BioCentury
WEEK OF JUNE 30, 2014

HOLIDAY NOTICE
BioCentury and *BioCentury Week in Review* will not be published next week in observance of the Independence Day holiday in the U.S. Both will return on the week of July 14.

STATES' RIGHTS

BY STEVE USDIN, WASHINGTON EDITOR

State right-to-try laws, which have been signed by a Democratic governor in Colorado and a Republican in Louisiana, are responses to deep dissatisfaction with the pace of drug development and frustration with the ways biopharma companies have responded to pleas for early access to experimental drugs.

The two new laws, and similar bills pending in other states, are based on model legislation drafted by the libertarian **Goldwater Institute**. They are promoted as giving patients with life-threatening conditions and no alternatives the right to access experimental drugs early in the development process — without enrolling in clinical trials or seeking **FDA** approval.

However, rather than creating new rights for patients, the initiatives actually attempt to create rights for drug companies to provide experimental drugs outside the framework of FDA regulation.

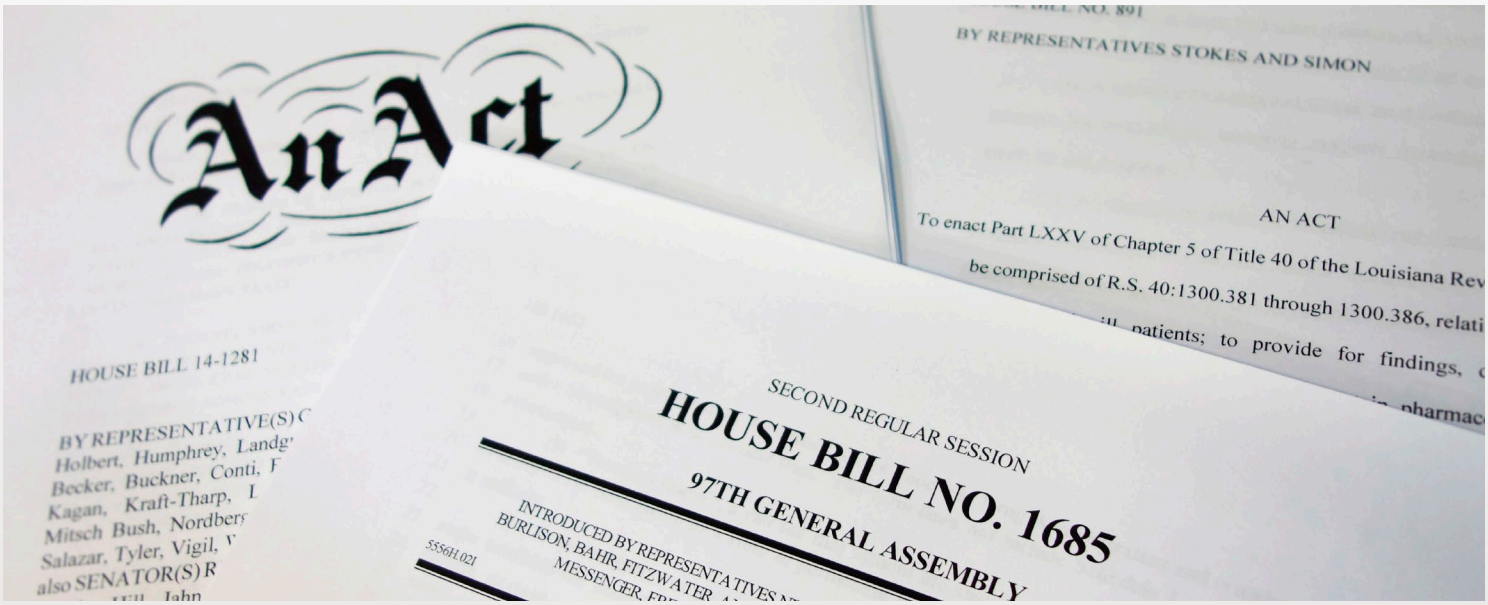
The RTT laws will be effective only to the extent that the underlying assumption is correct: that FDA is the principal barrier to accessing experimental drugs. To benefit patients, the laws must also withstand possible legal challenges, and biopharma companies must be willing to rely on state law to bypass FDA oversight.

These assumptions are being put to the test now in Colorado and Louisiana, and the experiment will likely expand as a dozen or more states are likely to enact RTT laws over the next year.

It is unclear whether the state laws will deliver on their promises to patients, but coming in the wake of several high-profile compassionate access campaigns, they are certainly focusing the attention of FDA leadership, the biopharma industry, patient advocates and members of Congress on the need to improve access to experimental drugs.

