

STUDIED TO DEATH: FDA Overcaution Brings Deadly Consequences

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DYING IN FEAR

Saving people from deadly diseases used to be much simpler when Dr. Joseph Gulfo got into the business almost 30 years ago.

Back then, innovative new treatments had to be proven safe for use in humans and effective in doing what they were supposed to do. That might be shrinking the size of cancerous tumors. It might be lowering blood pressure or cholesterol. Or it might be reducing glucose levels in diabetic patients.

That's what the law required then, and still requires today.

Fear has changed all of that, said Gulfo, who as a <u>drug company executive</u> led the development and approval of two cancer treatments and a device that detects early stage melanomas.

Regulators at the U.S. Food and Drug Administration(FDA) have grown ever more fearful that they might miss something, that a drug might be approved with unseen side effects or prove to be less beneficial in the long run than originally believed. If that happens, they will be hauled in front of Congress or pilloried in the media.

So in their quest for absolute certainty, agency bureaucrats have taken it upon themselves to <u>change</u> <u>the rules</u>, Gulfo said. They demand more studies, more tests, and more time.

Instead of having to prove a new treatment is safe for its intended use, the FDA now reviews drugs based on how they might be used by doctors to treat individual patients, effectively substituting the judgment of agency regulators for that of practicing medical professionals.

Instead of proving a drug achieves the medically beneficial results that its makers claim, the FDA requires proof the new treatment will improve long-term outcomes. So it is no longer enough, for instance, to prove a new drug will reduce blood glucose levels for diabetics. Drugmakers must show, somehow, that this will make patients live longer. The consequence of these ever more complex rules is that new and beneficial treatments for conditions ranging from heart disease and cancer to Alzheimer's and diabetes are not getting to doctors and patients. Instead, they are bottled up in the regulatory labyrinth of the FDA, or discarded altogether because drug developers cannot meet the ever-evolving standards and spiraling cost of agency demands to prove the basic requirements of safety and effectiveness, said Gulfo, who was on President Donald Trump's <u>short list</u> to be the new FDA commissioner but ultimately was not selected.

The end result is more preventable deaths and more diseases that go untreated because of a regulatory system that emphasizes caution over innovation and statistical certainty over getting new and effective treatments to patients as quickly as possible.

"The FDA is the lightning rod when anything goes wrong with an approved drug," said Gulfo, now a senior analyst at the biotech investment firm Altium Capital. "So the easiest thing to do is to then look for more and more proof that the drug is wonderful, to require higher and higher standards, and longer and longer trials. What that does is it dissuades innovation. Innovation comes from small companies. Small companies are going to avoid developing products for uses that require those kind of long-term studies. For a drug that might be used in tens of millions of people, you've got tens of millions of opportunities for something to go wrong."



<u>'INVISIBLE GRAVEYARD'</u>

Critics of the current system say the long delays and high cost of securing approval from an overcautious FDA are literally killing people.

They've coined the phrase <u>"invisible graveyard"</u> to describe the people who would have lived, but died instead because the cure that could have saved them was bottled up in the FDA regulatory process.

The most obvious example of this is when a terminal patient cannot <u>access new cures</u> that are still in late-stage testing or awaiting final approval from the FDA.

But it also applies to long-term chronic conditions like diabetes and heart disease, Gulfo said. It is far easier and safer to satisfy the FDA's regulatory demands by making small, incremental improvements to existing treatments that will benefit a small number of patients. It is much more difficult to win regulatory approval for a new drug that revolutionizes the treatment of chronic conditions that will affect millions, he said.

Because the FDA's standard approval process for new drugs has become so long and cumbersome, Congress and the FDA have passed a <u>series of laws</u> and regulations over the years to expedite it for certain types of unique new treatments, such as those targeting "orphan" diseases that affect fewer than 200,000 people nationwide. In 2017, 61 percent of all novel new drugs <u>approved by the FDA</u> were reviewed under one of those special designations rather than the standard approval process. About 40 percent of all new drug approvals targeted orphan diseases.

But those special designations are nothing more than patches on a broken regulatory system, implemented to relieve political pressure when public frustration at the pace of approving certain high-profile drugs gets too intense, Gulfo said. What is needed is a whole new approach to drug approvals, one that gets back to the fundamental purpose of the law, which is to approve safe and effective new medications as quickly and efficiently as possible.

Reformers are optimistic that the public's attitude toward drug regulation is changing as more people understand that too much caution and too much testing can actually cost lives.

Just as important, lawmakers and even to a degree FDA regulators are recognizing the current system of testing and approval, which has remained largely unchanged since it was developed in the 1960s, is too slow, expensive, and riddled with overcaution. That is particularly true as more innovative products are being developed from human tissues rather than mixing chemical compounds into pills. The technology that allows mapping of a person's genetic makeup, which can be critical in determining how an individual patient will respond to a specific treatment, did not exist when the current system for testing new drugs was created.

The agency's own subcommittee on science and technology concluded in 2007 that the "FDA's inability to keep up with scientific advances means that American lives are at risk."

The report also criticized the "risk-averse" culture at the FDA.

More recently, FDA Commissioner Scott Gottlieb acknowledged that the long and expensive quest for absolute certainty comes at a cost.

"If outdated regulations delay or derail the development of innovative, safe, and effective products, patients suffer," Gottlieb <u>said at a cancer conference</u> in June 2018. "And if FDA-approved drugs are priced out of reach of patients, then the full benefits of innovation won't be realized. Both of those outcomes should be unacceptable to us."

