

Standing Between You and COVID-19 Relief: The FDA

Ending the FDA's power to require proof of efficacy would save money and lives.

Since 1962, a new drug cannot be sold in the United States unless the U.S. Food and Drug Administration (FDA) is convinced that it is safe and efficacious: that is, not only will it not harm the people who take it, but also it will do them some good. It is easy to understand why there is a public interest in the safety of drugs. But why is government given the power to determine whether a drug works or not? And what difference does that make?

Virtually all of us want our diagnostics, vaccines and therapeutics to be effective. Even though a product is safe, poor efficacy means that we are wasting our money and our time and might be missing out on other products that actually work. There are two ways to ensure that drugs are effective: require strong evidence of efficacy before a product is marketed (“prove, then market”) or allow products to be marketed and let doctors try them out on their patients (“market, then prove”). While the first approach might seem more reliable, experience suggests that the second approach is actually superior.

Efficacy Isn't Universal

For all medicine, one unfortunate fact is universal: no drug is 100 percent effective. One might assume that an efficacious medicine will help all of the patients who use it, while an inefficacious drug will help none. If that were true, it might make sense for the FDA to assess and certify drugs before they are marketed.

Those that are ineffective would be rejected and the rest would be approved because they work. The decision to approve a new drug would be simple because, with all patients enjoying the same outcome, a small number of patients could be tested. If some benefited, we could assume they all would. The tests would take only a short time. Life would be good.

But it's not that simple. A survey of the pharmaceutical industry suggests that efficacy is normally in the 20 to 70 percent range. That means roughly half of patients who take a particular medicine will benefit and half will not.

To illustrate: triptans, which are used to treat migraines, have a stellar reputation because they are effective for approximately 70 percent of the sufferers. Even so, that means roughly a third of patients see no benefit.

At the lower end is Genentech's Herceptin, which is used with chemotherapy. Many consider it



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a “miracle drug.” In 2019 Herceptin was the sixth biggest selling drug in the U.S., with sales of approximately \$3 billion. Before Herceptin, chemotherapy was the standard of care for breast cancer. For doctors to give Herceptin to patients in conjunction with chemotherapy, it must offer an incremental advantage over chemotherapy alone. What is Herceptin’s incremental advantage? Clinical trial results show that only 23 percent of patients benefit.

Merck’s Keytruda has recently become one of the hottest drugs on the market. It received favorable press coverage when Jimmy Carter reported that he was cancer free after therapy with Keytruda. But Carter was lucky. In one clinical trial, Keytruda destroyed or reduced the tumors in only 34 percent of patients. Keytruda—which was the fourth biggest-selling drug globally in 2018 and brought in worldwide revenues of \$11.1 billion last year—is far from a sure thing.

There are occasional stars in the efficacy arena. Gilead Sciences tested a triple-combination therapy for hepatitis C infections. In a clinical trial with Vosevi (composed of sofosbuvir, velpatasvir, and voxilaprevir) the hepatitis C virus was undetectable for 12 consecutive weeks in 96 percent of patients, while the placebo helped exactly zero patients. That’s impressive. It’s also unusual.

AstraZeneca’s Iressa was approved by the FDA even though in one key clinical trial only 10 percent of patients enjoyed a clinical benefit.

David Kessler, who was FDA commissioner under both Presidents George H. W. Bush and Bill Clinton, confidently stated, “When the industry sells a drug, the drug works, and it does what it

says on the label. Take that away and we go back to snake oil.”

Not quite. Does helping 10 percent of patients show that “the drug works”?

Even With FDA Approval, You Still Need to Test for Efficacy

Effective medicines help cure afflictions. A triptan that works dispatches your migraine. A successful treatment for hepatitis C rids your body of that virus. When Keytruda works, your tumors shrink or disappear.

A regulatory agency such as the FDA must determine what the threshold is for efficacy for each new drug under consideration. Is 30 percent good enough? Or does it need to be 70 percent? Or some other percent?

