

DEAD ON ARRIVAL

**FEDERAL “COMPASSIONATE USE” LEAVES
LITTLE HOPE FOR DYING PATIENTS**



By Mark Flatten, National Investigative Reporter,
Goldwater Institute

YOU ARE DYING AND HAVE NO HOPE.

Your disease is 100 percent fatal. It's only a short time before it kills you.

There are no treatments that have been approved by the federal Food and Drug Administration.

There is a new therapy that could save your life. But it is still being tested in people who have the same disease in rigidly controlled studies called clinical trials that you are too sick to qualify for.

It will be a decade or more before the new drug is available to your doctor. You will be long dead by then.

What are you willing to do, and how much risk are you prepared to take to try to save your life?

Those are questions thousands of Americans face every year after being diagnosed with a deadly disease for which there is no cure, at least none that has been approved by the FDA.

For them, their only chance at survival will be to get access to an innovative new drug before it's too late.

It may be a faint hope, or even a false one. But it is their only hope.

The FDA's compassionate use program is supposed to be that one last chance.

Formally known as expanded access, compassionate use is meant as a way to treat dying patients with medications that are still being tested in clinical trials and are therefore not otherwise available. Compassionate use must be requested by the patient's doctor, endorsed by the company that makes the drug, and approved by officials at the FDA.

But an investigation by the Goldwater Institute shows that the entire system for gaining access to an unapproved

medication is so rigged with bureaucracy and disincentives that it is bound to fail in most cases. Critics say it was designed that way, ensuring that only a tiny number of patients are able to navigate the complex, costly, and time-consuming maze that must be cleared just to file a compassionate use application for the FDA to consider.

The problem with the current system is not just that it takes doctors 100 hours or more to complete the application process for FDA approval.

Or that clinical trials take too long and cost too much.

Or that new cures for deadly diseases like cancer are typically being developed by cash-strapped small companies that risk financial ruin if they grant early access to their products to save the lives of dying patients.

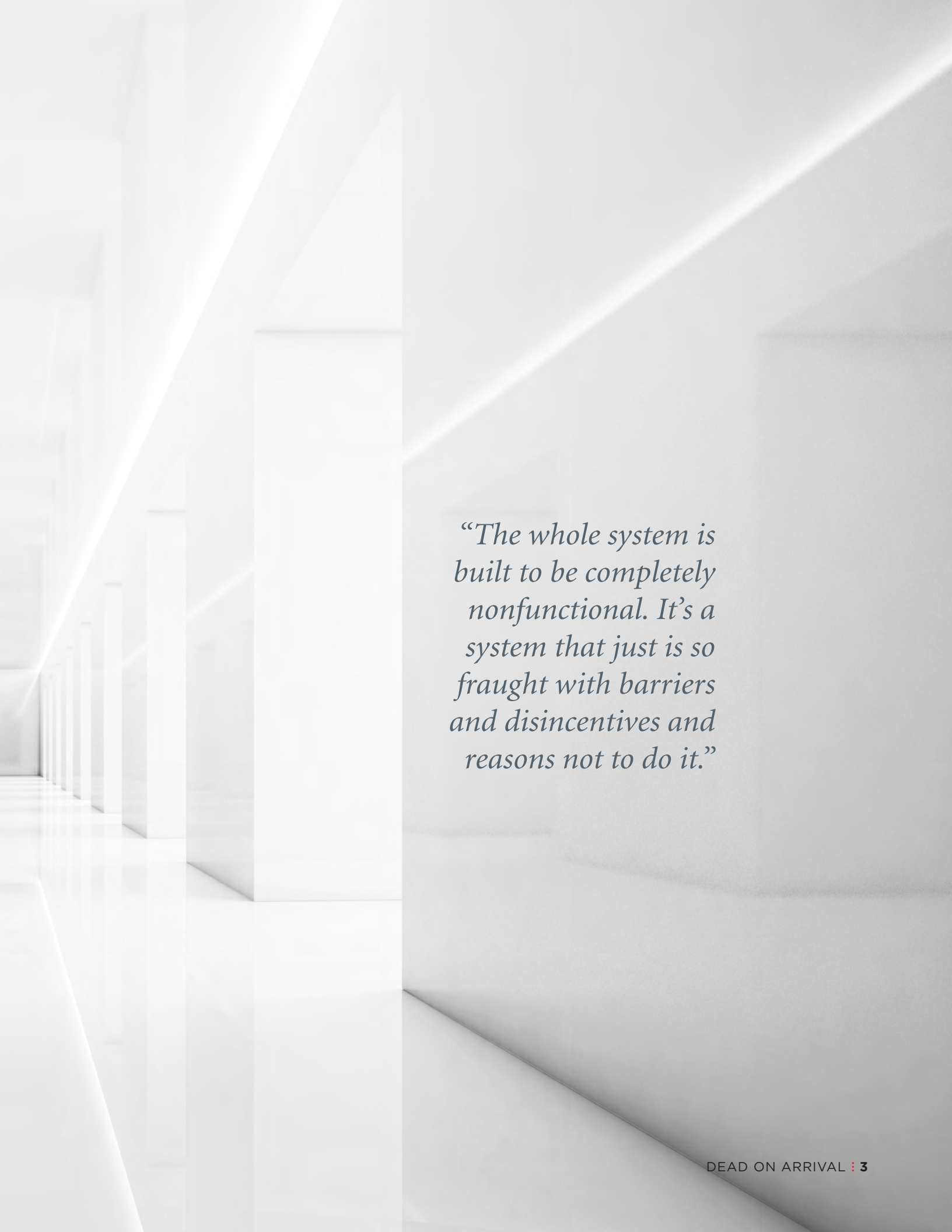
It's the way all of those things interconnect into an unworkable system that strips dying patients of their final option to save their own lives.

It is a system of all risks and no rewards.

And the lynchpin that binds it all together is the regulatory scheme created by the FDA.

To sell a new drug in the United States, and make any money off of it, pharmaceutical developers must get the FDA to certify that it is safe for use in humans and effective in treating the targeted condition.

The only way to prove that is through clinical trials: slow, tightly controlled, carefully monitored tests that normally consist of three phases in which the therapy is given to a select group of patients to gauge its effects.



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With everything riding on those trials, drug companies rarely do anything that could raise their risk of failure, or draw the ire of the FDA. That especially includes giving their treatment to a dying patient, whose death could be counted against the company seeking approval.

Those facing imminent death cannot access a drug while it is being tested, even if early results show that it works better than existing treatments, unless they are among the fortunate few who qualify for clinical trials. That amounts to a death sentence for most patients, even though their cure may have already been found.

It takes an average of 10–15 years for a new drug to get through testing and be approved by the FDA for sale to doctors and patients, according to government and industry estimates.

Most fail.

Drug companies spend an average of \$1.4 billion to get a product approved by the FDA. The cost of bringing revolutionary new treatments to market can reach \$5 billion. Virtually all of those costs must be paid by drug companies before they can sell their first dose.

The trials are all or nothing. Failure at any stage usually means the product is dead.

Small drug companies developing innovative treatments are normally a collection of scientists and businesspeople who find a new way to treat a disease and set about raising money from private investors to pay for the early stages of clinical trials, usually through the sale of stock or equities.

Once the product reaches later stages of testing and shows promise, the inventors typically sell it to a large drug company, either outright or through some type of licensing arrangement, according to industry experts and company records. That business plan evolved because few start-up drug developers will ever be able to raise the billions of dollars required to take a product through all phases of clinical testing, especially since they won't make any money from the drug until after the FDA approves it.

Only big pharmaceutical companies have that kind of money, staff, and regulatory expertise.

For the small innovators, making their drugs available to a dying patient through compassionate use is risky.

They often don't have the staff to deal with patients or the money to provide their products through compassionate use.

Their primary selling point to investors is that their drug shows promise in clinical trials that are proceeding smoothly. Any deviation is enough to send investors fleeing and potentially ruin the company.

Drug developers get no direct benefit from compassionate use.

They do not get government funding, and are rarely paid for making their products available.

Even if the patient does well and makes a miraculous recovery, that does nothing to help the product in formal clinical trials.

If something goes wrong, it is counted against the drug by the FDA.

All serious reactions or patient deaths, called "adverse events," must be reported to the FDA. The agency can, and has, suspended clinical trials because patients receiving treatment through compassionate use have died.

The FDA maintains that such suspensions are rare, but it is a widespread fear in the drug industry.

There also is the chance that a bad outcome will cause investors to question a drug's value and abandon the company's stock, leaving it with no way to raise the money necessary to continue testing.

Loaded with Disincentives

In short, the entire regulatory and financial structure of the drug industry is so loaded with disincentives that treatment under compassionate use is rare by design.