The most encouraging sign that change is coming is the recent passage of Right to Try, a <u>law long</u> <u>championed</u> by the Goldwater Institute and <u>signed in</u> <u>May</u> by President Trump.

The bill passed the Senate without opposition, and received lopsided, bipartisan support in the House. Right to Try laws also have been adopted in 41 states, typically with little or no opposition.

Right to Try allows patients with life-threatening conditions to access medications that could save their lives but have not received final approval from the FDA. The agency's approval is not required under Right to Try. "Perhaps Right to Try's greatest achievement is that it did not merely seek to reform this broken system. It challenged the system's very foundations," said Christina Sandefur, executive vice president of the Goldwater Institute. "And, for the first time, it really brought that discussion into the mainstream. It got people asking, 'Should the government have the power to make life-or-death decisions for individuals?'"

NEXT STEPS

The question now is what comes next.

Over the past several years, there have been various proposals in Congress to change the way at least some new drugs are approved, none of which has passed. The most sweeping, and to a limited degree successful, is generally referred to as "conditional approval." While the different plans vary, the idea is that after the safety of a drug is established in early clinical trials, and once it shows great promise of being effective, it could be conditionally approved for sale and used to treat patients. Those patients would be intensely monitored for any safety issues and to gauge the treatment's effectiveness. All of that data would be compiled and eventually form the basis for final approval.

Another approach, long pushed unsuccessfully by Sens. Ted Cruz of Texas and Mike Lee of Utah, both Republicans, would allow new treatments approved in certain other countries, such as Canada and those in the European Union, to receive near-automatic approval for use in the United States. Those countries have regulatory structures similar to those in the U.S., the thinking goes, and there is no reason why treatments approved there should not be available here.

At the state level, the Goldwater Institute is pushing what's called Free Speech in Medicine, which essentially would allow drugmakers to provide truthful information about their products to health professionals. That would include communication about <u>"off-label" treatments</u> for drugs that have been approved by the FDA to treat one condition but are prescribed by doctors to treat other conditions after new beneficial uses are shown outside the agency's regulatory process.

SAFE AND EFFECTIVE

To understand how the various reforms would benefit patients, it is important to first understand how drugs are developed, tested, and sold under the current system.

It goes back to 1960, when the drug thalidomide was gaining popularity around the world to ease morning sickness but <u>was not allowed</u> in the United States because of safety concerns. At the time, the FDA had the power to regulate drug safety but not to determine whether it was effective.

It turned out thalidomide caused severe birth defects and led to an unknown number of miscarriages.

Congress responded to the thalidomide crisis with a <u>complete rewrite</u> of federal drug laws in 1962. The new amendments gave the FDA the power to determine a drug's effectiveness, as well as its safety. Both have to be proven through a series of tests called clinical trials.

Defenders of the FDA and the current system still cite the agency's caution about thalidomide to justify maintaining the status quo, even though its use was blocked under the old law because it was unsafe, not because it was ineffective.

Human trials are basically divided <u>into three</u> <u>phases</u>. In the first, the new treatment is tested in a small group of volunteers to determine its safety. A second round of trials is conducted on a larger group to test its effectiveness in treating the targeted condition.

Once safety and strong indications of effectiveness are established, the third phase dispenses the new drug to a large number of people, hundreds or thousands, to fully test whether it works and is a significant improvement over existing therapies.

Once all of that data is compiled, the new drug application is submitted to the FDA for review. Agency regulators can approve or reject the application based on the evidence provided. If they are not convinced, they can order additional and more complex trials. Even after a drug is approved, the FDA sometimes will require it to be monitored in general use to determine whether any hidden side effects emerge in what are called Phase 4 trials.

The system was designed in an era when medical breakthroughs were new pills created by mixing chemicals. But many of today's most promising breakthroughs are being designed at the genetic and even molecular level, using human tissues—science that was little more than a fantasy in the 1960s.

In 2018, the Nobel Prize in Physiology or Medicine was awarded to a <u>pair of scientists</u> who pioneered the field of immunotherapy, changing the way individual cells operate in the body to attack diseases such as cancer. The work of Drs. James Allison of the United States and Tasuku Honjo of Japan led to a new class of treatments called checkpoint inhibitors, which allow the body's own immune system to identify and attack cancerous cells. That has revolutionized the treatment of cancer and added a powerful new treatment option over the traditional methods that involved invasive surgery, radiation, chemotherapy, and hormone therapy.

RISK AND REWARD

All drugs have risks. But the equation is supposed to be whether a drug's benefits offset its dangers.

New drugs are typically approved for a single condition, the one targeted in clinical trials, on what is called its "label." However, since the FDA regulates drugs and not medical practitioners, a product approved for one condition can be dispensed "off label" to treat others. For instance, a new therapy for lung cancer may prove beneficial in treating other types of cancer. Doctors can usually use the drug to treat patients off label. But drug companies are not allowed to discuss or publicize its benefits for any condition that has not been recognized by the FDA. To do that, new agency approvals are required for each additional ailment.

Very little in this process has changed since it was implemented after the 1962 amendments to the drug safety laws, except that the trials have gotten longer and much more expensive. In the 1970s, it cost about \$100 million in inflation-adjusted dollars to get a new drug approved by the FDA, according to research from Tufts University, which has long studied drug development costs. It now costs about \$1.4 billion in out-of-pocket expenses, according to a <u>Tufts report in 2016</u>.