RTT LAWS

Colorado House Bill 1281, which added an article to state law on access to treatments for terminally ill patients, passed both houses of the state legislature



on voice votes with no opposition. It was signed into law by Gov. John Hickenlooper, a Democrat, on May 17.

Adapting model legislation drafted by the Goldwater Institute, the Colorado law says patients with terminal illnesses "do not have the luxury of waiting until an investigational drug, biological product, or device receives final approval from the United States Food and Drug Administration."

It adds that these patients "have a fundamental right to attempt to pursue the preservation of their own lives by accessing available investigational drugs, biological products, and devices."

To be eligible, patients must have a terminal illness, have "considered all other treatment options currently approved" by FDA, be unable to participate in a clinical trial for the terminal illness within 100 miles of their home, or not have been accepted into a trial within one week of completing an application.

The patient must also receive a written recommendation from a physician for the investigational product.

The law applies to compounds that have "successfully completed" a Phase I trial, remain "under investigation" in an FDA-approved trial, and have not been approved for marketing.

The Colorado law frees insurers and providers of any obligation to pay for the experimental compound or treatment associated with its use.

Under the law, manufacturers are under no obligation to provide access to investigational products.

In a May 30 statement announcing his signature on Louisiana's Right to Try Act, House Bill 891, Gov. Bobby Jindal, a Republican, said individuals with terminal illnesses "should have every opportunity to live life to the fullest and that is often possible through experimental drugs or treatment."

The statement also noted the "Goldwater Institute supported the bill and is currently working with legislators in nearly two dozen states to pass or introduce the Right to Try Act."

The Missouri legislature unanimously passed an RTT bill in May. Gov. Jay Nixon, a Democrat, has not indicated whether he intends to sign it into law.

The Arizona legislature has voted to submit an RTT law to voters as a ballot initiative in November.

The RTT laws that have been enacted and introduced are vague or silent about several important issues. For example, while they allow access following a Phase I trial as long as a Phase II trial is under way, they do not have provisions for withdrawing access if unanticipated safety issues are discovered, or if there is a definitive determination that a product is not effective.

They also do not require the systematic collection, reporting or dissemination of outcomes or safety data that could help physicians and patients make decisions about using an experimental drug.

UNLOCKING CURES

One of the premises of the RTT movement is that a plethora of effective compounds is languishing at biopharma companies that could extend or save lives if patients had access.

"The Goldwater Institute designed the Right to Try Act because there are over a million Americans dying every year of terminal illness and there are many drugs that could be lifesaving, but they're locked out of the process to access them," spokesperson Lucy Caldwell said in an interview broadcast on *BioCentury This Week* television. "The Right to Try Act is going to change all that. It's going to fix the broken system by allowing terminally ill patients, with their doctors, to gain access to experimental treatments that could save their lives."

"I HAVEN'T SEEN AN INSTANCE WHERE A PATIENT WANTED ACCESS, A COMPANY WANTED TO PROVIDE IT, A PHYSICIAN RECOMMENDED IT, AN IRB WAS GOOD WITH IT, AND FDA SAID NO. MORE OFTEN THAN NOT IT IS THE COMPANIES THAT SAY NO."

JOHN CROWLEY, AMICUS

Advocates also say FDA has set the hurdles too high for demonstrating safety and efficacy, especially for life-threatening conditions that have no adequate therapies.

Caldwell acknowledged that allowing RTT access could negatively affect clinical trials, and suggested this would be a good thing. "Instead of asking whether Right to Try is going to negatively impact our backward, double-blind clinical trial process, what we should be asking is why we have a double-blind clinical trial process in this country that locks dying patients out of drugs for a decade plus," she said.

Caldwell suggested FDA's public posture on compassionate access is deceptive. The agency says it approved 99.4% of expanded access applications submitted from October 2009 to September 2013.

According to Caldwell, "many drug companies are singing a different tune." In private discussions with the Goldwater Institute, she said, companies report it is "very hard to get the FDA to be cooperative when they're trying to get drugs to patients."

Caldwell declined to identify the companies.

According to Steve Walker of the **Abigail Alliance**, FDA's statistics account only for "completed IND applications for access, not requests for access." Walker co-founded the alliance, which advocates for early access to experimental drugs.

"The number of completed applications is a small (in fact almost certainly tiny) fraction of the number of requests," Walker told BioCentury in an email. "The hurdles for completing an IND application for even a single patient cause the number of completed ones to be exceedingly small. The actual number of requests, depending on how they are defined, would be in the many thousands to FDA, and many tens of thousands or even hundreds of thousands every year" to physicians and companies.