"The whole system is built to be completely non-functional. It's a system that just is so fraught with barriers and disincentives and reasons not to do it," said Steve Walker of the Abigail Alliance, a patient advocacy group. "Our entire system is set up, including with very unchallengeable enforcement authority by the FDA, to prevent people from gaining access to a drug of any kind that has not yet been approved by the FDA."

The Goldwater Institute has spearheaded the adoption of state Right to Try laws, which allow doctors and drug companies to proceed without FDA approval in providing treatment to dying patients who have no other options. Those laws have passed in 24 states with overwhelming bipartisan support and almost no opposition.

Critics of Right to Try say it is not needed, that compassionate use under FDA rules is the appropriate mechanism for dying patients to get the treatment they need. Drug companies are unlikely to risk the wrath of the FDA by providing their products to patients based on state laws alone, so the laws will not lead to widespread access to investigational medications, they argue.

But even critics concede that Right to Try laws have raised public and political pressure on the FDA to change its system for allowing those with no other options to seek treatment with investigational drugs. That includes Dr. Arthur Caplan, director of the

division of medical ethics at the New York University Langone Medical Center.

“Right to Try, as much as I fume and fuss about it, has brought the issue forward,” he said. “It has pushed the issue to the forefront. Congress must pay attention. Ethicists must pay attention; companies, media. Even if I think the laws are not going to get us far in getting drugs to people, I think it put the issue front and center.”

‘Successful Program’

FDA officials and their defenders insist the current system works well, and the agency is not an impediment to terminal patients getting the care they need. Their primary talking point is that the FDA approves 99.5 percent of the applications it receives for compassionate use.

Since 2010, the FDA has approved an average of about 1,200 applications for compassionate use per year. In 2015, it approved 1,256 applications and rejected six.

“I would say it’s a very successful program. The agency has an extremely good track record,” Richard Klein, director of the FDA’s patient liaison program, said at a recent conference about expanded access.

But critics say the FDA’s numbers are meaningless.

All they show is the total number of formal applications that were approved and rejected by the FDA. They do not show the number of requests that were squelched because of agency regulations before they were ever filed.

The FDA does not track those numbers.

No one knows how many requests for compassionate use drug companies receive or reject. They are not required to keep or report that information. One indication is that the number of ongoing clinical trials open to compassionate use is a tiny fraction, far less than 1 percent, according to the government-run website clinicaltrials.gov.

Drug companies cannot be compelled to approve a compassionate use request. If a company refuses to provide the drug, the application cannot be forwarded to the FDA.

When Rep. Mike McCaul, R-Texas, was crafting a bill in 2014 aimed at simplifying the compassionate use process, he initially wanted language that would require drug companies to confidentially disclose that information to the Government Accountability Office. The idea was to allow the GAO to compile overall industry data on the number of requests made to companies, how many were approved and rejected, and the reasons why.

Drug industry lobbyists considered that provision a deal killer, and it was stripped from the bill that McCaul later introduced.

Beyond that, there is no way to know how many doctors simply refuse to make compassionate use requests for individual patients because of the long, cumbersome, and costly process required by the FDA.

“If you have to deliver the application at the top level of Mount Everest, they will approve it,” said Garo Armen, chief executive officer of Agenus Inc., a small biopharmaceutical company developing immunotherapies to help treat cancer and other diseases. “The FDA will do the approval process, but everything that needs to be put into place, which is an FDA requirement, makes the process very onerous.”

The best evidence against the FDA’s claim that it is not an impediment to compassionate use is the numbers themselves, said Carla Mann Woods, formerly a medical device industry executive, and now a board member of the Alfred E. Mann Institute for Biomedical Engineering at the University of Southern California.

About 600,000 people die annually of cancer alone. Add to that the millions of people facing other life-threatening or debilitating diseases, and the 1,200 compassionate use applications approved by the FDA annually is shown to be a paltry figure, Woods said.

“In this era of both scientific revolution and information where anyone can find anything on the Internet, ask yourself this: Can you actually believe that only 1,200 dying Americans want to live badly enough to find a legitimately applicable, unapproved therapy and ask to get it?” she said.

Too Much To Bear

Nick Auden does not exist in the FDA’s statistics. No drug company would allow its product to be used to save him, so no formal application ever reached the FDA to approve or reject.

Auden, a 41-year-old father of three, died in November 2013.

The Australian lawyer and corporate executive was living in Denver when the first sign surfaced of melanoma, a type of skin cancer.

In October 2011, Auden felt a lump under his arm. When he had it checked, his doctors told him he had late-stage melanoma that had spread to his spine, arm, and leg.

Doctors gave him a 10 percent chance of survival, considering the treatments available at the time. Most patients in his condition lasted six to nine months.

Auden tried the FDA-approved treatments, undergoing intensive immunotherapy that seemed to work at first. But then the cancer returned, and his doctors suggested clinical trials. Auden seemed like a perfect candidate. He maintained an active lifestyle and, aside from the cancer, remained physically strong and emotionally upbeat.

A black and white photograph of a long, empty hallway. On the left side, there is a long wall of large windows that stretch into the distance. The floor is highly reflective, mirroring the windows and the ceiling. The ceiling has a series of horizontal panels. The hallway leads to a bright, open area at the far end.

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Auden managed to get into one trial using a new drug that targets a type of genetic mutation linked to about half of melanoma patients. It worked for several months, but then the tumors started growing again. That was enough to get him kicked off the trial.

Auden's doctors were familiar with a new line of drugs being developed, known as anti-PD 1 therapies, which allow the body's immune system to target and attack cancerous cells.

Merck and Bristol-Myers Squibb were testing versions of anti-PD 1 drugs in clinical trials.

It seemed Auden's miracle cure may have been found. His doctors scrambled to get him into one of the trials. Then came the complications.

Auden developed a brain tumor, which disqualified him from trials.

The tumor was treated with a type of radiation surgery, but by the time he was eligible to qualify for a clinical trial a second tumor appeared, which again was treated with the same procedure.

In July 2013, Auden's brain tumors were considered stable, and he was finally

accepted into a Merck trial. By then he had spent almost seven months trying to qualify for the testing—about the same amount of time he was initially told most patients like him could expect to live.

As Auden was preparing to fly to Los Angeles to begin treatment, he experienced a partial bowel obstruction, which got him disqualified from yet another round of clinical trials.

Auden's doctors told him his last option was compassionate use.

His past business connections gave him contacts inside Merck. He and his wife, Amy, tried working those contacts to get the company to approve their application for compassionate use. Their efforts were rejected, and the contacts told them to stop calling.

Merck officials said the company only made enough of its drug for people in clinical trials. It was not available to anyone through compassionate use.

Auden was told his only option was to enroll in a clinical trial. When he responded he'd tried that, and been rejected, he was told there was nothing more the company could do.

Dealing with Bristol-Myers was even more frustrating, Amy Auden said.

Officials there refused to even discuss compassionate use, saying only that its drug was too unsafe to use outside of clinical trials.

Wall Street Watching

What investors were hearing was much different.

Researchers touted the new line of anti-PD 1 drugs at a meeting of the American Society of Clinical Oncology in mid-2013 as showing unprecedented safety and success in treating melanoma and other types of cancer.

Wall Street took notice, with the price of Bristol-Myers and Merck shares increasing more than 3 percent in a single day following the oncology conference, the *New York Times* wrote in an extensive article about the new miracle cure in June 2013. Billions of dollars in potential sales were at stake for the company that got its drug approved by the FDA first.

That was particularly galling, Amy Auden said.

"The word unsafe made me so angry because their share price increased when they announced this breakthrough drug at the conference," she said. "You can't say to someone who's got a death sentence that there is no hope for you, even though we've got this drug that we're talking on the television about and it's a breakthrough. That doesn't wash."

After getting the runaround from both Merck and Bristol-Myers, the Audens took their story public, doing media interviews and launching a social media campaign called "Save Locky's Dad," named after their oldest son, Lachlan, which gathered more than a half-million signatures in support.

Both companies refused to back down, even after Auden got assurance from the FDA that there were no safety concerns and their application for compassionate use could be approved within 24 hours once a drug manufacturer agreed to provide the medication.

By November, his health was starting to deteriorate. In a last-ditch attempt to save his life, Auden flew to Houston to receive a different kind of therapy unrelated to the anti-PD 1 drugs.

While in Houston, he had a massive seizure and was unable to tolerate further treatments.

He and Amy flew back to Denver to spend his final days with their children, and he died soon after.

Less than four months after Auden's death, Merck announced it would make its anti-PD 1 drug available to dying patients through expanded access.

The Merck version, now called Keytruda, and the Bristol-Myers version, Opdivo, were both approved to treat melanoma patients in late 2014, about a year after Auden died.

The system failed Nick Auden, said Amy, who lives in Australia, where she is raising their three children, now ages three, seven, and 10.