Consider a hypothetical new migraine drug that is safe for all patients but provides a therapeutic benefit to only 50 percent of patients and is approved by the FDA as “safe and effective.”

What happens next?

Each individual patient, under the care of a doctor, must experiment to see if the new drug successfully treats the migraines of that particular person at that particular time. So, even after the FDA determines that the drug is sufficiently efficacious, each patient must still run his or her own experiment. This duplicative process is necessary because each patient is unique and the FDA can’t tell beforehand which patients will benefit.

The Economic Cost of FDA Regulation

The information that an FDA approval provides is valuable to patients and doctors. All else equal, we benefit from a third-party reviewing each

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drug's characteristics and certifying that that drug is efficacious. Unfortunately, all else is not equal. The FDA slows things down and adds costs in three ways.

First, patients must wait for the FDA to finish its assessment—a process that takes years—before they can start theirs. With a disease such as COVID-19, for which there were no proven therapies early in the pandemic, the value of the FDA's assessment must be weighed against the value of actually having access to a new drug in a timely manner.

Second, some products may fall through the cracks. Consider a drug that helps so few patients that the FDA rejects it due to insufficient efficacy. If you were one of the few that it would have helped, the FDA just blocked you from an effective treatment. Patients care whether a drug works for them. The FDA approves drugs for whole populations.

Third, the FDA's requirement that drug companies show efficacy before a drug can be marketed ("prove, then market") increases the costs of drug development and reduces the probabilities of success. That means fewer companies—especially smaller ones—will be in business; fewer drugs will be discovered, developed, and marketed for the patients who need them; and, with the reduced competition, drug prices will generally be much higher.

The cost to discover and develop one new drug is now a startling \$3 billion.^{1,2} About 65 percent of that cost is just to prove efficacy.³ This price tag has been increasing at 7.5 percent annually for decades. At that growth rate, the cost of a new drug will more than double every ten years.

The Health Cost of FDA Regulation

With costs so high, have fewer drugs actually been developed than would have been otherwise? Yes.

Before 1962 and the passage of the Kefauver-Harris amendments, companies needed to show only safety. The change in the law gives a good opportunity to study the "before" and "after" situations.

In 1973, UCLA economist Sam Peltzman analyzed the effect of the 1962 rules by

comparing the number of new chemical entities (not just drug reformulations) approved by the FDA before and after the law was changed. He found that the actual number was a shocking 60 percent below estimates based on the

previous trend. According to Peltzman's analysis, there should have been about 40 new drug approvals each year. Instead, there were just 16.⁴

Was it just the bad drugs that were weeded out? No. Multiple researchers have concluded that it wasn't just the bad drugs. Peltzman estimated that, at most, the percentage of ineffective drugs being marketed before 1962 was ten percent. As a result of the Kefauver-Harris amendments the percentage may have dropped to five. Yet the 60 percent drop in all drugs meant that many efficacious drugs never made it to patients. Commenting on this large reduction in new drug approvals after 1962 and the small improvement in the percentage of drugs that were efficacious, Peltzman said it was as if "an arbitrary marketing quota...had been placed on new drugs after 1962."

Why weren't there more ineffective drugs on the market and why hasn't the FDA had

Because the FDA slows things down and adds costs, fewer drugs have been developed than would have been otherwise.

more of an effect? Peltzman concluded that, “The penalties imposed by the marketplace on sellers of ineffective drugs before 1962 seem to have been sufficient to have left little room for improvement by a regulatory agency.”

This doesn’t answer the question of whether the 1962 Amendments were beneficial overall. We need to weigh the costs against the benefits. Peltzman’s conclusion was that the costs clearly outweighed the benefits: “It appears that a form of ‘shot-gun therapy’ has been applied to the problem of ineffective drugs: for the sake of excising (part of) the potentially offending 10 percent, 60 percent of potential innovation is eliminated,” he wrote.

Can Markets Determine Efficacy?