The timeline also has grown, as has the complexity of the trials demanded by the FDA, according to Tufts.

The cost, time, and complexity of drug development have created their own dynamics that sometimes have deadly consequences, said <u>Mary Ruwart</u>, a former pharmaceutical researcher and author of the book <u>Death By Regulation</u>, which examines whether the FDA's quest for absolute certainty ends up killing more people than it saves.

It does, she concludes.

There is no evidence the 1962 law improved drug safety, Ruwart maintains. The percentage of new drugs approved by the FDA and later withdrawn from the market has held remarkably steady since the 1960s.

About a third of all new drugs approved by the FDA later have some kind of safety issue after reaching the market, <u>according to a study</u> of 10 years of data published last year. Not all are withdrawn. Most often, additional warnings are added to the product's label.

The problem is that since FDA approval is all-or-nothing, drugmakers design their clinical trials to ensure their greatest chance of success. To do this, they test their products on a similar group of patients, screening not just for such things as age and sex, but also based on the stage of the targeted disease, other medications and medical conditions, and in some cases, even the genetic makeup of test subjects.

The problem with that is that at the end of the clinical trials, they have a great deal of information about patients who meet that criteria, but little or none about how the drug will work in the population as a whole.

So the bottom line is no one really knows how safe and effective a drug will be for the general population until after it secures FDA approval and is being dispensed to the public. "For the most part, it's because we don't have the science to predict from these limited clinical trials what's going to happen in the wider population," Ruwart said in a recent interview with the Goldwater Institute. "That's where this narrow focus on a select population creates a safety issue."

Another critique of the current system is that the cost of taking a new drug through trials stifles innovation and <u>puts a premium</u> on the most expensive treatments. If a company has to spend billions of dollars to secure FDA approval, it makes more sense to spend it on a high-dollar treatment that will ensure regulatory costs are recouped and big profits are generated.

That problem is even worse when it comes to fully researching the health benefits of existing products. Adding a new condition to a product's label requires more testing and separate approval from the FDA. Since the product can already be used off label, there is usually no payoff for drug companies to conduct the additional research and expand their labels, particularly for low-cost drugs.

"Companies kind of know before they invest a lot of money in researching in a certain area if there's going to be some profits for them," Ruwart said. "And they simply don't do any research in areas where they don't see profit."

MIRACLE CURE

While these dynamics are in play for all new drugs that go through the FDA's regulatory process, from a new pill to a cellular-based genetic therapy, the one that Ruwart and other FDA critics cite as carrying the most deadly consequences is aspirin.

Since aspirin was already in use when the 1962 amendments were passed, it did not require new FDA approval for uses known at the time, basically fever reduction and relief from pain and inflammation. However, the law prohibited drug manufacturers from making any new health-related claims that had not been approved by the FDA.

Research in the 1960s established aspirin worked as an anticoagulant in blood, essentially preventing platelets that cause clotting from binding together.



There wasn't much incentive for aspirin manufacturers to fully research its benefits, according to the book <u>Aspirin: The Remarkable Story of a Wonder Drug</u>. The exclusive rights to the product, originally held by the German pharmaceutical firm Bayer, expired about the time the U.S. entered World War I in 1917. Any drug company could make aspirin, which still sells for pennies per dose. Consequently, government public health agencies, not drug companies or the FDA, funded virtually all of the studies to fully explore new potential benefits.

By 1980, there was proof that aspirin was very effective in preventing a second heart attack in patients who'd already suffered their first one. There also was strong but less conclusive evidence that taking an aspirin daily could prevent a first heart attack in certain patients who were at elevated risk.

Using this academic research, Sterling Products Inc., which acquired the Bayer Aspirin trade name in the U.S., applied to the FDA in 1980 to allow it to tout aspirin's benefits in preventing a second heart attack, the first step in including those benefits on its label. By then, academic studies showed daily aspirin use reduced the risk of a second heart attack by about 25 percent.

The application was rejected. FDA reviewers were skeptical of evidence not gathered in traditional FDA-supervised clinical trials, the kind required under the 1962 law.

Sterling continued to pursue the FDA's approval so it could communicate the heart benefits of aspirin—at least to doctors—still using the results of academic studies rather than conducting its own clinical trials. An FDA review panel again rejected the application in 1983. But the studies continued to pile up, some showing daily aspirin use reduced the risk of a fatal heart attack by more than 40 percent.

Finally, in 1985 the FDA's internal review panel recognized the benefits of aspirin in preventing a second heart attack. Margaret Heckler, then secretary of Health and Human Services, the parent agency of the FDA, <u>announced the findings</u> and said a daily dose of aspirin for people with heart conditions could prevent up to 50,000 deaths per year.

When the FDA published its final rule on aspirin labeling in 1998, it recognized aspirin's benefits in preventing a second heart attack. It did not authorize any claims that it could prevent a first heart attack, which it calls primary prevention.

In 2002, the U.S. Preventive Services Task Force (USPSTF), an independent but government-funded public health advisory panel, and the American Heart Association broke with the FDA. They recommended a <u>daily dose of aspirin</u> to prevent a first heart attack for much of the population, basically those between 50 and 70 years old with a higher-than-normal risk of heart trouble and not prone to bleeding concerns.