"It beggars belief that people still have to deal with the illness and then fight to get the drug too, which is proven safe," she said. "Unless you are going through something like this, you don't know what the system is.



But the system was so frustrating that I can't believe it was allowed to exist like this.

"To not get the benefit of that, given that it was available in Nick's lifetime, was just too much to really bear."

Judgment Call

Just asking for compassionate use is a logistical nightmare. Dying patients must first convince their doctors to make the application. Patients cannot petition the FDA directly.

To qualify, the patient must have a condition that is immediately life-threatening or serious. To be considered immediately life-threatening, a disease must be at such a stage that there is a reasonable likelihood of death within months, or in which premature death is likely without early treatment.

What counts as "serious" is a judgment call by the FDA. Federal regulations say a serious condition is one that substantially affects day-to-day functioning, and includes such factors as whether it is likely to cause



*Nick Auden
with his family*

death and whether the disease is likely to progress without treatment.

Also, a patient must have exhausted all traditional FDA-approved treatments for a deadly disease like cancer. That means those seeking compassionate use tend to be in the later stages of their illness, wracked by complications such as weakened organs or immune systems, and often taking other medications to cope with pain and debilitation. Those facts alone are enough to prevent most such patients from qualifying for clinical trials of investigational treatments. By definition, they also face the highest risk of dying and are least likely to respond to last-ditch treatment.

Logistical Nightmare

For doctors and patients, the first hurdle is just knowing that a medication exists and finding out whether the company that makes it might be willing to authorize its use.

Most drug companies do not have policies on compassionate use, or at least do not make them

easily accessible. A review of more than 100 companies developing multiple potential cancer treatments shows that fewer than 20 had compassionate use policies clearly posted on their websites. That number includes companies whose websites say their medicines are *only* available through clinical trials. Those that did post compassionate use policies tended to be the largest companies, not the smaller ones which are developing most of the innovative treatments that might offer the best new hope for those near death.

The doctor must agree that there are no other viable treatments available, and that the risks of administering the unapproved medication are outweighed by the risks of the disease.

Just to fill out the FDA's application form, doctors who think a drug undergoing clinical trials can save their patient must commit to spending 100 hours or more compiling extensive information about the patient and technical data on the drug, which may be proprietary information they have no way of knowing. They need to write treatment and monitoring plans that are acceptable to both the FDA and the drug manufacturer, which become part of the application.

All of that goes into the 100-hour estimate.

In February 2015, the FDA published proposed guidance in the Federal Register to begin allowing a new, shorter form to be used by doctors to apply for compassionate use. If approved, it will shave about seven hours off the time it takes to fill out the agency's paperwork, according to the notice.

If the application for compassionate use is ultimately approved, the doctor will have to abide by whatever dispensing and monitoring requirements are imposed by the company, which is unlikely to make its product available without such restrictions. Those requirements typically mirror the protocols for the ongoing clinical trials to minimize unpredictable incidents and reactions.

Both the company and the FDA will also require that data be kept and reported on the patient's medical condition, progress, and reactions. That usually means extensive and expensive medical tests that are rarely paid for, since most insurance companies do not cover experimental treatments.

In short, a doctor who agrees to sponsor an application is essentially responsible for designing, running, and usually paying for, a miniature clinical trial for a single patient.

The next step is to get approval by the Institutional Review Board at the hospital or medical clinic where the patient will be treated. IRBs are internal panels that weigh the ethical considerations of treating people with medicines that have not been approved by the FDA. They usually meet infrequently, adding weeks to the approval process.

Beyond that, applications normally must be approved by the hospital or clinic's lawyers and business executives, or board of directors. Though not required by the FDA, those steps are necessary to ensure that treating the patient will not expose the institution to lawsuits or prohibitive uncompensated treatment costs, according to doctors and drug industry executives who have been involved in compassionate use cases.

Triage

"Of course there is triage," said Razelle Kurzrock, director of clinical trials and the Center for Personalized Cancer Therapy at the Moores Cancer Center at the University of California, San Diego. "The number of patients that we would give compassionate use drugs to would probably be much, much higher if the bar for compassionate use was not so high."

Kurzrock set up and ran early-stage clinical trials at the MD Anderson Cancer Center in Houston from 2004 until 2012, eventually building it into the largest such program in the country before she left.

About 1,300 patients went through the trials in her department every year. Kurzrock said her unit only tried to get compassionate use for about one patient annually because of the time and runaround involved in preparing the application.

Even before starting the process of assembling the data and filling out the form, Kurzrock spent hours on the phone calling the FDA and drug companies to find out if there was even a chance that the request would be approved. In most cases, the answer was no.

"So you never get to the point where you put in an application," she said. "It's almost a self-fulfilling prophecy for the FDA to say they approve everything, because you don't even put in the application before you sort of get a verbal approval from the FDA that it's worth doing."

Even with her level of expertise, assembling the information and filling out the FDA form would take about 50 hours, including the first round of phone calls and other research needed to find out if there was any point in seeking approval, Kurzrock said. For a front-line physician, the 100-hour estimate could even be low.

"The fact that we did maybe one a year in our department, which was the largest of its type, probably in the world, I think says it all," she said. "There's only two possibilities: that there was only one patient per year that needed compassionate use, and that's really laughable. Or that there were so many barriers that even at one of the best places in the world and one of the largest departments that did this as their day in and day out job, it was still very challenging."

The FDA disputes that it takes 100 hours to fill out the application, even though that number appears

on the form itself. The paperwork the FDA uses to apply for compassionate use was designed for a drug company applying to run clinical trials, not for individual physicians wanting to treat a single patient.

Many of the fields in the existing form do not have to be filled out by doctors applying for compassionate use, according to Klein of the FDA. The new form, once it receives final approval, will limit the application to the eight appropriate fields.

There is nothing on the form or in the agency's instructions directing doctors to ignore the fields that are not required. Klein did not explain why it took so long to make that clarification by developing a new form, or when doctors can begin using it, given a year has passed since it was proposed.

Roadblocks

If the doctor and hospital agree to take on the task of applying for compassionate use, the patient faces the biggest roadblock of all: getting approval from the drug company.

Drug makers cannot be forced to make their products available for compassionate use. If they refuse to participate, the application cannot proceed.

While no one knows how many requests they receive and reject, there are indications the numbers are high.

A single company had more than 100 applications in September 2015 alone, according to its former chief executive officer.

For drug makers, participating in compassionate use is risky business, regulatory and financial experts told the Goldwater Institute.

Drug makers can charge patients the actual cost of manufacturing their products. But they seldom do because they do not want to disclose their actual costs and potential profit margin in the event that the drug is ultimately approved. So when a company does make its product available to dying patients, it almost always provides it for free.

That can be a major expense. Many new treatments make use of expensive compounds or genetic therapies.

In the early stages of clinical trials, only small quantities of an experimental new drug are manufactured to keep costs down. That raises fears that making the medicine available in compassionate use cases could mean there is not enough to use in clinical trials.

About the only upside for companies under the current system is the good publicity that can result if a patient survives against all odds. However, even that must be balanced against the risk of bad publicity if an already hopeless patient dies, even if it had nothing to do with the drug.

Bad Outcomes

But the biggest fear in the industry is that bad outcomes in compassionate use cases can derail or delay the all-or-nothing clinical trials that often will determine whether the company itself lives or dies.

Good news doesn't help.

If a patient does well and begins to recover, that information does nothing to help the drug company get its product through clinical trials. Since compassionate use patients do not meet the statistically controlled requirements of those in clinical trials, positive results are not deemed statistically significant.

Bad news, however, does count in weighing the product's risks.

All major adverse events, especially the death of an already dying patient, must be reported to the drug company and the FDA if they occur in a compassionate use case.

That could prompt the agency to halt the clinical trials. It could also require the drug manufacturer to post additional warnings on the product's instructions, known as its label, if it is eventually approved and marketed.

Agency officials have long insisted that they understand that compassionate use patients are already near death when treatments are administered, and that it would be unfair to count adverse events against the drug's clinical trials. However, the FDA has no formal, written policy promising not to hold such incidents against companies.

Then in November 2014, a company called CytRx was participating in compassionate use on an advanced-stage cancer patient who died. The FDA put a partial hold on the clinical trials for the drug, aldoxorubicin, and forced the company to rewrite its testing protocols and add new patient-screening assessments.

CytRx stock tanked, dropping about 9 percent the day the clinical hold was announced.

The hold was lifted in January 2015, and by then the company's stock had begun to creep back up, but the damage was done.

The FDA's action sent a chilling message to the industry that trials could be jeopardized by participating in compassionate use, said Steve Walker, cofounder of the patient advocacy group Abigail Alliance, and its expert on the FDA regulatory process.