John Crowley, chairman and CEO of **Amicus Therapeutics Inc.**, and the father of two children with the rare lysosomal storage disorder Pompe's disease, doesn't think FDA blocks access to experimental drugs.

"I've been down this road many times, and I've always found the FDA very open to expanded access and compassionate access protocols," Crowley told BioCentury. "I haven't seen an instance where a patient wanted access, a company wanted to provide it, a physician recommended it, an IRB was good with it, and FDA said no. More often than not it is the companies that say no."

FDA'S POSITION

FDA has not taken a position on state RTT laws, and Commissioner Margaret Hamburg told BioCentury she will not speculate about whether the agency would challenge them or attempt to dissuade companies from making experimental drugs available outside the agency's jurisdiction.

Hamburg did express skepticism that the laws will help patients.

"I'm not sure the kinds of approaches the laws are outlining are really the things that will make the most difference for patients," she told BioCentury.

"I don't think we are a barrier to access for patients; often we are a facilitator," Hamburg added. "We can often be an advocate for the patient with the company. The company at the end of the day has to make the decision, and there have been a number of instances where we have moved the company toward making the treatment available for a given patient."

According to Hamburg, state RTT laws and media attention on compassionate access requests have prompted FDA to consider whether it could help improve access to experimental treatments. "The conversation around expanded access has been brought into greater focus by the activities at the state level and continued concerns and effort by patients to get access to experimental therapies that are not through the review process," she told BioCentury.

PATIENT ADVOCATES SPLIT

Not all patient advocates are on board. The notion that clinical trials should be circumvented worries Diane Dorman, VP for public policy at the National Organization for Rare Disorders (NORD).

Dorman told *BioCentury This Week* television that providing access to investigational drugs after Phase I is "really unsafe."

She said access to a compound should occur after it is in "Phase II, and in patient populations that are affected by this particular condition, to see if it actually works, because we want to make sure that the clinical trials are conducted in an efficient [manner] and as speedily as possible, to get these therapies to the patients, to wider populations, as quickly as possible."

Melissa Hogan, the mother of a child with the rare lysosomal storage disorder mucopolysaccharidosis II (MPS-II, Hunter syndrome) and a rare disease advocate, also opposes RTT laws, but for other reasons.

RTT laws are "a double negative for patients because they won't improve access to [experimental] drugs, and they take away from the work that

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actually needs to be done, which is improvement of the compassionate use system," Hogan told BioCentury.

The Colorado and Louisiana laws "give people false hope because there is no right created by the laws," she added. "They are not much different from the current system" because decisions about granting access will continue to be made by drug companies.

"Companies do not want to provide their drugs, and right to try does nothing to change that," according to Hogan.

Hogan also is critical of provisions in RTT laws that limit access to patients with immediately life-threatening illnesses because patients like her son who have fatal, progressive diseases might not qualify.

In addition, provisions allowing patients who live more than 100 miles from a trial site to access experimental drugs "don't reflect the reality of the world of rare diseases," Hogan said. "For rare diseases, there is hardly ever a clinical trial within 100 miles."

Distance provisions could make it impossible to test Orphan drugs because too many patients would opt for access under RTT, she said.

Hogan disagrees, however, with Dorman's contention that compounds should not be made available based on Phase I data. "Should certain drugs be available after Phase I? Yes, if the risk to the patient [from the disease] is equal to or greater than the risk of the drug," said Hogan.

She noted that for life-threatening conditions, especially rare diseases, Phase I trials can be conducted with patients who have the disease rather than with healthy volunteers.

Some patients support RTT, even if they don't think the laws are perfect.

Advocates for autologous mesenchymal stem cell therapies view state RTT laws as a path around FDA regulation, according to SammyJo Wilkinson, a spokesperson for the advocacy organization **Patients for Stem Cells**. In February, the U.S. Court of Appeals for the District of Columbia rejected arguments that autologous stem cell procedures are a "procedure of medicine" that cannot be regulated by FDA.

"Many of us at Patients for Stem Cells have benefited from stem cell therapy, and even though we are mostly chronic patients with illnesses like COPD, progressive MS or cerebral palsy, we share the same no-hope scenario as terminal patients who have no FDA-approved therapies," Wilkinson told BioCentury. "If the FDA doesn't get heavy-handed with the states on RTT, this will at least save some lives for the most vulnerable."

Wilkinson, who would like RTT laws to include chronic diseases, added that Patients for Stem Cells is lobbying for enactment of an RTT law in Georgia.

Some advocates hope state RTT laws will help tip the scales in favor of access for children, who are often ineligible for clinical trials of novel drugs.