A year later, Bayer HealthCare, which had reacquired the rights to its aspirin brand, applied to the FDA to amend its label to allow communications with doctors about the benefits of aspirin to prevent a first heart attack. Bayer relied largely on the recommendations of the USPSTF and the Heart Association, and the underlying studies on which they based their recommendations. It did not conduct FDA-supervised clinical trials on its own.

More than a decade later, in May 2014, the FDA rejected the application, concluding again that the academic studies as to primary heart benefits are inconclusive. It also implied, but did not state outright, that if Bayer or any other aspirin maker wanted to include primary prevention on its label, it should rely on clinical trials designed to FDA specifications.

In 2016, the USPSTF <u>revised its guidance</u> to include the additional benefit of the drug in preventing colorectal cancers in certain patients, yet another benefit of the drug established in studies outside the FDA regulatory context. Today, the FDA still <u>refuses to authorize</u> any claims from drugmakers that aspirin can prevent a first heart attack, even in those patients specifically targeted in the guidance from the USPSTF and the Heart Association. It also does not allow manufacturers to claim that aspirin can help prevent colon cancer.

DEATH TOLL

Ruwart said the FDA's refusal to accept overwhelming evidence from outside studies of aspirin's benefits stalled its widespread use and led to more deaths than the agency prevented by its overcaution. Just the five years between 1980, when Sterling filed its first application, and 1985, when HHS Secretary Heckler publicly acknowledged aspirin's benefits, account for a quarter-million deaths if Heckler's estimate of 50,000 preventable deaths annually is accurate.

Beyond that, the FDA's continuing refusal to allow manufacturers to discuss any benefits in preventing a first heart attack and colon cancer still inhibits the free flow of information that could save lives, Ruwart said.

The medical community and the public have largely bypassed the FDA's guidance, driven largely by publicity about the academic research and the recommendations of the Heart Association and other groups like the USPSTF. A <u>survey published in 2015</u> showed that about 52 percent of Americans between the ages of 45 and 75 take a daily dose of aspirin, and four out of five of them take it to prevent a first heart attack or stroke. About 18 percent of these aspirin users say they take it to prevent cancer.

Most people who take aspirin daily do so on the advice of their doctors.

Ruwart credits daily aspirin use as being the single biggest drug-related factor in the roughly <u>60</u> percent drop in the death rate from heart disease in the United States since the 1950s.

Dr. Robert Bonow, <u>professor of cardiology</u> at the Northwestern University Feinberg School of Medicine and past president of the American Heart Association, said there is some hyperbole in statements like that. Statin drugs, for instance, are more effective than aspirin in some patients. But statins are only available by prescription and are not as widely used as aspirin.

Lifestyle changes such as smoking cessation and losing weight are bigger factors in the drop in heart attack deaths than any drug.

That said, when the cost, availability, and widespread use of aspirin in appropriate patients are considered, "I wouldn't argue strongly that aspirin is not the single most important drug," Bonow said.

<u>NEW STUDIES,</u> <u>OLD RESULTS</u>

The results of two major studies on the risks and benefits of aspirin in preventing a first heart attack, including one conducted by Bayer, were published in 2018. Both of them seemed to confirm what was already known: There is no proof that daily aspirin use benefits patients at <u>low risk of heart trouble</u>, or those <u>older than about 70</u>. However, neither study shed new light on the key question of whether aspirin is effective in preventing a first heart attack or other cardiovascular event in patients between 50 and 70 who have an elevated risk of heart trouble, Bonow said.

Proving that is extremely difficult.

Establishing benefits for people who have already had a heart attack is relatively simple because they have already shown they are at high risk of having a second one, Bonow said. However, it is very difficult to predict whether a person will have a first heart attack, even though risk factors are known.

The USPSTF guidance targets people who have a 10 percent or greater risk of having a heart attack within the next 10 years. But that still means there is a 90 percent chance someone in that risk group will not have a first heart attack, and there's no way to determine which category an individual patient will fall into, Bonow said.

However, doctors and medical researchers do know that blood clots and arterial inflammation trigger heart attacks, and that aspirin is effective in preventing clotting and reducing inflammation. The bleeding risks of aspirin also are well known. So it's clear from the way aspirin works that it is an effective means of preventing heart attacks in appropriately targeted and screened patients, Bonow said.

"Clearly it's going to reduce heart attacks," he said.

HIDDEN COSTS

The aspirin example illustrates many of the frequently cited flaws in the current FDA regulatory structure.

The most obvious is that the agency's reluctance to approve a drug—or in this case a new use for a drug—can actually cost lives. It also shows how the law prohibiting drugmakers from sharing accurate information about a drug's proven benefits, even to doctors, can end up harming the public's health.

Beyond that, it demonstrates drug companies are reluctant to spend the kind of money required to run clinical trials needed for FDA approval for low-cost products. It also shows drug companies are reluctant to spend the kind of money required to run clinical trials needed for FDA approval for low-cost products, and that the FDA is reluctant to accept the findings of studies done outside its own regulatory context, regardless of how large or numerous they may be.

Ultimately, the most important lesson from aspirin, at least to reformers, is that patients and their doctors are willing and able to judge for themselves the risks and benefits of a medication if they are given accurate information, regardless of what the FDA says. That is the same attitude that drove passage of Right to Try and will ultimately lead to more significant reforms in the way innovative new drugs are tested and approved in the United States, said Bartley Madden, a retired managing director of Credit Suisse HOLT, who advocates bringing <u>free-market principles</u> to FDA reform.