"That plays into this fear of the drug companies that doing things outside the controlled clinical trials can only work against them," said Walker. "For a small company, an adverse event could not just kill their drug. It could kill their company. So they tend to be very conservative when it comes to doing anything more than what they have to do in a very careful and controlled way to move their drug toward the market."

Walker's wife, Jennifer McNellie, died in 2003 of colon cancer at the age of 47 after she was unable to access potential cures then in clinical trials.

"So you never get to the point where you put in an application. It's almost a self-fulfilling prophecy for the FDA to say they approve everything, because you don't even put in the application before you sort of get a verbal approval from the FDA that it's worth doing."

RISKY BUSINESS

Even if a patient's death does not cause a halt in clinical trials, it will likely force the drug developer and treating doctor to do an investigation to determine whether the product was to blame, Walker said.

If it wasn't, that will have to be proven to the FDA's satisfaction.

If it was, it could further endanger the clinical trials, force new trial designs, or ultimately lead to a cautionary warning on the product's label when it eventually is sold.

That adds time, expense, and investor uncertainty.

Even people who traditionally defend the FDA and the current regulatory system say the agency must address companies' perception that adverse events can endanger final approval of their drugs.

"They are absolutely afraid," said Caplan, the New York University ethicist. "It's not the company. For the little guys, it's the investors ... the people who say, 'I'm putting up money as an early investor in a high-risk thing. I may be a big winner, but I'm taking a lot of risk. I don't want the company doing anything to make things riskier.'"

Caplan added that verbal assurances from the FDA asserting adverse events will not endanger clinical trials is not enough.



“The FDA should put their approach to interpreting adverse events when they occur in the context of compassionate use in writing,” Caplan said. “They say, ‘We’ve talked about this at public forums.’ That’s all well and good. Write it down. It’s not going to calm fears to say, ‘I gave a speech about this and we made our position clear.’ Write it down.”

Representatives of CytRx would not agree to an interview.

Neither would officials at the FDA. In an email response to questions, Deborah Miller, health programs coordinator at the agency, said patients’ conditions are taken into account when adverse events in compassionate use cases are evaluated.

“For the most part, the information is considered anecdotal, outside the context of the trial data,” she wrote.

A recent FDA study found that only two drugs out of more than 1,000 had their clinical trials suspended in a 10-year period because of an adverse event in a compassionate use case.

As to why there is no formal policy, despite concerns routinely cited by industry executives, Miller said the FDA is developing guidance “which will provide greater clarity on how the program operates.”

Nervous Investors

Investor nervousness can kill a company.

Most small drug companies, the ones that tend to be developing innovative treatments to deadly and debilitating diseases, live or die on the smooth operation of their clinical trials, according to a review of dozens of financial reports filed with the U.S. Securities and Exchange Commission.

Typically, they have one or two products undergoing trials, and have never had a product approved by the FDA or made any money from their new treatments.

Instead, they survive solely on their ability to attract new money from investors, who are wary of anything that could jeopardize the clinical trials that are likely to go on for years and cost billions of dollars.

SEC disclosures also routinely warn investors about the dangers of adverse events and the stakes if they cause a glitch in clinical trials.

"Adverse events caused by our product candidates could cause us, other reviewing entities, clinical study sites or regulatory authorities to interrupt, delay or halt clinical studies and could result in the denial of regulatory approval," a company called Chimerix said in its August 2015 report to the SEC. "If our product candidates are not successfully developed or commercialized, or if revenues from any products that do receive regulatory approvals are insufficient, we will not achieve profitability and our business may fail."

Chimerix went through the highs and lows of compassionate use in 2014.

The company was developing a new antiviral drug called brincidofovir, which had shown remarkable improvement from existing treatments in ongoing clinical trials.

About 400 patients had been treated with brincidofovir through a compassionate use program, funded in part by a government grant to study its usefulness against an outbreak of smallpox. But when that funding ceased in 2012, Chimerix stopped accepting new requests for compassionate use.

Miracle Cure

Meanwhile, 7-year-old Josh Hardy was dying. He'd battled kidney cancer since he was a baby. After 10 intense regimens of chemotherapy, his immune system was depleted.

Following bone marrow therapy treatment, he developed an infection. His body was too weak to fight it, and approved treatments proved ineffective.

Doctors at St. Jude Children's Research Hospital, where Josh was being treated, were aware of the potential miracle cure that brincidofovir could represent. In February 2014, they asked Chimerix to make brincidofovir available to treat Josh through compassionate use. The company refused.

Less than a month later, Josh was in the intensive care unit with renal failure and was not expected to last more than a few days. His weakened immune system could not fight off the infection.

Doctors again requested brincidofovir. Chimerix again refused.

On March 6, Josh's mother Aimee wrote a Facebook post describing his dire condition and the company's refusal to help. That touched off a firestorm on social media and a public relations disaster for the company.

Chimerix executives were flooded with calls and emails demanding Josh be given access to brincidofovir. Their personal information and home addresses were posted on the Internet.

There were death threats and stories sympathetic to Josh's plight on the national news, said Kenneth Moch, CEO of Chimerix at the time.

Private security was hired to protect company officials.

Behind the scenes, there were phone calls between company executives and the FDA, said Debra Birnkrant, the FDA official whose unit was in charge of the drug's trials. The agency was unaware of the volume of requests for compassionate use access to brincidofovir that the company had been receiving.

"I didn't fully understand why in this one particular case this child was not getting access to this drug," Birnkrant said at a conference in October in which she appeared on a panel with Moch to discuss the ramifications of Josh's case. "In my mind, this was not the case to say no to. The media storm was too major."

By March 11, Chimerix backed down and allowed Josh to be treated with brincidofovir. He quickly recovered.

About three weeks later, Moch was forced to resign.

Josh was not treated through compassionate use. Instead, Chimerix and the FDA devised a work-around that allowed about 20 patients to be treated in a hastily approved clinical trial that tested the drug's effectiveness in treating the type of infection that was killing him.

Handling Josh's request that way, as opposed to using traditional expanded access, allowed the company to benefit in clinical trials from the information gleaned from the patients that were being treated, Birnkrant said.

The dilemma for the 55-person company was that it was deep in debt, had limited financial resources, and did not have enough of the drug to provide it to everyone seeking access and still have enough to use in clinical trials, according to Moch and company financial records.

Getting brincidofovir through clinical trials and approved by the FDA was deemed the best way to protect the company and help future patients.



Andrea Sloan

"It's the moral dilemma of the many versus the few, the future statistical people versus the current absolute need," Moch said. "There was no consideration of the ethical and moral dilemmas in the social media program. Social media in this case and in many cases is a public temper tantrum."

Moch initially agreed to an interview with the Goldwater Institute but then backed out at the last minute, saying he would convey his thoughts at the October conference in which he appeared with Birnkrant.

While Moch couches the Josh Hardy case as an ethical dilemma, it had financial ramifications as well.

Publicity over Josh's quick recovery caused Chimerix stock to soar almost 50 percent. A few months later, brincidofovir was used on a compassionate use basis to treat Thomas Duncan, a Liberian man who was the first of several patients in the United States diagnosed with Ebola.

Duncan died in October 2014. And although there was no indication that brincidofovir had anything to do with his death, Chimerix stock plummeted by 15 percent within 30 seconds of the announcement, Moch said.

Company officials still warn of the financial dangers of participating in compassionate use.

"The risk for adverse events in this patient population is high which could have a negative impact on the safety profile of brincidofovir, which could cause significant delays or an inability to successfully commercialize brincidofovir, which would materially harm our business," the company said in its August 2015 report to the SEC.

'Safer That Way'

Investor expectations do put pressure on small companies to avoid any risk that could endanger clinical trials, including participation in compassionate use, explained Victoria Buenger, who teaches strategy and management at the Mays Business School at Texas A&M University and has a joint appointment in the school's biotechnology program.

Chimerix was already deep in debt and its stock volatile before Josh Hardy's doctors made their first request for brincidofovir, said Buenger, who helped organize patient advocates to get Josh treatment.

"It would be very hard to explain to investors why you were going ahead and doing this kind of risky behavior when you were already losing money and you

were trying to put every bit of effort at the company into getting the trials completed so that you can have positive cash flow," Buenger said. "To the extent that the stock price is already struggling and you start getting the hint of something that might make investors nervous, I think it is a place that becomes very, very strange territory."

Buenger helped form the Coalition Against Childhood Cancer, a patient advocacy group, after the 2009 death of her daughter, Erin, from neuroblastoma, a type of nerve-cell cancer.

Companies also face risks when they refuse to participate in compassionate use. Chimerix was besieged with negative publicity when it refused to provide Josh the treatment that ultimately saved his life. Rightly or wrongly, the company was seen as putting profits ahead of saving a child's life.

That explains why there is such vehement opposition from the drug industry to disclosing the number of compassionate use requests they receive and reject, Buenger said.