Even drugs that have successfully navigated the FDA’s rigorous procedures may not have been fully tested for the particular condition your doctor wants to treat. Why? Because once they are marketed, drugs can be used in ways not specifically approved by the FDA. Such usage is called “off-label” and about one in every five to ten prescriptions today is for an off-label purpose.⁵

Off-label usage is fully legal and helps patients because they get what their doctors believe are the best available therapies for their conditions. Off-label uses save lives. Consider Genentech’s Rituxan, which the FDA approved for a particular type of non-Hodgkin’s lymphoma (NHL). In a matter of years, sales surpassed what would have been expected even if all Americans with this type of NHL took Rituxan. What happened? Oncologists reasoned that a drug that worked for some kinds of NHL patients might also work for other kinds of NHL patients or even for

other cancers. Since cancer is often a deadly disease, it’s better to try something that might work rather than trying nothing at all. In many cases, Rituxan did work. According to *Oncology Business Review*, “Rituxan has not only changed the natural history of NHL, it has significantly changed the way cancer is treated and how cancer research is approached.”⁶

There are many examples of FDA-approved drugs being used off-label. Roughly 50 percent of cancer patients, for example, are prescribed drugs for off-label uses.⁷

Soon after Merck launched Proscar to treat enlarged prostate glands, physicians started sharing stories of men reporting new hair growth. “One of the doctors said that was impossible,” recalled Merck spokeswoman Janet Skidmore. It wasn’t impossible. Proscar lowers levels of the hormone dihydrotestosterone, making it effective for both shrinking prostate glands and

growing hair. Merck turned this off-label usage into a second product, specifically designed for hair growth: Propecia.

Physicians’ off-label usage of Rituxan, far from

being inappropriate or rogue, reflected the best medical thinking at the time and was ultimately vindicated by the FDA itself for a number of additional conditions. Off-label usage naturally precedes formal FDA approval because off-label usage comes from the latest research, while the slow, official FDA approval process is initiated only after that research is released. The FDA is typically one of the last organizations to acknowledge that a drug works for other diseases.

Eli Lilly’s Prozac was originally approved to help people deal with depression. But doctors found

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that it often helped women with pre-menstrual syndrome (PMS), and they started prescribing it for that. Prozac was later approved by the FDA for a severe form of PMS. In this case, the drug came first, the definition of the condition came second, and the FDA approval was last.

Markets—which involve doctors, nurses, patients, hospitals, researchers, third-party payers, and the media—can determine what works and what doesn't even with no input by the FDA. One reason for this is that, while medicines don't work for every patient and the FDA doesn't know how each individual patient will respond beforehand, patients and the doctors who treat them do discover, through trial and error, who responds.

While the FDA knows a lot about psoriasis, for example, the FDA doesn't know who you are, whether you even have psoriasis, whether you took a particular ointment, and, if you did, how you responded. You have relative expertise in your psoriatic condition. You know about your affected skin areas, what causes flare-ups, how it affects your life, and how a particular ointment works for you. And you have the most at stake, too, having the most (ahem) skin in the game.

Because you have this knowledge and markets are made up of people like yourself, markets can answer fundamental questions that vex government agencies. The FDA might know more than you about whether a drug works for whole populations, but you know more than the FDA about whether the drug works for you. Multiply this by millions of patients and their doctors and we can understand how markets

respond.

This helps explain why Peltzman found little room for improvement by a regulatory agency.

Promotion of Off-Label Uses Is Illegal

Even though off-label uses are legal and widespread, it may surprise readers to know that the companies that produce these drugs can't talk about their off-label uses. Companies are, in most situations, prohibited from even providing factually correct information to doctors if that information is perceived as promoting an off-label use of a drug.

If, for example, Merck had even slightly promoted Propecia for hair growth before the official FDA nod, Merck would have exposed itself to millions or even billions of dollars in fines.

During a particularly aggressive enforcement push in 2009-2010, the Justice Department collected over \$6 billion from drug companies for off-label promotion cases.

Sometimes the penalties are even harsher.