"The notion of freedom and making an informed decision, and taking responsibility for one's health, is now on the national radar screen. That's a big change," said Madden, who for the past 15 years has been pushing a variant of conditional approval that he calls Free to Choose Medicine. "In the current system, everything moves at a snail's pace, and it's designed for super-safety—call it deadly overcaution."

- Bartley Madden Retired Managing Director of Credit Suisse HOLT

Madden's plan is similar to other <u>conditional</u> <u>approval concepts</u> that have come out in recent years. The basic idea is that after safety has been proven in the first round of clinical trials, and strong evidence the new medicine works as intended is verified in Phase 2 trials, the drug could be sold and dispensed on a conditional basis. This would bypass current Phase 3 trials, by far the longest and most expensive.

Drug companies also could follow the traditional track, leaving the current system available for patients who do not want to try a medicine that has not received final approval from the FDA.

Patients would be closely monitored, and all of their identity-protected data would be fed into a massive database that would be used to assess a drug's safety and effectiveness. Ultimately, the data could form the basis of final FDA approval in lieu of traditional clinical trials, or be used to support a final decision when coupled with Phase 3 clinical trial results.

NEW APPROACH

Madden said his proposal would fix the most destructive elements of the current laws.

It could make medicines available for use five to seven years sooner than under the current system because doctors and patients could access them before they receive final approval, he said.

It would bypass the FDA's risk aversion because oversight of conditionally approved drugs would be farmed out to a different agency, such as the National Institutes for Health. The new approach would also lower the cost of drug development, and ultimately the price consumers pay, he added. Small drug companies, the industry's real innovators, will begin making money off their products sooner, allowing them to recoup some of their ongoing regulatory expenses. This in itself would spark competition. Under the current system, few small drug developers can raise the millions of dollars needed to complete Phase 3 trials and shepherd their new drug application through the FDA bureaucracy. So they are forced to sell the rights to their products to big drugmakers, which have the money and expertise to win final FDA approval.

"Free to Choose Medicine puts the premium on scientific skill in developing breakthrough new medicines and dramatically lessens the advantage of being able to navigate the FDA," Madden said.

But the most important benefit of switching to conditional approval is it would improve both the safety and effectiveness of new drugs because of the huge amounts of data generated when patients use the new product in the real world, Madden said.

Because the trials are currently designed so narrowly, little is known about a drug's safety and efficacy in the population as a whole until after it has been approved by the FDA and is being used by the general public.

The dangers of <u>the painkiller Vioxx</u> triggering heart attacks, for instance, were not fully realized until after it was approved by the FDA and a broader spectrum of patients began using it. Vioxx is considered the FDA's deadliest failure in recent years, and the dangers that surfaced after its approval have been linked to as many as <u>60,000 deaths</u>. Ultimately the manufacturer, not the FDA, <u>voluntarily withdrew</u> it from the market in 2004.

With conditional approval, more data would be generated continuously on a more diverse mix of patients. Side effects that go undetected in traditional clinical trials would surface almost immediately. So would evidence as to a drug's effectiveness, especially in subgroups of the population who do not qualify for Phase 3 trials. Drugs that are unsafe or don't work could be withdrawn almost immediately. Those that show better-than-expected results would gain acceptance more quickly.

As more people begin using the new treatment, even more data would be generated, and there would be an ever-growing amount of information as to its risks and benefits.

"In the current system, everything moves at a snail's pace, and it's designed for super-safety—call it deadly overcaution," Madden said. "The free-to-choose world is designed for fast-paced innovation. Everyone learns at this incredibly fast pace. That has huge implications for jump-starting innovation."

TRIAL AND SUCCESS

The approach is not as radical as it might sound. It is already being used in other developed countries, and some of its key elements are slowly becoming FDA policy.

In 2006, the European Medicines Agency (EMA), which handles drug approvals for the European Union, instituted conditional approval for certain new drugs. To qualify, the product must fill unmet medical needs, have a positive risk and benefit profile as proven in early clinical trials, and show potential that the public health benefit "outweighs the risk inherent in the fact that additional data are still required."

For the most part, the rules apply to drugs that treat serious or life-threatening conditions, or what are called "orphan" drugs which treat very rare conditions.

In the first 10 years, 30 drugs followed the conditional approval track, according to a <u>study done</u> for the EMA, published in 2017. Of those, 11 were converted to standard market authorizations, two were withdrawn for commercial reasons, and 17 remained under conditional authorization. None were revoked or suspended.

About 80 percent of the drugs targeted seriously debilitating or life-threatening conditions. The majority were either for conditions that had no alternative treatment, or significant improvements to already approved medications. Japan, the world's second-largest pharmaceutical market behind the United States, launched its <u>own</u> <u>conditional approval</u> system in 2014 for cellular-based therapies, such as treatments developed from stem cells or other human tissues. Even critics of the Japanese system say it has not compromised safety, though it may have allowed some treatments that are not particularly effective to be approved.

Both the Japanese and European systems rely on collection of real-world data to drive their review and ultimate approval decisions, and both impose strict safety requirements before a treatment can be marketed under conditional approval.

One important difference between those two systems and the drug market in the United States is that Japan and the EU countries have government-paid healthcare. So it is unclear whether private insurance companies will pay for treatment with a conditionally approved drug. Madden is confident they will, particularly as massive amounts of data add up.