"Some drug companies would like there to just be a cloak where you can't see what's happening or even ask that question, because it's just safer that way," she said.

‘Saving My Life’

What drug companies hate worst of all is social media campaigns that put a human face on an otherwise calculated business decision.

That’s what Andrea Sloan did in 2013 when she launched a social media campaign seeking a cure to the cancer that ultimately killed her. In the process, she drew the wrath of one drug manufacturer and inspired a push for reform in Congress.

Sloan was a successful attorney in her late 30s when she was diagnosed with ovarian cancer in 2006. For more than seven years, she underwent the standard treatments. She had five surgeries, a stem cell transplant, and two full regimens of chemotherapy. Eventually, they stopped working, and she could no longer stave off the spread of the disease. Her doctors at MD Anderson first raised the prospect of compassionate use.

A new line of drugs was being developed that specifically targeted her type of ovarian cancer and genetic makeup. Known as PARP inhibitors, they allow the body to attack cancerous cells without damaging healthy tissue.

Several companies were testing similar drugs, but none were approved by the FDA for use outside of clinical trials.

BioMarin Pharmaceutical had reported promising results for its version, BMN-673, in a press release aimed at investors and financial media.

Sloan met all of the FDA’s requirements for compassionate use. When she initially contacted the agency, she was told there were no safety concerns about the drug, and her application would quickly be approved once BioMarin agreed.

The company refused.

BioMarin officials would not answer basic questions, including whom Sloan could talk to about applying for compassionate use, according to Sloan’s close friend Michelle Wittenburg, who helped her navigate the compassionate use application process.

“They just summarily turned her down,” Wittenburg told the Goldwater Institute. “She asked and they said no, all the while telling their shareholders in investment meetings and documents that they were the best thing since sliced bread and the highest performers in this classification of drugs.”

Frustrated and running out of options, Sloan launched a social media campaign to pressure the company to stop stonewalling and allow her compassionate use access to BMN-673. Sloan also started a Change.org petition that eventually received about 200,000 supporters. Her battles with cancer and BioMarin eventually became national news and attracted the attention of elected officials in Texas,

including Congressman McCaul, who authored a compassionate use reform bill he called the Andrea Sloan CURE Act.

“I do have to tell you that I’m a little frustrated at our inability to have an open dialogue about how we might be able to get to a solution that both advances your goals of making sure that this treatment is available to everyone and advances my goal of saving my life,” Sloan said in a video she recorded in September 2013, aimed at BioMarin CEO Jean-Jacques Bienaime.

‘Spoiled, Petulant Brat’

Things turned ugly when Bienaime responded directly to Sloan supporters. In one email, he decried “a sorry illustration of the risks associated with politics and lobbying taking precedent (sic) over science.”

In another, he forwarded a message from someone else saying Sloan “comes across in the media as a spoiled, petulant brat!”

A third and apparently internal email that reached a Sloan supporter discussed the need to hire a public relations agency. The company was more reserved in official statements to the media.

“It’s our policy to provide access to unapproved drugs only after substantial evidence on safety and efficacy has been collected, and registration applications with health authorities are underway,” spokeswoman Debra Charlesworth told the International Business Times. “The FDA has not approved the drug for compassionate use.”

She did not say whether BioMarin had ever sought approval.

A social media campaign was not something Sloan wanted to launch, Wittenburg said. She was by nature a private person, so going public was not easy for her, especially to talk about terminal ovarian cancer.

But BioMarin’s absolute refusal to even talk about her options left her no choice.

“You only pull those triggers when you have to,” Wittenburg said. “If there was a more expeditious compassionate use, a more navigable and expeditious grant of drugs for someone who is legitimately qualified, those things would never be in the press and people would never know.”

A different company developing a similar drug did agree to supply it to Sloan about October 2013, on the condition that its name not be disclosed. Nearly three months had passed since she first sought compassionate use treatment.

Sloan responded well at first. But she developed pneumonia, which her body was too weak to fight off. She died on January 1, 2014.

“A company took a chance on her. They gave her the drug and it worked,” Wittenburg said. “That is

wonderful. It is sad that she did not get it in a timely manner because of the rigmarole of the system. We were all clumsy and cumbersome at navigating the system because nobody really totally knew what you needed to do.

“Any delay in time like that when you’re terminal, it’s a sure-fire killer.”

BioMarin sold the rights to BMN-673, now called talazoparib, to Medivation in August 2015, for \$410 million and up to \$160 million in additional milestone and royalty payments.

Sloan would be included in the FDA’s 99.5 percent approval rate for compassionate use, despite BioMarin’s rejection of her requests. Another drug company did allow treatment, even though it came too late to save her life.

Balancing the Risks

After a dying patient finds a doctor and drug company to endorse an application for compassionate use, the final hurdle is to get the blessing of the FDA, which has its own set of rules.

The FDA will determine whether the patient qualifies for an ongoing clinical trial. If not, FDA officials must agree that the risks of the disease outweigh the risk of administering a treatment that has not been fully tested and approved.

The FDA also must be satisfied that treating an individual patient or a small group of patients will not interfere with ongoing or future trials.

Only then will it approve an application and allow a patient to be treated.

The time and expense of clinical trials created the need for compassionate use.

The FDA has two missions when it comes to approving a new drug: getting genuine cures to the public as quickly as possible, and preventing unsafe or ineffective drugs from being sold.

The risk-averse culture at the FDA puts those two missions in conflict, according to critics who say agency officials are more worried about approving an ineffective drug than getting real cures to patients.

If the FDA approves a drug that does not work or has unforeseen side effects, the agency risks a barrage of negative media stories and congressional hearings punctuated by anecdotes from patients who were harmed. Failing to approve an effective drug may mean more people will die for lack of treatment, but those deaths are harder to quantify, and will not happen until sometime in the future.

“When promising treatments are kept off the market, the patients who fail to benefit go unseen,” Avik Roy, founder of a health care investment research firm and a senior fellow at the Manhattan Institute,

observed in a 2012 analysis of how FDA regulations stifle innovation in the drug industry. “What is seen, by contrast, are concerns about drugs that were approved by the agency and later turned out to pose problems. When this happens, FDA officials are often hauled before Congress and asked to defend their decisions. At the agency, expeditious approval of innovative drugs is risky; excessive caution is not.”

Roy would not agree to an interview.

Risk Aversion

The very power of the FDA to regulate the effectiveness of drugs was borne from risk aversion.

Drugs were essentially unregulated until 1902, when in response to a series of deaths caused by a diphtheria vaccine, Congress passed the Biologics Control Act. Four years later, it passed the Pure Food and Drug Act that prohibited false or misleading labeling on food and drugs.

Modern FDA regulation began in 1962, in response to birth defects linked to mothers who had taken the drug Thalidomide to ease morning sickness.

Most of those occurred in Europe, where the drug was commonly used. In the United States, use of Thalidomide had been blocked by a single FDA doctor, Frances Oldham Kelsey, who worried about possible side effects.

Because of Kelsey’s persistence, the drug was not sold in the United States.

Kelsey was hailed as a hero who had saved countless children from horrible disfigurement, and was presented the nation’s highest civilian award by President Kennedy at a White House ceremony.

Congress also responded by granting the FDA its modern power to control both the safety and effectiveness of new drugs. To prove a new drug worked, manufacturers were required to submit to the FDA data from “adequate and well controlled investigations.”

They were also required to report adverse reactions to the FDA. The testing process established by the FDA was a simpler version of the trials in use today. But they still delayed the time it took to bring a new treatment to market, and drove up the costs necessary to begin selling the product.

Then came the AIDS crisis of the 1980s.

People were dying of the previously unknown disease. There was no FDA-approved treatment to cure it or vaccine to prevent it.

A drug known as AZT, originally developed to treat leukemia, was tested on patients with the Human Immunodeficiency Virus, or HIV, which causes AIDS. However, the drug had not been approved by the FDA, and therefore was not available under the laws at the time.



“Any delay in time like that when you’re terminal, it’s a sure-fire killer.”

Intense political pressure prompted the FDA to revise its practices, and AZT was made available to AIDS patients. Soon patients with other incurable conditions, including cancer, were lobbying for expanded access to investigational medications.

Compassionate use was put into law in 1987, and in 2009 the FDA adopted rules that created the modern expanded access program.

Political pressure changed the law. But it did not change the mindset at the FDA.

“Every FDA reviewer wanted to be the next Frances Kelsey,” wrote Dr. Scott Gottlieb, a former deputy commissioner of the FDA and a resident fellow at the American Enterprise Institute, in a 2012 article on the agency’s risk-averse culture.

“The episode had a lasting effect on the FDA’s work,” wrote Gottlieb. “It fostered an idealization of the lone reviewer championing an issue of safety against the prevailing orthodoxies, especially when it meant taking on corporate interests.”