"Right-to-try laws are a very good idea; they will help broaden access to drugs that might help save children and other patients," said William Burns. Burns is the uncle of Josh Hardy, an eight year-old whose life was saved because he received access to **Chimerix Inc.**'s brincidofovir as a result of a viral social media campaign.

Burns told BioCentury incentives should be created to encourage companies to provide compassionate access, and FDA should provide assurances that adverse event reports from compassionate access will not impede approval.

Burns is a member of the **Coalition Against Childhood Cancer**, an umbrella organization that coordinates the efforts of a number of pediatric cancer patient advocacy groups.

The coalition is considering establishing a committee to screen requests to advocate for compassionate access, Burns said.

"There needs to be a mechanism for patients who face life-threatening illnesses where there is no FDA-approved drug to access investigational drugs," said Jonathan Agin, a member of the coalition.

"We are facing a crisis in this country in terms of science far outpacing drug development because of the cost of commercialization, so overall I'm in favor of right to try," Agin told BioCentury.

The coalition is prepared to dust off the playbook it used for Josh Hardy, according to Richard Plotkin, a member of the board of directors of the **Max Cure Foundation**.

Plotkin arranged for Josh's mother, Aimee Hardy, to appear on national television news programs to publicize her plea to Chimerix to provide brincidofovir, and he organized a social media campaign that reached at least 1.5 million people in three days.

"If the right situation arose, I would certainly call upon all the people I called on before," Plotkin said.

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INDUSTRY SKEPTICISM

Drug industry trade associations have not taken formal positions on RTT, but they, along with many of their members, have expressed skepticism about the bills.

Rachel King, CEO of GlycoMimetics Inc. and chair of **BIO**'s board of directors, said RTT laws that allow companies to bypass FDA are aiming at the wrong target. "Because FDA generally does approve expanded or compassionate use requests, I think they are trying to solve a problem that doesn't really exist," she said.

Crowley doesn't think state RTT laws will provide patients better access to experimental treatments.

"Right-to-try laws are more an employment act for lawyers than a right for patients," he said. "I don't think anything [in the laws] compels a company in Colorado or Louisiana to give a medicine. The company has to consent, so the law doesn't solve that problem."

PhRMA is concerned the state laws try to circumvent FDA oversight.

"I and the industry in general have serious concerns about any approach that would make an investigational drug available outside the oversight of the FDA and that seeks to bypass the FDA and the clinical trial process," Sascha Haverfield, VP for scientific and regulatory affairs at PhRMA, told BioCentury.

One company, Neuralstem Inc., told BioCentury it plans to offer its compound for amyotrophic lateral sclerosis (ALS) under RTT, which it said will supplement, not replace, clinical trials (see "Neuralstem's Plan," page 6).

While Haverfield and King don't think RTT laws will have their intended effects, they agree the process for providing access to experimental drugs should be improved.

"State-by-state right-to-try legislation, while well-intentioned, is unlikely to achieve the goal of getting safe and effective medicines to patients as soon as possible," Haverfield said.

"What I think needs to happen is all the stakeholders — patients, healthcare providers, regulated industry, FDA and lawmakers at the state and federal levels — need to look at how can we improve the expanded access process that is in place," he said.

Haverfield suggested that FDA guidance indicating how the agency uses safety and efficacy data from expanded access could reduce industry concerns that granting access will have negative regulatory consequences.

"FDA has said on multiple occasions that it has never failed to approve an application based on an adverse event reported in expanded access," Haverfield said. "It has not said that such reports have not led to additional clinical trial requirements or requirements for additional trials based on data that is extremely difficult to interpret."

Haverfield added it would be far better to get life-saving drugs approved more rapidly.

"We need to ask, does the urgency of the approval system we have in place match the urgency of an immediately life-threatening disease? We need to ensure that the urgency of the drug development and approval system matches patients' urgent needs," he said.

Concerns that data from compassionate access will create setbacks for drug development are misplaced, according to Crowley. "To avoid granting requests, CEOs give the excuse that they need to preserve integrity of studies and data, that if they give [an experimental drug] to really sick people, it may not help them and that would set back the whole program. I don't think that's the case; companies are overly conservative," he said.

Hamburg told BioCentury FDA is "trying to clear up misperceptions on the part of companies" that think providing an unapproved product to a very sick patient might complicate the review and approval of the drug.

WHEN IS 'EARLY'?

There is also disagreement within industry about when access should be granted to experimental drugs.

King disagreed with provisions in RTT laws that allow access to compounds after Phase I.