That publicly available data will quickly show which treatments work better than those already on the market. Drug companies will have an incentive to keep prices down because the more people taking their medication, the more money and data will be generated. This will enable them to both finance and complete the research they need for final FDA approval.

At the same time, insurance companies and government payers will quickly learn from data analysis if a lower-cost and more effective drug is available through conditional approval, allowing them to reduce costs and ultimately save more customers' lives.

Once the data of a conditionally approved drug demonstrates it is more effective than existing treatments, insurers would have good reason to cover it, particularly if it is cheaper, Madden said.

"The insurance companies would be motivated if they saved money," Madden said. "If the FDA-approved drug is expensive, and it's not really doing very well, and there's a free-to-choose drug that's much less expensive and it seems to be doing much better for the patient, the economics suggest the insurance companies will learn they can make money by covering the more effective drug."

INCREMENTAL STEPS

So far, neither Congress nor the FDA has fully embraced conditional approval. Bipartisan <u>bills were</u> <u>introduced</u> in both the House and Senate in 2016 that would have <u>allowed conditional approval</u> for new cellular therapies, similar to the Japanese plan. They ran into stiff opposition from industry groups concerned that the change would sacrifice safety and effectiveness for speedy approval. The push fizzled when its prime backer lost his Senate reelection bid in 2016.

However, in the sweeping drug reform bill called the <u>21st Century Cures Act</u>, passed in 2016, Congress did include language prodding the FDA to break from its reliance on traditional clinical trials and make better use of data generated in the real world, a basic tenet of conditional approval.

The Cures Act directed the secretary of Health and Human Services to develop standards to make more extensive use of real-world data both to monitor drugs after approval, and to approve new conditions that can be added to an existing drug's label, essentially what is now its off-label use.

Under pressure from Congress, the FDA has cautiously embraced a key component of conditional approval: the use of real-world data to help <u>guide</u> <u>its decisions</u> on medical devices, which include such things as pacemakers, breast implants, and surgical lasers.

In guidance issued in 2017, agency officials did not say outright that real-world data could replace clinical trials for initial approval of medical devices.

The guidance indicates real-world data might be used to include what are now off-label uses to a device's label. It also might be used to collect follow-up safety and effectiveness information after initial approval, the equivalent of current Phase 4 monitoring.

The guidance does not apply to new drugs, including cell-based biologics, or indicate whether real-world data would ever be sufficient to replace traditional clinical trials for initial approval.

CHANGING ATTITUDES

FDA Commissioner Scott Gottlieb, in a July 2018 blog post, went further in explaining the agency's thinking on the use of real-world evidence to support its regulatory decisions.

Gottlieb conceded traditional clinical trials are so narrowly designed they do not always predict the safety and benefits of a drug in the population as a whole.

"Clinical trials provide a picture of a medical product's potential in a narrow and highly controlled setting," Gottlieb wrote. "But they do not provide a complete picture as to how a product works outside of that setting. This can limit our broader understanding of how a new product will work in the real world."

Gottlieb went on to tout a \$100 million request in the President's 2019 budget proposal that would allow the FDA to set up a massive database to track the electronic health records of about 10 million patients, whose identities would be protected. This would be the foundation of the agency's efforts to make better use of real-world evidence, which will ultimately reduce the time and cost of securing new drug approval. This might allow the agency to lessen the requirements in preapproval clinical trials with the caveat that robust data collection would be used to monitor a drug's safety and effectiveness after approval.

"Such an enterprise can not only support our evaluation of safety and benefit using data derived from real-world settings, but it can also make the development of new innovations more efficient," he wrote. "If we have more dependable, near-real-time tools for evaluating products in real-world settings, we can allow key questions to be further evaluated in the post-market setting. This can allow some of the cost of development to be shifted into the post-market, where we can sometimes access better information about how products perform in real-world settings."

The Goldwater Institute sought clarification from the FDA's press office as to whether Gottlieb's comments signaled a willingness to move toward some type of conditional approval. The agency did not answer directly. It did send links to previous speeches, which did not give additional insights. The sort of massive data collection Gottlieb talks about is already being done and is being used to shape clinical trials and monitor drug treatments in the real world. For instance, the Phoenix-based Translational Genomics Research Institute (TGen) has been <u>mapping the genetic makeup</u> of patients with diseases ranging from cancer to Alzheimer's disease since it was founded in 2002.

The data can be used by drug companies to target patients who are most likely to respond to a particular treatment in clinical trials. Drugmakers also can use the billions of data points to determine how new medications work on individual patients based on their genetic makeup, since some patients respond better to a given treatment than others.

In September, TGen, a nonprofit research organization, helped launch the <u>Kids First Data Resource</u> <u>Portal</u>, which is supported by the National Institutes for Health. The portal is a way to help diagnose, monitor, and treat children with cancer and a variety of other diseases by giving scientists and physicians access to TGen's data. It will eventually become the largest collection of genetic data on childhood diseases of its kind.

RED TAPE

Another approach to speeding drug approval is reciprocity with certain other countries, the <u>bill pushed</u> <u>by Sens. Cruz, Lee, and Ron Johnson, R-Wis.</u>, who led the effort in Congress to pass Right to Try legislation.

Under their plan, the FDA would have 30 days to approve or reject drugs, medical devices, and biologic treatments approved in certain designated countries. If the agency rejects the application, Congress could override that decision with a joint resolution.

The bill would cover approvals from the European Union, Canada, Australia, Japan, and Israel, all of which have drug-approval processes similar to those in the United States.