PHASES OF TESTING

Clinical trials are divided into three and sometimes four phases, not including the initial research and animal testing.

In phase 1, the new drug is given to a small group of healthy volunteers, usually between 20 and 100, to determine if it is safe enough to continue testing. This involves monitoring patients for side effects and gaining initial information on dosage levels.

Phase 2 is where the drug’s effectiveness is tested. Those trials normally include a few hundred patients with the disease the drug is meant to treat. Appropriate dosing levels are refined and the product is further evaluated for potential safety risks and side effects.

Phase 3 trials involve hundreds or potentially thousands of patients with the disease. Additional safety and efficacy information is gathered to determine whether the risk of the medicine is outweighed by the risk of the disease, and whether the new drug is better than existing treatments.

In some cases, a Phase 4 trial is required to continue monitoring the side effects and effectiveness of the drug after it is approved for sale.

Failure in any phase of trials can mean failure of the product and the company that makes it.

Adverse events in any phase of the trial must be reported to the FDA, which at any time can halt the trials, require the protocols to be rewritten, or impose additional screening, testing, or monitoring requirements.

After all clinical trials are completed, a final New Drug Application is filed with the FDA, which spends months, sometimes more than a year, to decide if there is sufficient data to declare the drug safe and effective. Only then can a new medicine be made available to doctors for prescription, and sold for use in patients.

The whole process takes more than a decade on average, according to the Pharmaceutical Research and Manufacturers of America (PhRMA), an industry trade and lobbying group.

Hitting a Bullet

Once a drug has been approved for any condition, doctors can prescribe it as they like through what is called “off label” use. That means if a drug has been proven effective in fighting, for instance, one type of cancer, doctors can use it to treat a different type without restrictions.

With everything riding on clinical trials, drug companies do everything they can to ensure trials are completed as quickly and predictably as possible. They select patients based on rigid criteria regarding health, age, stage of disease and other conditions to remove as many variables as possible that could lead to unforeseen reactions. Companies also select test subjects most likely to show positive results, since gaining approval for a single condition is all that is needed to take drugs to market for either the targeted disease or any off-label use doctors later deem fit, said Walker of the Abigail Alliance.

“They are literally trying to hit a bullet with a bullet when they design a clinical trial,” Walker said. “They try to pick a very narrow population of patients that they believe gives them the greatest chance of hitting a

very small statistical target at the lowest cost and in the shortest amount of time to get that very first indication.”

The consequence of that is many patients with terminal conditions do not qualify for clinical trials because they are too sick or have other conditions unrelated to the disease itself.

And since drug companies often try to ensure the patients they approve for compassionate use are statistically similar to those in clinical trials, someone in an advanced stage of the disease is especially unlikely to be approved for treatment, Walker said.

Kurzrock, the UC San Diego oncologist who used to run clinical trials at MD Anderson, recounted one case in which she sought compassionate use for a 19-year-old woman who was dying of cancer and deteriorating quickly. All conventional treatments had proved ineffective, and Kurzrock was familiar with a particular drug she hoped could save the woman's life. When she contacted the drug company, she was told compassionate use would only be allowed if the patient had perfect organ function.

Fortunately she did, and was approved for treatment.

Conditions like those, coupled with the convoluted process doctors must go through to file an application, can mean the difference between life and death, Kurzrock said.

“Sometimes an alternative today may not be viable next week, especially if compassionate use demands, as in the example I gave, that the patient maintain near perfect organ function,” Kurzrock said. “Perfect or near perfect organ function is not typical for people dying of cancer. A clinically irrelevant blip in a blood test can make the patient ineligible.”

‘You’re in a Slaughter’

Just such a blip could kill Mike DeBartoli.

For 28 years, DeBartoli worked as a firefighter, most of it in Sacramento. About three years ago, he returned to the station after a fire and noticed cramps in his hand, not an uncommon ailment given his profession.

But the pain persisted. Over the next several weeks, the cramps got worse. Then his fingers began twitching. He thought he might have nerve damage.

What doctors eventually told him could not have been worse.

DeBartoli had amyotrophic lateral sclerosis, or ALS, more commonly known as Lou Gehrig's disease because that is what killed the baseball star.

ALS is 100 percent fatal.

There is no cure or effective treatment.

Before he dies, his body will deteriorate and he will no longer be able to care for himself.

His life expectancy could be anywhere from six months to five years.

There was nothing doctors could do.

“You don't know how devastating it is to face your own death,” DeBartoli told the Goldwater Institute in a recent interview. “You're in no battle. You're in a slaughter. You have nothing to fight against this disease and you just get massacred by it, and you are supposed to just sit there and wait.”

The only glimmer of hope for DeBartoli was enrollment in a clinical trial for new drugs being developed to slow the progression of ALS. He tried unsuccessfully to get into several.

He was rejected for one study because his disease was too far advanced.

Another turned him down because he took medicine for high blood pressure and depression.

Drug companies want people who are “pure” so they can get the test results they need to get their



Michael DeBartoli

products approved, DeBartoli said. Those unlucky enough to fall outside the statistical models are left to die.

"They're just studying the drug," he said. "They're not trying to make you better."

Debartoli was finally accepted into a clinical trial for an investigational drug that may slow the progression of the disease, which he began taking in December. He doesn't know whether it's working.

'Horror Story Stuff'

DeBartoli still has another worry: placebos.

The standard way to test a drug's effectiveness is to give it only to some of the volunteers being tested. The rest get placebos (sugar pills, basically) or are treated with existing therapies that may not be effective. A drug's success is determined by whether the patients who get the real drug do substantially better than those who don't.

"What we do is ghoulish; it's horror story stuff," said Walker of the Abigail Alliance. "If you are in one of the trials you are a lab rat. They are going to put you on a sugar pill, and wait for you to die on the schedule of an untreated patient for the good of science They are willing to waste you to answer a statistical question."

One criticism of both compassionate use and Right to Try laws often cited by the pharmaceutical industry is that clinical trials could be endangered if too many patients seek treatment through those means. It is couched in terms of the greater good. If people don't enroll in clinical trials, it will take longer for the drug to receive FDA approval and be made available to all patients with a particular disease. That means more people in the future will die because of delays caused by efforts to treat patients today.

"While PhRMA has not taken a position on any of the state or federal expanded access or 'right to try' proposals, we have serious concerns with any approach to make investigational medicines available that seeks to bypass the oversight of the Food and Drug Administration and clinical trial process, which is not in the best interest of patients and public health," Sascha Haverfield, vice president of Scientific and Regulatory Affairs at PhRMA, said in an emailed statement to the Goldwater Institute.

No one from PhRMA would agree to an interview.

The industry's arguments are bogus, said Frank Burroughs, who cofounded the Abigail Alliance with Walker after Burroughs' 21-year-old daughter Abigail died of cancer in 2001.

Drug companies typically pay for the treatment of patients in clinical trials, a powerful incentive to enroll.

The main thing that discourages people from participating is the reliance on placebos, which for most life-threatening diseases are not needed, Burroughs said.

Modern technology allows doctors to monitor things like tumor shrinkage in cancer patients. Yet the FDA's model has remained relatively unchanged since its inception in the 1960s, Burroughs said. Also, doctors and scientists already know the natural progression of most terminal diseases like lung cancer, so it makes no sense to continue giving patients placebos to come up with a statistical equation on the death rate of those left untreated.

"If you have a drug that is efficacious in clinical trials, you have people whose length of their lives is sacrificed for an unnecessary placebo arm," Burroughs said.

Barrier to Entry

The time and expense of clinical trials means most small companies will be unable to take their product all the way from invention to approval, regardless of its success, according to industry financial analysts and some drug company executives. So at some point they are forced to partner with or sell to one of the big players in the drug industry, which have the money and regulatory expertise to complete clinical trials and navigate the FDA's approval process.

And that's the way big pharmaceutical companies like it, critics say.

"The barrier to entry is maintained by Big Pharma," said Woods, who holds over 40 patents for medical devices. "They like it that way. They have the money to go and pick and choose what they want to buy. A mom-and-pop company has no chance of coming up and competing against my billion-dollar cancer drug unless I decide to buy it myself, because they can't do it without me. So they definitely want to maintain the status quo. It's in their interest because it will prevent competition."

Only about 12 percent of the new drugs that enter clinical trials will ever be approved by the FDA for sale, according to PhRMA. Of those, about 20 percent generate enough money to cover the cost of research, testing, and approval.

Cost estimates vary. A Tufts University study, published in 2014 and frequently cited by PhRMA, says the real cost of developing a new drug is about \$2.6 billion on average, including about \$1.4 billion in actual out-of-pocket expenses paid by the drug developer. Another \$1.2 billion represents the lost revenue investors forego because of the long development timeline.

