: Tics, Obsessions, Compulsions, Anorexia — Nothing Cute About This. *ACN Latitudes*, May 5, 2010. Accessed at latitudes.org/pandas-tics-obsessions-compulsions-anorexia-nothing-cute.
9. National Institute of Mental Health. PANDAS: Fact Sheet about Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections. Accessed at www.nimh.nih.gov/health/publications/pandas/index.shtml.
10. Burke, CM, Lanier, WL, and Wittich, CM. Ten Common Questions (and Their Answers) About Off-Label Drug Use. *Mayo Clinic Proceedings*, 2012;87(10):982-990. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC3538391.
11. Kolata, G. How Fen-Phen, A Diet 'Miracle,' Rose and Fell. *The New York Times*, Sept. 23, 1997. Accessed at www.nytimes.com/1997/09/23/science/how-fen-phen-a-diet-miracle-rose-and-fell.html.

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