"Americans suffering from chronic and life-threatening conditions will be able to access drugs and devices, which are currently saving lives in other developed countries, but have not been approved in the U.S. because of FDA red tape," the senators said in a joint press release announcing introduction of the bill.



So far, the bill has not gotten a hearing in the Senate.

One example of how reciprocity might have changed things happened in March 2013, when there was an <u>outbreak of meningitis</u> at Princeton University, and later at the University of California, Santa Barbara.

Meningitis is an often fatal disease that inflames the tissues surrounding the brain and spinal cord. Many survivors are left with permanent brain damage or amputated limbs. More than 4,000 new cases are diagnosed every year in the U.S., about 10 percent of which are fatal.

At the time of the outbreak, no vaccine to battle the particular strain of meningitis, Type B, had been approved by the FDA for use in the United States. However, a vaccine was available in Canada, Europe, and Australia.

As a result, the treatment used in other countries could not be used to deal with the outbreaks at the U.S. universities.

The U.S. Centers for Disease Control <u>successful-</u> <u>ly lobbied</u> the FDA to grant emergency authorization to use the vaccine at Princeton in December 2013, nine months after the first case was reported. The FDA did not <u>grant approval</u> of the medication for general use in the United States until January 2015.

Nine people were afflicted in the Princeton outbreak, and <u>four at the UC Santa Barbara campus</u>, where the vaccine was also used on an emergency basis. One <u>person died</u> and another, a lacrosse player, had his <u>feet amputated</u>.

In the House of Representatives, a drug <u>reciprocity bill</u> similar to the Senate proposal was introduced, but failed to get a hearing. The House version would require an expedited review by the FDA of drugs approved in the European Union.

Critics of both bills argue reciprocity would create a <u>"race to the bottom"</u> in which drug companies would flock to countries that have the cheapest and quickest approval process, which would allow new drugs to enter the lucrative U.S. market without meeting U.S. testing standards. A significant difference between the Senate and House bills is that the Senate version would allow Congress to override the FDA's rejection of a drug approved in other countries, while the House bill would not. Critics say this would inject politics into what should be a public health decision. But backers say it is needed to break the FDA's stubbornness.

BURNED

The FDA has already demonstrated how it deals with congressional meddling.

Since 1978, the FDA has regulated <u>sunscreens as</u> <u>drugs</u>. So to add a new active ingredient, makers of the lotion that gets slathered on at swimming pools and beaches need to go through the same FDA-approval process as if they were proposing a new drug.

In Europe, Japan, and most other countries, sunscreen is considered a cosmetic, and therefore not subject to the same rigorous testing and approval requirements. As a result, the U.S. has 16 permitted sunscreen active ingredients while countries in the European Union can use more than two dozen, and in Japan there are more than 40.

Sunscreen is an effective method of preventing skin cancer, the most common type of cancer in the United States. About 5 million Americans are treated every year for skin cancer, including its most deadly form, melanoma.

The Surgeon General, Centers for Disease Control, and the FDA all recommend sunscreen to block the harmful UV rays that are linked to the disease.

It took the FDA 33 years to <u>finalize its standards</u> for sunscreen testing and labeling. The last time the FDA approved a new sunscreen ingredient was in 1999.

Frustrated at the slow pace of the FDA bureaucracy, and under pressure from manufacturers as well as cancer-prevention advocates, Congress passed and President Obama signed the <u>Sunscreen Innovation Act</u> in 2014. The law gave the FDA until late February 2015 to render a decision on pending applications for new sunscreen additives, some of which had languished since 2002. The FDA rejected all eight applications pending at the time. The new law only required the agency to render a decision by the deadline, <u>agency officials</u> <u>argued</u>. It did not require any be approved. Before that could happen, manufacturers would have to conduct more studies and go through the standard drug-approval process, which would involve extensive, and expensive, testing on both animals and humans.

That's not likely to happen, according to a <u>report</u> <u>published in 2017</u> by the Government Accountability Office. No sunscreen manufacturer has pursued FDA approval of the additives commonly used in other countries. The primary reason cited is that meeting the FDA's requirements makes no economic sense.

Even with FDA approval, there would be little profit in adding the new ingredients, despite their being more effective in blocking cancer-causing UV rays.

"Sponsor representatives said the testing FDA requested is extensive, would cost millions of dollars, or take several years to conduct," the GAO reported. "The sponsors are reluctant to spend money on additional testing, because many of these sunscreen active ingredients have been on the market in other countries for many years."

Risk aversion helped drive the FDA's decision. Despite the widespread use and proven effectiveness in preventing skin cancer in many of these additives, agency officials remain concerned there is insufficient information as to what harm these new ingredients may cause when absorbed through the skin. The fact that the additives had been used in other countries for years did not change their thinking.

FDA officials also blamed a lack of funding for the agency's long delays in reviewing sunscreen applications.

SPEAKING FREELY

At the state level, the Goldwater Institute is pursuing another reform that would allow drug companies to share accurate information about their products with doctors. Federal law prohibits drugmakers from making any health claims that have not been approved by the FDA. This means they cannot communicate the off-label benefits of a drug, even to doctors, or freely discuss the findings of other research that shows promise in treating other conditions.

Again, aspirin is the best example.

Aspirin makers can discuss with doctors its benefits in preventing a second heart attack because that use has been approved by the FDA. However, they cannot tout its benefits in preventing a first heart attack or colorectal cancer.

