“Right to Try” Legislation Moving Through Congress
But Drug Companies and Some Patient Groups Want Changes

Stephen Barlas

The aggressive social media campaign launched by the family of Josh Hardy in 2014 gave a kick-start to new pressure on states to let terminally ill patients obtain access to unapproved therapies in phase 1 trials. The Hardy “stimulus” to the “Right to Try” (RTT) movement resulted in numerous states—Pennsylvania just made it 38—passing various iterations of such laws. These state laws have now created pressure in Washington for Congress to follow up with a federal law, which would remove some of the obstacles erected by the Food and Drug Administration (FDA) that RTT advocates say prevent pharmaceutical companies from initiating or expanding compassionate care programs.

But it is a very odd exercise in congressional sausage-making because most patient advocacy groups that represent the terminally ill and the drug industry virulently oppose the RTT bill passed by a 94–1 vote in the House and apparently on its way to similar passage in the Senate. The patient groups are concerned that the bill dispenses with the current requirement that the FDA approve a request from a patient’s physician, a request already approved by the drug company offering the investigational drug.

“NORD [National Organization for Rare Disorders] and most other patient organizations that represent individuals who seek access to investigational therapies outside of clinical trials oppose Right to Try,” explains Paul Mehlmeyer, Director of Federal Relations for NORD. “This is because Right to Try will not succeed in increasing access to investigational therapies. Removing the FDA from the approval process potentially opens the door for nefarious companies or individuals to take advantage of our patients. This bill solves nothing and will likely do more harm than good.”

The press secretary for Senator Ron Johnson (R-Wisconsin), sponsor of the Senate bill, did not respond to a request for a list of patient advocacy organizations supporting his Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017.1 That bill has been promoted by the Goldwater Institute, a conservative group. Naomi Lopez Bauman, Director of Healthcare Policy for the Goldwater Institute, says, “When fewer than one-half of 1% of terminal patients can access the system, the system is clearly not working. These state laws not only restore patient autonomy, but make the system more equitable so that more patients—not just a select few who are wealthy, well-connected, or lucky enough to get into a trial—can try to save their own lives.”

The Biotechnology Innovation Organization (BIO), the trade group that represents many smaller biopharmaceutical companies, especially those involved in biologics, also opposes the bill. It is not clear whether the Senate bill—which has a House counterpart that was recently the subject of House hearings2—would improve the current FDA expanded access program that has been in existence since 1987 and has been upgraded administratively a number of times, including recently. But the apparent problem is not the current FDA program, but other FDA policies that serve as a disincentive to companies that might otherwise establish expanded access programs.

Seven-year-old Josh Hardy was a patient at St. Jude Children’s Hospital in Memphis in February 2014. He had been diagnosed at the age of 9 months with a malignant, highly aggressive, and rare form of kidney cancer. In November 2013, a bone marrow biopsy revealed that he had a bone marrow failure. After a bone marrow transplant, he was moved to the intensive care unit for heart failure and five days later was put on a ventilator. He then developed an adenovirus infection as a result of his compromised immune system. His physicians asked Chimerix, Inc., to provide brincidofovir, which the company was developing to prevent the reactivation of cytomegalovirus in bone marrow stem cell transplant recipients. Chimerix had started an expanded access program in 2009 and widened it substantially in 2011 after receiving an $88 million grant from the Biomedical Research Advanced Development Authority for a 200-person trial. But when that funding ended in 2012, Chimerix closed the expanded access program for brincidofovir to focus its resources on the formal regulatory approval process. For that reason, Chimerix twice denied the Hardy request and all others like it. The company provided brincidofovir to 430 individuals prior to closing the expanded access program in 2012 and denied the drug to more than 300 additional patients after that date, according to Kenneth Moch, President and Chief Executive Officer of Cognition Therapeutics, Inc. Moch was Chimerix’s president during the 2009–2014 period. He related the pressure Chimerix was under as a result of the Hardy request at the House health subcommittee hearings in September.