The most expensive part of the process is Phase 3 testing, which accounts for up to 90 percent of the development costs of those drugs that are eventually approved and marketed, according to Avik Roy of the Manhattan Institute.

New Business Plan

The ever-increasing cost and complexity of clinical trials spawned a new business model for the pharmaceutical industry, said Mark Pauly, professor of health care management, business economics, and public policy at the Wharton business school.

Twenty years ago, big pharmaceutical manufacturers were in the drug development business from start to finish. They had their own scientists who would develop a new product, and would run their own clinical trials through all phases and apply for final FDA approval before manufacturing and selling their drugs.

That proved to be an inefficient way of doing business because of high failure rates in early stages of testing, Pauly said.

So rather than inventing their own new cures, most big companies now favor allowing the early research and testing to be done at smaller firms that will invent the new product and take it through sufficient testing in clinical trials to show it is both safe in humans and more effective than existing treatments.

Once that has been proven, and there is a strong likelihood the new drug will be approved and turn a profit, the big companies will buy the patent rights or the company itself.

From the small company's perspective, there is little chance they will be able to raise the billions of dollars needed to get their products through all phases of testing, particularly Phase 3, since investors are not likely to wait a decade or more before the firm can begin selling the drug and turn a profit.

"Once the product gets to a stage where it does show sufficient promise, usually in Phase 2, then at that point there's this large mountain to climb of FDA approval and Big Pharma knows how to do that," Pauly said of the small companies developing new drugs. "They are mostly founded by scientists, occasionally with a visionary venture capitalist. They are not good at dealing with large entities. Now they come face-to-face with that big bureaucracy in the form of the FDA, and they have to be able to cope with that alternative environment."

High research and development costs are driving record levels of mergers and acquisitions in the pharmaceutical industry, according to reports from Fitch.

There are exceptions.

Some big drug makers still develop and test their own products.

Overall, about 20 percent of the clinical trials for new cancer drugs are being run by the world's 15 largest pharmaceutical companies, according to a Goldwater Institute analysis of a list of investigational cancer drugs published by PhRMA.

There are also some small companies that have taken their products through the regulatory process and become major players in the industry. But those are rare exceptions, according to industry experts.

Bells and Whistles

The new business model works only because of the time and expense of getting through clinical trials and FDA approval, said Garo Armen, chairman and chief executive of Agenus Inc. Smaller companies may have a better drug, but not the money or regulatory expertise to navigate the federal bureaucracy.

"Are Big Pharma companies sitting down and coming up with this conspiracy? The answer is they are too dumb to do that," Armen said. "Is all of this happening by default? The answer is yes. Of course it's happening by default. It's the sweet spot that's been created organically because of all the bells and whistles within the system. Do you think Big Pharma is going to protest against it? Hell no, because it's helping them."

Pauly agreed that big pharmaceutical companies have an interest in preserving the status quo, since it allows them to avoid early research failures and cherry-pick the most promising new drugs.

"It's certainly true that Big Pharma, which has a lot of expertise in that model, is not particularly eager to see alternative ways of generating information about the effectiveness and safety of drugs brought into existence," Pauly said.

Big pharmaceutical companies have more than the expertise needed to navigate the FDA's regulatory system. They have the political muscle to preserve it.

The pharmaceutical and health products industry is by far the biggest spender in federal lobbying, with expenditures of more than \$235 million in 2015, according to data compiled by the Center for Responsive Politics. PhRMA alone spent about \$18.5 million.

One consequence of the industry's new business model is it is even harder for people to get compassionate use access to new drugs in early testing. Smaller drug companies are the ones least likely to have the money or expertise to make their products available through compassionate use. They also run greater risk since they are often reliant on one or two products, and are subject to the whims of investors who may panic if there is any glitch in clinical trials.

"They are generally on a much shorter leash," Pauly said of small drug companies. "Even now there's a lot of money sloshing around at Big Pharma firms, and they can use it to cover the administrative expenses of doing the compassionate use part."

"In some ways, the fundamental question is why would a profit-seeking firm do compassionate use at all? The answer, in large part, is because they

want to curry favor, produce a good reputational effect. But that's a luxury that many small firms really can't indulge in. Nobody's going to remember their brand name anyway. For the most part, a good reputation is more important for a Merck or a Pfizer than it is for XYZ Pharma."

Obvious Risks

The current structure of the drug industry and pressure from investors does make it tough for small companies developing promising new products to treat patients through compassionate use, said Robert Erwin, president of iBio, Inc., a small firm developing treatments and vaccines using plant-based proteins.

Money is always tight. There is always the fear that if something bad happens, it could harm the clinical trials or scare away investors, Erwin said, adding he believes those fears are overblown.

Executives at small companies also tend to play it safe because that's what investors expect.

Their natural inclination is to say no.

"From the perspective of a small company, the deviation from the standard accepted practice is difficult because they have to deal with investor psychology," Erwin told the Goldwater Institute. "There's a lot of comfort in doing what everybody else is doing. So more than the actual economic analysis or an actual risk analysis, that comfort of not deviating from the standard is part of the psychological problem."

Erwin has seen the compassionate use debate from all sides. He spent his career as an executive in pharmaceutical companies. He came face-to-face with the hurdles of getting potentially lifesaving treatment when his wife, Marti Nelson, developed breast cancer.

Nelson, a practicing physician, underwent the standard treatments. After they all failed, she sought access to a drug then under investigation through compassionate use, but she was rejected after what Erwin called "the classic runaround."

Nelson died in 1994 after she and Erwin cofounded the Marti Nelson Cancer Foundation, which helps patients navigate the complicated process of seeking early access to drugs that are still being tested.

Erwin, president of the foundation, also advises patient advocacy groups on technical aspects of the drug industry, and sometimes helps drug makers develop their own compassionate use programs, all without charge.

Hidden Rewards

Despite the risks, Erwin now preaches to drug companies about the hidden benefits of participating in compassionate use. It allows executives and researchers to talk about their products in ways they

otherwise could not because of the confidentiality of clinical trials and the federal rules restricting what companies can say to investors, Erwin said.

Success in treating otherwise untreatable patients can create a buzz among doctors and patient support groups, especially those who specialize in rare or incurable diseases.

That is why when big drug makers set up a compassionate use program, they typically will bring in both medical and marketing people, he said.

"They started to see expanded access as a potential marketing tool," Erwin said. "Companies began to see that operating expanded access was a way to tout their product long before it was FDA approved, to communicate with thought leaders in their market, and to begin cultivating some experience with the product beyond the fairly narrow criteria of the clinical trial population."

The short-term benefit from success is heightened investor interest. It can also make it easier to recruit volunteers for clinical trials. The long-term interest is a built-in brand acceptance of the product when it is eventually approved and sold.

Yet Erwin acknowledges the downsides, including fear of how adverse events will affect clinical trials or public perception if a patient dies.

Even if an adverse event does not cause problems with the FDA, it would likely be something a small company would have to disclose to investors, which can make it harder to raise money, Erwin said.

For a big drug maker with dozens of different products, a single patient death involving one investigational drug would not pose a major threat to its financial health. But it could devastate a small company that has only one or two products, and would have to be reported in its SEC filings.

That is often used as an excuse by industry executives and corporate boards unwilling to participate in compassionate use out of fear that such treatment could disclose problems with their product, Erwin said.

In any case, the inclination of executives at small drug companies is still to say no unless there is a strong advocate on the inside pushing for expanded access.

"It takes somebody to go and present a rationale that they can look at in business terms backed by scientific evidence that the rationale makes sense in the context of their particular product," Erwin said.

"I view it as a judgment call evaluating risks versus benefits ... The problem is a fundamental problem that we're never going to be able to address very well, and that's this risk/benefit analysis and when in the process it shifts enough for a company to see it as a favorable prospect."

Right To Try

Changing that risk and reward equation is not easy.

Even small attempts at reform have drawn stiff opposition from big drug manufacturers and less-than-enthusiastic responses from the FDA.

State Right to Try laws are an effort to bypass the federal bureaucracy by using state laws to give dying patients better access to investigational medications. Pushed by the Goldwater Institute and patient advocacy groups, the laws have been adopted in 24 states, always with bipartisan support and virtually no opposition from lawmakers.

States have broad powers to regulate health and safety issues, including the licensing of doctors and hospitals. Under Right to Try, patients, doctors, and drug companies decide whether a patient has access to a drug being tested in clinical trials if certain requirements are met. The FDA does not have veto power.

The requirements to qualify for Right to Try vary slightly by state, but are similar to the federal compassionate use requirements.

Only a patient who has a terminal illness and has considered all available FDA-approved treatments can receive investigational medicines under Right to Try. A doctor must agree that the investigational product represents the patient's best chance at survival.

Only drugs that have been shown safe enough to continue testing after Phase 1 clinical trials can be used, and those trials must be ongoing for them to continue to qualify.