"I recognize that when people are desperately ill they are willing to take greater risks," she said. "Until a drug has a positive efficacy signal in a clinical trial, we really don't know if it might work, so I think that until there is a positive signal, we need to restrict it to the clinical process."

King added: "If the positive signal is so strong it is generally accepted the drug works, maybe we need to make the drug available through some kind of accelerated approval."

NEURALSTEM'S PLANS

At least one company has announced its intention to make a product available to patients under state right-to-try laws.

Neuralstem Inc. President and CEO Richard Garr told BioCentury the company is training surgeons and identifying a hospital and neurologists in Colorado who can administer the biotech's experimental human neural stem cell (hNSC) therapy to treat amyotrophic lateral sclerosis (ALS).

He said Neuralstem will not apply for an IND or other permission from **FDA** to provide the therapy in Colorado.

hNSCs have completed a Phase I trial in 15 patients with ALS. An open-label, dose-escalation U.S. Phase II trial in up to 15 ambulatory patients has begun. The company plans to start a Phase III trial next year.

Garr said the RTT program will offer hNSCs to patients who do not qualify for the trials.

Neuralstem has not determined whether it will charge Colorado patients. "A lot will depend on the numbers. We can't treat hundreds of patients without having fiscal problems," he said.

Garr wrote on Neuralstem's blog, "RTT is a scaffold on which an industrywide national infrastructure can be built, state by state if that's what it takes, to help patients across the spectrum of fatal diseases participate actively in trying to find a cure for their disease; and become active partners in the process rather than passive victims."

Garr also wrote that Neuralstem will not offer hNSCs under RTT "if the FDA tells it not to."

Garr is chair of the **Goldwater Institute**'s Right to Try National Advisory Council.

— STEVE USDIN

Crowley said he is a strong supporter of compassionate access, "but that doesn't mean that as soon as you have an inkling of efficacy and safety anyone should have access to the drug."

Leighton Reid, a venture partner at Alloy Ventures, told BioCentury he supports the use of state RTT laws to provide access to compounds after Phase I in some cases. States are "laboratories of democracy," and "elected state governments should be free to experiment with the provision of investigational drugs outside FDA oversight for patients with terminal illnesses who have run out of options," he said.

"We will learn whether these reforms have too many unintended consequences or are a path for others to follow," Reid told BioCentury.

CHALLENGING RTT?

While FDA clearly is hoping to avoid instigating a legal challenge to state RTT laws, it probably would win a case based on the preemption of federal drug regulation over state laws, according to Kurt Karst, a director at Hyman, Phelps & McNamara P.C., a firm specializing in FDA law. "If PhRMA or FDA were to challenge [state RTT laws], they have good precedence behind them to prop up their cases," he told BioCentury.

Karst added: "I really wonder whether FDA or PhRMA would take on the challenge. It is easy to put up a desperate patient who would die without [access to an experimental drug] and here's big bad PhRMA or FDA suing to take it away from them."

Coleen Klasmeier, who leads the food, drug and medical device regulatory practice at Sidley Austin LLP, agreed. "It would be very politically tough for the government to stand in the way," she said.

Klasmeier added: "It reminds me of what is happening with marijuana where you have a federal administrative architecture that gives states a lot of leeway to be responsive to what's happening on the ground."

State RTT laws are a response to a "seismic shift" in social and political attitudes toward the regulation of drugs and patient empowerment, according to Klasmeier.

"Maybe nothing is changing in FDA's or the industry's postures, but what is changing is the tolerance of patients for a restrictive regulatory regime," according to Klasmeier. "It is not just changes in case law, but broader atmospheric changes that make it obvious the regulatory and enforcement environment has to change. Patients will not tolerate government getting in the way of access to investigational drugs."bc

COMPANIES AND INSTITUTIONS MENTIONED

Abigail Alliance, Lorton, Va.
Amicus Therapeutics Inc. (NASDAQ:FOLD), Cranbury, N.J.
Biotechnology Industry Organization (BIO), Washington, D.C.
Chimerix Inc. (NASDAQ:CMRX), Durham, N.C.
Coalition Against Childhood Cancer, Washington, D.C.
Neuralstem Inc. (NYSE-M:CUR), Rockville, Md.
GlycoMimetics Inc. (NASDAQ:GLYC), Gaithersburg, Md.
Goldwater Institute, Phoenix, Ariz.
Max Cure Foundation, New York, N.Y.
National Organization for Rare Disorders (NORD), Danbury, Conn.
Patients for Stem Cells, Seattle, Wash.
Pharmaceutical Research and Manufacturers of America (PhRMA), Washington, D.C.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.