The denial to Hardy set off a social media campaign by Josh’s family, which included a Facebook page and Twitter campaign called “#SaveJosh.” Major media coverage resulted, which painted Chimerix as a villain. CNN’s print headline was “Company Denies Drug to Dying Child.”10 Fox News carried the headline “Company Denies Drug to 7-Year-Old Boy Struggling Against Curable Virus.”11 Ultimately, as a result of conversations with the FDA, Chimerix announced in a press release that “it has reached agreement with the FDA for the immediate initiation of a pilot trial of open-label brincidofovir for the treatment of adenovirus infections in immunocompromised patients. … This study is expected to begin with Josh Hardy as the first patient enrolled on Wednesday, March 12, 2014.”

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Minor improvements in the FDA's expanded access program. The 21st Century Cures bill Congress passed in 2016 made some changes, but the process is not clear. The FDA is expected to do its best to provide access to investigational drugs. However, even with that protection, some companies and others have argued that big expanded access programs lead to smaller clinical trials, which diminish the incentive for terminally ill patients to enroll in the latter.

Moreover, the pharmaceutical industry worries the FDA will use adverse reactions suffered in expanded access programs as an element when considering a new drug application (NDA). For example, according to a study using FDA data, there were only two instances from 2005 to 2014 in which adverse events from expanded access programs led to the FDA from using data from an expanded access program as an element when considering a new drug application (NDA). What none of the state laws do is require drug companies to establish expanded access programs or to approve applications once they are received.

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The Goldwater Institute had been pushing for state adoption of RTT laws prior to the Hardy campaign, though the young boy’s plight resulted in an avalanche of new states succumbing to the Goldwater Institute’s efforts. Today 38 states have what are referred to as Right to Try laws, which, in fact, don’t give terminal patients any “right” at all. Under these state laws, if you have a terminal diagnosis and you have exhausted all other options, you may seek, under your doctor’s care, investigational treatments that have passed phase 1 of FDA clinical trials and are continuing to undergo FDA evaluation. These laws provide liability and licensing protections for manufacturers and providers under state law if an adverse event—such as a serious reaction to a treatment—occurs in patients who were allowed access to investigational drugs. However, even with that protection, some companies and others have argued that big expanded access programs lead to smaller clinical trials, which diminish the incentive for terminally ill patients to enroll in the latter.

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“Right to Try legislation provides nothing to patients except the right not to be barred from seeking access to experimental products,” said Andrew McFadyen, Executive Director of the Isaac Foundation, who appeared before the Senate Committee on Homeland Security and Governmental Affairs at hearings in September 2016. “Legislation has, however, created a misguided belief among vulnerable patients that they already have been desperately searching for has arrived. A more apt title would be ‘Right to Ask’ because this is the only entitlement Right to Try legislation provides patients.”

Drug manufacturers have often hesitated to answer that “ask” positively because of the lack of clarity regarding whether the FDA uses adverse reactions in that program as a factor in determining whether to approve a drug once phase 3 trials are completed and an NDA is submitted. That hasn’t happened often, however, according to the Government Accountability Office (GAO), which published a report on expanded access in July 2017. For example, according to a study using FDA data cited by the GAO, there were only two instances from 2005 through 2014 in which adverse events from expanded access programs contributed to a decision to have a clinical hold placed on a drug. That GAO report stated: “However, several stakeholders we spoke with, including the selected manufacturers we interviewed, raised concerns that FDA is not clear about how it uses expanded access adverse events data in its review of drugs being considered for sale and marketing in the United States.”

In fact, not only has the FDA not used the data to scuttle NDAs, of the 1,000 or so applications it received annually in recent years, it authorized 99% of these requests. Emergency requests for individual patients are usually granted immediately over the phone and nonemergency requests are generally processed within a few days. The FDA is expected to do even better going forward, if that is possible, because the 21st Century Cures bill Congress passed in 2016 made some minor improvements in the FDA’s expanded access program.