Consider the case of former InterMune CEO W. Scott Harkonen, M.D. InterMune's lead product was Actimmune, which was approved by the FDA to treat two rare inherited diseases. InterMune was studying Actimmune for a third disease, idiopathic pulmonary fibrosis (IPF), hoping to expand Actimmune's label. When this incident took place, there was no good treatment—and no FDA-approved drugs—for this nasty, fatal disease that causes lungs to fill with scar tissue and leads to death in three to five years.

Some preliminary work showed that Actimmune benefited patients with IPF, so, starting in 2000, InterMune ran an FDA-approved

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clinical trial in 58 hospitals around the world to further explore those preliminary results. The new trial showed that while 17 percent of those on placebo died, only ten percent on Actimmune suffered the same fate. Unfortunately, this result fell a bit short of the level of the statistical significance the FDA requires. InterMune clearly described these and other “failing” grades in a press release. That wasn’t the problem.

The problem was that InterMune reported that the benefits to a subgroup, mild-to-moderate patients, was highly statistically significant. The press release essentially said: we narrowly failed our primary objectives due to a lack of statistical significance, but the results showed promise overall and a benefit to one particular subgroup.

While this press release seemed innocent enough, the FDA reacted like a bull to a matador waving a red cape.

The FDA claimed that InterMune and Harkonen should have limited the press release to the “we failed” part. The fact that the subgroup results were added, claimed the FDA, comprised off-label

promotion and Harkonen himself was charged with “wire fraud relating to the dissemination of false and misleading statements about the results of a clinical trial.” Never mind that everyone involved, including the government prosecutors, agreed that the numbers and conclusions in the InterMune press release were factually correct. “The government has always agreed that there was no falsification of data here,” said Allan Gordus, a Justice Department lawyer.

While Harkonen avoided jail, he was sentenced to three years’ probation with six months of home confinement with frequent monitoring. He was ordered to pay a \$20,000 fine and to perform

200 hours of community service. Worse, he is now forbidden to work in any manner with the government’s Medicaid and Medicare health programs, effectively ending his careers as a pharmaceutical executive and as a medical doctor.⁸

Muzzling the People Who Could Save Your Life

While the InterMune case is extreme, companies must forever be diligent lest they violate the FDA’s off-label promotion prohibition. This prohibition may be one of the greatest costs of the FDA’s “prove, then market” approach.

Consider this hypothetical conversation:

Drug company sales rep: Doctor, have you tried Drug X for any of your melanoma patients?

Doctor: Yes. I’m very happy with the results I’ve

seen. What I really need, however, is a drug for my ovarian cancer patients. Do you know of anything that would help those patients?

Drug company sales rep: As a matter of fact, an as-yet unpublished study out of MD Anderson Cancer

Center suggests that Drug X benefits patients with ovarian cancer. The results are similar to the results seen in melanoma.

That’s the “wrong” answer and this sales representative just exposed his company to potentially billions of dollars of fines from the FDA. The “correct” answer is:

Drug company sales rep: I’m sorry that your ovarian cancer patients have such a bad prognosis. Unfortunately, the FDA has approved Drug X only for treating melanoma patients.

When we think of governments withholding important information from citizens, we typically

The FDA’s off-label promotion prohibition may be one of the most costly results of its “prove, then market” approach.



think of highly authoritarian governments. For instance, the Soviet government hushed up the Chernobyl disaster. More recently, the Chinese government muzzled Li Wenliang, the ophthalmologist who first alerted the world to COVID-19. How many people have died in China and throughout the world as a result of that repression? The FDA is in a similar position in this country. How many patients die or otherwise suffer every day in this country because doctors can't get important information from the company making the drug about to be injected into a patient's arm, or don't even know that a drug is available that should be injected into that patient's arm?

Potential Value of Good Diagnostics and Vaccines

The U.S. government is planning on spending or lending \$2.2 trillion through the CARES Act because state governments reacting to the COVID-19 disease required tens of millions of Americans to stay home. Much of this would have been unnecessary if we had had a good diagnostic test for the coronavirus and/or a good vaccine.