Drug companies and their representatives who violate these rules are subject to criminal prosecution.

As a result, doctors treating patients do not have complete access to information about the benefits and potential risks of the off-label use of a particular drug, even though that information is known to the manufacturer.

"Companies are at constant risk of prosecution and criminal penalties for 'misbranding,' or communicating off-label uses for a product outside of a narrow and often murky set of federal requirements," a Goldwater Institute report <u>published in June 2017</u> states. "Manufacturers, doctors, and patients will suffer from the lack of clear standards regarding what information can be shared about treatment options so long as Congress and the courts continue to allow the FDA to censor speech by medical experts about the legal use of legal medicines."

Off-label uses account for about one-fifth of all prescriptions written annually in the United States.

These are drugs that have been approved by the FDA to treat the specified conditions tested in clinical trials. Once a drug enters the market and doctors begin treating patients, they often discover beneficial side effects or more effective dosages. Almost 60 percent of drug therapy innovations were discovered by doctors practicing in the field, not by academic studies, manufacturers, or through FDA-related testing, according to one study.

Doctors, researchers, and advocacy groups are free to cite these newly discovered benefits. Drug companies and their representatives are not, except in limited circumstances such as forwarding to doctors an article or study published in a medical journal that meets the FDA's strict criteria.



Even then, manufacturers are required to include a disclaimer that the findings of the article or study have not been approved by the FDA, and they run the risk of being charged with misbranding if they fail to follow all the rules in the agency's <u>20-page guidance</u> <u>document</u>.

The FDA is on shaky legal ground in enforcing this restriction, said Christina Sandefur, executive vice president at the Goldwater Institute and co-author of the 2017 report.

Pharmaceutical companies have First Amendment free speech protections when engaging in commercial speech, the U.S. Supreme Court ruled in a 2011 case that voided a Vermont law restricting drug manufacturers from providing certain information to doctors. Attempts to censor that speech are unconstitutional, the Court held.

A year later, the FDA tried to prosecute a drug company sales representative for promoting the off-label benefits of one of its products. The Second U.S. Court of Appeals ruled that the agency's restrictions violated the free speech rights of the defendant, who was only communicating accurate information about the drug's legal off-label use.

"As off-label drug use itself is not prohibited, it does not follow that prohibiting the truthful promotion of off-label drug usage by a particular class of speakers would directly further the government's goals of preserving the efficacy and integrity of the FDA's drug-approval process and reducing patient exposure to unsafe and ineffective drugs," the court held in <u>United States v. Caronia</u>. "Prohibiting off-label promotion by a pharmaceutical manufacturer while simultaneously allowing off-label use 'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information; such barriers to information about off-label use could inhibit, to the public's detriment, informed and intelligent treatment decisions."

LEGAL LOOPHOLES

The FDA has largely sidestepped the clear language of that decision, taking the position that it would not prosecute off-label promotion, a direct affront to free speech. However, it will consider it evidence of the crime of "misbranding."

The FDA did not appeal the *Caronia* case, or subsequent rulings in other courts that upheld the free speech rights of drug companies. As a result, the ability of drug companies to communicate with doctors remains murky, Sandefur said.

Free Speech in Medicine is an attempt to protect the free <u>flow of information</u> so that doctors know everything they should when dispensing a drug off label. The Goldwater proposal encourages states to adopt laws that allow truthful and nonmisleading information to be shared between drug manufacturers and medical professionals, even if it is not solicited. It would also allow truthful communication with insurance companies.

Arizona <u>adopted the first</u> Free Speech in Medicine law in 2017.

Going state to state rather than directly seeking federal legislation follows the same model that led to passage of Right to Try, Sandefur said. After momentum built with the adoption of state laws, Congress took notice and passed the federal legislation.

One argument that came up against Right to Try, and is likely to be raised as more states pass Free Speech in Medicine laws, is that federal law generally takes precedence over conflicting state laws. However, Sandefur said there is no conflict, because Free Speech in Medicine is more consistent with federal court rulings than the FDA's current enforcement position.

"We are confident that, if challenged, the state laws would prevail because the federal law would be deemed unconstitutional," she said.

The Goldwater Institute has endorsed the concept of reciprocity with certain other countries but has not endorsed any specific legislation. It has not taken a position on conditional approval, though it is supportive of efforts to break the regulatory logjam at the FDA, Sandefur said. Both reforms are consistent with the core principle of Right to Try: Patients and their doctors should have more say over their treatment decisions.

The current system of approving new drugs is broken, Sandefur said. It has failed to keep up with advances in both science and technology. As a result, it takes far too long and costs far too much to bring new treatments to doctors and patients so that lives can be saved and improved.

What is needed is a new method that rewards innovation and allows patients and their doctors to take greater control over medical decisions, she said.

Like Right to Try, ideas like conditional approval, reciprocity, and Free Speech in Medicine are attempts to do that. "We need a system that is more patient-centric, one that makes safe and effective treatments available to patients sooner and at a lower cost, and one that allows patients—in consultation with their doctors to make personal decisions about those treatments," Sandefur said.

"I believe that Right to Try is the start of a broader movement—one that reclaims for patients the freedom to make fundamental choices for themselves. The growing popularity of these reform efforts is a recognition that our drug-approval system should teach, aid, and empower patients—not dictate to them the terms on which they will live their lives. That is what freedom is all about. It's what makes life more than mere existence."



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