Drug companies are not obligated to provide their products, and can charge for the cost of making and administering the treatments.

Patients must sign an informed consent form saying they understand the risks of using a drug that is not yet approved, and agreeing not to sue.

Insurance companies are not required to pay for the care.

No approval is needed from the FDA.

There are other differences between Right to Try and federal compassionate use. Institutional Review Boards do not need to approve treatment under most of the state laws, and patients are required only to have considered all FDA-approved treatment options, not to have tried them.

Critics, including the FDA, warn that treatment with medications that have not been fully tested through clinical trials can be dangerous and could do patients more harm than good.

But Darcy Olsen, president and chief executive officer of the Goldwater Institute, counters that the basic safety of the drugs is established in Phase 1 trials before they are available under Right to Try. The medications dispensed to patients under the law are the same ones now being given to patients in clinical trials.

"The risks are exactly the same as they are for patients who get into clinical trials," said Olsen, author of the book The Right to Try. "For patients suffering from conditions for which there is no approved known cure, the FDA's traditional role of protecting patients from drugs and devices that have not yet proven effective has little meaning. These medications have already been deemed safe enough to enlarge the group of patients involved in the clinical trial to several hundred or even several thousand individuals."

Both supporters and skeptics of Right to Try laws say drug companies are unlikely to make their products available under state laws alone. They are unwilling to risk the wrath of the FDA, which has absolute power to prevent their new drug from being approved and sold commercially.

"They ain't going to do it," Caplan said. "In the real world it's never going to happen. And the other problem in the world of really getting access, until you give them some incentive, they're not going to do it. There are a few companies with nice leaders and nice boards who would say, 'Okay, we're going to try and do this a little bit.' But for the most part they're like, 'This is getting me delayed, slowed. I'm not paid. I can't deal with this.'"

Changing the Equation

Olsen believes changes in federal law may be required before there is widespread treatment of dying patients with investigational medications under Right to Try or federal compassionate use. Those changes should remove the risks drug companies face and create positive incentives to participate, such as allowing them to charge for their products and making drugs more available to desperate patients while they are still being tested and monitored.

Similar laws have been in place in Europe for more than 20 years, she said.

Rep. Matt Salmon, R-Ariz., introduced a bill last year that would prohibit the federal government from interfering with the use of investigational drugs on dying patients under state laws. The bill, which now has five cosponsors, was referred to two House committees, but neither has held a hearing on the proposal.

There are other federal proposals that would make simple fixes to the system.

Rep. McCaul, the Texas congressman, is trying to force the FDA to issue formal guidance on how it treats adverse events in compassionate use cases. His bill would require the FDA to "clearly define" how it interprets those events.

That bill is unlikely to pass. However, the provision was included in a broader reform bill called the 21st Century Cures Act that has bipartisan support and better odds at becoming law.

Another McCaul proposal that made it into the omnibus bill would require drug companies seeking expedited review of their applications under various FDA programs to publicly disclose their compassionate use policies. It does not dictate what the policy must be, only that the company have one.

Weight of Evidence

McCaul's provisions seek to ease some of the drug industry's worry about participating in compassionate use, but they would not create positive incentives.

Rep. Morgan Griffith, R-Va., is trying to do that by taking the FDA largely out of the business of regulating compassionate use.

Griffith has written two bills to allow certain lifesaving drugs in early clinical trials to be prescribed to dying patients. One prohibits the FDA and other federal agencies from interfering with the dispensing, sale, or importation of investigational drugs or devices to terminally ill patients. The other bill is similar but adds restrictions regarding which drugs can be dispensed.

Both proposals curb the FDA's ability to force drug companies to report adverse events, which would help remove some of the risk of participating in compassionate use.

Griffith believes the best approach would be to allow both good and bad outcomes to be weighed equally as anecdotal evidence to supplement data from clinical trials. That would begin to create incentives for drug companies that really have developed an innovative treatment to help dying patients, because success could help them in clinical trials.

"We need to be able to say that, good or bad, it comes into the evidence," said Griffith, a lawyer by trade. "The weight of the evidence will clearly be much lower than it would from a clinical trial. But the evidence comes in. Right now the negative evidence is at least believed to be used by the FDA, but none of the positive evidence is. So if you let all of it in, the positive and the negative, and have it at a lower level than a clinical trial, it's still a part of the report and a part of the process, then you have some benefit."

Big pharmaceutical companies oppose Griffith's bills. Industry representatives have told him the current clinical trials system "is the gold standard of drug regulations and we don't want to mess with that," he said.

"I really have a hard time understanding it. Since I can't understand it, I really can't come up with what their motivation would be."

Raising the Rewards

Griffith's concept is not new. A similar approach was endorsed by the FDA's own science and technology subcommittee in 2007, and, on a more limited basis, by the President's Council of Advisors on Science and Technology in 2012.

Bipartisan bills have been introduced in Congress to create provisional approval since at least 2005.

The idea is to allow certain drugs that are superior to existing treatments to be prescribed by doctors and sold to terminal patients after they have been shown safe through Phase 1 testing in clinical trials. The testing would have to continue for a drug to be available on a provisional basis, and the drug would still need to go through the standard FDA approval process before it could be prescribed and sold to the general population.

Doctors would be able to normally prescribe the medication to patients who meet the requirements, which are similar to those for patients seeking compassionate use. No approval would be required by the FDA or an institutional review board.

Drug companies could charge for the products, allowing them to begin recouping the cost of developing the drug and paying to take it through clinical trials.

If done right, insurance companies would also pay for treatment since the investigational drug would be prescribed like any other approved medication, said Burroughs of the Abigail Alliance.

Details of various proposals vary. Some would allow provisional approval only after Phase 2 testing. Others would allow only drugs that have received an expedited designation from the FDA to be available to patients.

But conceptually, provisional approval would allow dying patients early access to potentially lifesaving drugs, allow doctors to treat patients without going through the FDA's red tape, and create a financial incentive for drug companies to participate, according to Carla Woods, who produced a documentary called Fight to Live, which describes how the current compassionate use system prevents dying patients from getting the care they need.

In the existing system, small drug developers have to raise money from investors who know there will not be any income from a particular product until it passes clinical trials and is approved for sale by the FDA, Woods said. Under provisional approval, companies could begin making at least some money from a product after early testing; in three to five years instead of 10 to 15. That money could be used to finance subsequent clinical trials, and create an early income stream for investors.

DOA

That means small drug companies would no longer be forced to sell the rights to their most promising products to the big players who are the only ones able to afford the billions of dollars needed to complete Phase 3 testing and get FDA approval under the existing system.

That would completely reshape the pharmaceutical industry. And that's why big pharmaceutical companies will do everything they can to prevent it, Woods said, calling it "a game changer" for the industry.

"They will no longer be dependent on getting to market at the whims of Big Pharma," Woods said of small drug developers. "If an independent company gets to market without them, then Big Pharma's existing products are threatened. Thus, Big Pharma will do anything to prevent this from happening."

There are other advantages, both financial and regulatory, supporters say.

It would do away with the "all or nothing" approach that often forces drug developers to abandon promising treatments for financial rather than medical reasons, said Roy of the Manhattan Institute, who advocates provisional approval of a broader class of medications after Phase 2 testing.

Provisional approval would also allow data to be collected on both the benefits and risks of a new drug in a broader population than is available in the statistically controlled clinical trials, according to an analysis from Strategy&, a consulting subsidiary of PricewaterhouseCoopers.

Calling their plan "real-world evidence," Strategy& recommends allowing drugs to be prescribed normally after basic safety and effectiveness have been established,

sometime during traditional Phase 2 testing. Data collection would continue, but instead of expensive, lengthy, and highly structured Phase 3 testing, data would be generated by monitoring the much larger population of patients in the real world.

That would reduce the time it takes to bring a new cure to market by about five years, and cut the cost by about 60 percent, according to Strategy&.

It would be no more risky than traditional Phase 3 testing, because rare safety issues even now are missed before a product is approved, thanks to the limited sample sizes in clinical trials.

There are other proposals to create incentives for drug companies to participate in compassionate use, such as expediting the FDA's review of their drugs or extending their exclusive patents once the products are approved for sale.

One Last Shot

Something needs to change, said Mike DeBartoli, the California firefighter who knows he faces a slow and debilitating death from Lou Gehrig's disease if he is not allowed at least to try the new treatments that could bring hope.

The current system is a death sentence, he said.

"I have no hope now. I will take false hope," DeBartoli said. "To live the rest of my life knowing that I'm not even given a shot. What is that?"

"I don't know who the FDA thinks they are protecting. Who are they to tell me what I should be hopeful for or not hopeful for? You're telling me you won't approve me to take a possible medication that doesn't hurt me, that will possibly save my life, because you want to have your fingers in it? I just don't understand it." ●





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