Stated differently, diagnostics and vaccines might have saved us from a trillion dollars or more in costs. If 200 million Americans received a yet-to-be-approved vaccine, it would make economic sense even if the price were \$5,000 a shot (and that ignores the value of preventing pain, suffering, and death). If the vaccine were priced at a more reasonable \$50 per injection, the value might be over 100 times the cost.

Multiple experts have bemoaned the lack of

quick and accurate testing of COVID-19. With good information, we could have employed targeted quarantines instead of the broad "shelter in place" mandates that have crippled the economy. When the test released by the Centers for Disease Control was found to be defective, the FDA persisted in forbidding

With quick and accurate testing of COVID-19, we could have avoided the broad "shelter in place" mandates that have crippled the economy.

established diagnostics companies from marketing other tests for COVID-19 until it was convinced the tests were accurate. This was after the disease had a four-month head start.

On March 20, the FDA warned about "unauthorized fraudulent

test kits that are being marketed to test for COVID-19 in the home." This forced companies that had marketed tests to rescind them. The FDA finally approved the first serum antibody test—to see if you've had the disease—on April 3 and the first virus tests—to see if you have the disease—on March 27. One test, by industry-leading Abbott Laboratories, will deliver a response in five minutes and Abbott has the capacity to run five million tests per month. Abbott is a world leader in point-of-care diagnostics and the system upon which the COVID-19 test is based has been successfully used since 2014. It could have been distributing this test weeks before it did.

On March 30, the FDA had the gall to say: "The FDA's regulations have not hindered or been a roadblock to the rollout of tests during this pandemic."⁹

How many people who have wondered about their COVID-19 status would have preferred to wait for FDA approval? How many more would have taken their chances on Abbott's test before approval? It really didn't have to be one or the

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other. Without the FDA's gatekeeper role, those who were more cautious could have waited for FDA approval while those who wanted an answer more quickly could have used the Abbott device, potentially weeks ago.

Conclusion

Let's finally learn from our experience with COVID-19. Let's end the FDA's power to require proof of efficacy. Overall, "market, then prove" is the superior approach, saving our economy and our lives.

¹ Tufts Center for the Study of Drug Development, Cost of Developing a New Drug, 18 November 2014, http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014..pdf

² Joseph A. DiMasi, Henry G. Grabowski, and Ronald W. Hansen, "Innovation in the pharmaceutical industry: New Estimates of R&D Costs," *Journal of Health Economics*, Vol. 47, May 2016: 20-33. At: <http://www.sciencedirect.com/science/article/pii/S0167629616000291>

³ Joseph A. DiMasi, Henry G. Grabowski, and Ronald W. Hansen, "The price of innovation: new estimates of drug development costs," *Journal of Health Economics*, *Journal of Health Economics* 22 (2003) 151–185, Table 5.

⁴ Sam Peltzman, *Regulation of Pharmaceutical Innovation*, University of Chicago, 1974. <https://www.aei.org/research-products/book/regulation-of-pharmaceutical-innovation-the-1962-amendments/>

⁵ April S. Fitzgerald and Patrick G. O'Malley, "Staying on Track When Prescribing Off-Label," *Am Fam Physician*, January 1, 2014, Vol. 89, No. 1, pp. 4-5

⁶ Candice J. Bruce, "Rituxan Anniversary: 10 Years of Progress," *Oncology Business Review*, November 2007.

⁷ U.S. General Accounting Office Report: Off-Label Drugs. GAO/PEMD 91-14. Government Accounting Office, 1991

⁸ See David Brown, "The press-release conviction of a biotech CEO and its impact on scientific research," *Washington Post*, September 23, 2020. https://www.washingtonpost.com/national/health-science/the-press-release-crime-of-a-biotech-ceo-and-its-impact-on-scientific-research/2013/09/23/9b4a1a32-007a-11e3-9a3e-916de805f65d_story.html

⁹ Stephen M. Hahn, "Coronavirus (COVID-19) Update: FDA expedites review of diagnostic tests to combat COVID-19," FDA Press Release, March 30, 2020



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