The Congressional Push

Those statistics notwithstanding, Johnson introduced an earlier version of the Trickett Wendler bill in 2016. He held hearings on the bill in the Senate Committee on Homeland Security and Governmental Affairs, which he chairs, in 2016. The bill had bipartisan support, but Senator Harry Reid (D-Nevada), the Senate Majority Leader in 2016, refused to let the bill come up for a vote on the Senate floor. Reid retired at the end of that year, and Senator Mitch McConnell (R-Kentucky), the new Republican Senate Majority Leader, allowed the bill to come up for a vote on August 3, 2017, after Johnson threatened to hold up a floor vote on the FDA user fee bill. Johnson agreed to some changes in the bill, and it passed by a vote of 94–1.

The bill would authorize the use of unapproved medicines by patients diagnosed with a life-threatening illness as long as the drugs in question have already gone through preliminary testing on humans and continue to be evaluated in research the FDA oversees. Eligible patients would have to exhaust other treatment options and be unable to participate in ongoing clinical trials. The provision that has mostly troubled patient advocacy groups is the one that requires the federal government, i.e. the FDA, to allow unrestricted manufacturing, distribution, prescribing, and dispensing of experimental drugs, biological products, and medical devices that are: 1) intended to treat a patient who has been diagnosed with a terminal illness, and 2) authorized by state law. The federal government must allow unrestricted possession and use of such treatments by patients certified by a physician as having exhausted all other treatment options.

Johnson accepted some amendments on the Senate floor, which made the bill palatable to some but not many of its opponents. The tweaks Johnson agreed to include requiring the FDA to receive reports of safety events that occur in Right to Try situations. It also forbids patients from being charged more than the cost of production for the medicines. More importantly, perhaps, given industry hesitancy, the bill forbids the FDA from using data from an expanded access program to “adversely impact” review or approval of the treatment. It also removes any threat of federal legal liability.

It is hard to see, however, that the “adverse impact” exemption will make a huge difference in industry willingness to create programs. The GAO report from last July indicated that the FDA was not penalizing NDAs because of adverse reactions suffered in expanded access programs. Bauman at Goldwater thinks the language in the congressional bills will make a difference. “One important aspect of the proposed federal law specifically addresses how the FDA will treat adverse events, which is also a current concern under the current system,” she says. “While the FDA recently changed the guidelines around which adverse event data must be reported, it has continued to state how that data will be used.” So she argues the threat of penalty still exists.

However, drug companies, some public health groups, patient advocacy groups, and the FDA have problems with the bill, which in the House is called the Right to Try Act of 2017. Hearings on that bill and a second bill called the Compassionate Freedom of Choice Act of 2017 were held in the House subcommittee on health on October 3. At those
hearings, Scott Gottlieb, MD, Commissioner of the FDA, suggested some changes to the Right to Try Act sponsored by Representatatives Brian Fitzpatrick (R-Pennsylvania) and Andy Biggs (R-Arizona). One was narrowing the eligibility from patients who face a “life-threatening disease or condition” to those facing a “terminal illness.” Dr. Gottlieb added that the term used in the bill for “terminal illness” would benefit from a clear definition. “We recommend defining it as ‘a stage of disease in which there is a reasonable likelihood that death will occur within a matter of months,’” he said. Dr. Gottlieb also pointed out that the FDA’s current requirements to label investigational products as such, restrictions on promoting and commercializing investigational drugs, and limits on the amount a patient may be charged should be applied to a wider range of people, including “any person who manufactures, distributes, prescribes, dispenses, introduces or delivers for introduction into interstate commerce, or provides to an eligible patient an eligible investigational drug.” The bill would apply those restrictions only to sponsors and investigators, too narrow a population from Dr. Gottlieb’s standpoint. He also wanted clarifications aimed at establishing the FDA’s authority to take enforcement action against sponsors and others who violate sections of the Food, Drug, and Cosmetic (FD&C) Act and FDA regulations related to clinical trials, premarket approval, and labeling. “We believe that the Senate intended FDA to retain authority to address violations of other sections of the FD&C Act, for example, those pertaining to good manufacturing practices, intentional adulteration, and truthful and not misleading labeling, and suggest edits to clarify this,” he said.

Research pharmaceutical companies are not enthusiastic about the bill. Moch, testifying on behalf of BIO, noted the severe scientific and patient-impact limitations of phase 1 clinical trials, which are designed to detail obvious toxicities and identify a tolerable range of potentially effective doses before the drug advances to a larger phase 2 trial. “Nor is the efficacy of an experimental medicine well understood after phase 1 testing,” he said. Expanded access might be particularly burdensome for smaller companies. “There are circumstances where companies do not have the resources, the experimental medicine itself, or the personnel to provide oversight, to simultaneously conduct clinical trials and participate in expanded access,” he said.

Moch offered an alternative to the House and Senate bills. One way to meld the intent of Right to Try laws with the existing FDA expanded access process would be to create a more explicit regulatory pathway that allows expanded access safety and efficacy data to be incorporated into the label of a new medicine once it is formally approved for its primary indication via “traditional” placebo-controlled trials.

It is somewhat head-scratching that a bill presented as a boon to terminally ill individuals is opposed by so many groups representing them. In September, a large group of advocacy organizations, including but not limited to the American Lung Association, American Society of Clinical Oncology, Cystic Fibrosis Foundation, Leukemia and Lymphoma Society, and NORD, sent a letter to House members in advance of the health subcommittee’s September hearing opposing the identical House and Senate bills.

The FDA Program

The FDA’s expanded access program remained static for a decade until 1997 when Congress passed the Food and Drug Administration Modernization Act of 1997 (FDAMA), which included provisions concerning expanded access to investigational drugs for treatment use. It took the FDA until 2006 to propose a rule to further address the concerns that motivated the FDAMA changes, including problems of inconsistent application of access policies and programs and inequities in access based on the relative sophistication of the setting in which a patient is treated or on the patient’s disease or condition. When that rule was finalized in 2009, it established three categories of access: to individual patients, intermediate-size patient populations, and larger populations under a treatment protocol or treatment investigational new drug application (IND).

To qualify for the program, the patient’s treating physician has to determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the patient’s disease or condition. Once the physician makes this determination and together the patient and physician decide that it is appropriate to pursue this treatment option, the physician approaches the pharmaceutical company to obtain agreement from the sponsor/company that it will provide the drug being sought. Neither the FDA nor physicians or patients can compel a company to make a product available—and companies may decline requests for a variety of reasons, according to the GAO. For example, they may have produced only a limited quantity of the product (companies ramp up manufacturing after marketing approval), have minimal resources to administer expanded access requests, or have concerns that granting requests for expanded access may exacerbate the challenge of recruiting clinical trial participants and delay product development.

If the company agrees, the physician then submits the request to the FDA. Key protections are included for patients receiving experimental treatments through the expanded access program. These protections include specific labeling requirements, prohibitions on promoting or commercializing investigational drugs by sponsors and investigators, and limits on the costs charged to patients for investigational drugs. While the agency permits almost all expanded access applications to proceed, it makes meaningful changes in approximately 10% of these cases to enhance patient safety. For example, modifications may be made to adjust dosing amounts, increase safety monitoring, and bolster informed consent. The changes are based on the scientific and medical expertise of the FDA staff and informed by confidential information provided to the FDA by product sponsors during the course of development. “This information is often unavailable to the treating physician—and the larger medical community—and becomes available only after a drug is approved,” Dr. Gottlieb told the House subcommittee. “It is important to note that access to investigational products requires the active cooperation of the treating physician, industry, and FDA in order to be successful. The most common obstacle to access to the investigational product is the willingness or ability of companies to provide it.” If the FDA does approve the request, it is up to the physician to get informed consent from the patient and approval from the institutional review board.

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The FDA has recently made changes to meet criticisms that the 2009 final rule failed to address stubborn problems with access. The application form was simplified in the last year. “We clarified when and how patients may be charged for investigational drugs, notably that the sponsor may generally recover only its direct costs of making the drug available to the patient,” Dr. Gottlieb explained at the House hearings.

The fact that the RTT bill passed so easily in the Senate means that the House probably does not have to make many, if any, changes to the bill for it to pass in that chamber. But given the criticism from patient advocacy groups and BIO, the House would probably be wise to make modifications if only to insulate itself should wider availability create a negative storm, for some reason, down the pike.

REFERENCES


