

Executive Summary

Findings on “Right to Try” Laws and Pre-Approval/Compassionate/Expanded Access to Investigational Medical Products

The first “right to try” law, designed to allow terminally ill patients pre-approval (or compassionate or expanded) access to experimental drugs, was enacted in May 2014. Since then, 31 states have passed similar laws, and federal bills have been introduced in both the House and Senate.

“Findings on ‘Right to Try’ Laws and Pre-Approval/Compassionate/Expanded Access to Investigational Medical Products” represents two years of study by the NYU Langone Medical Center Working Group on Compassionate Use and Pre-Approval Access (<http://www.med.nyu.edu/pophealth/divisions/medical-ethics/compassionate-use>). It is intended to inform legislators, policymakers, patients, and others interested in current and proposed policy concerning pre-approval access to experimental drugs.

A few of the findings:

- The total number of requests for experimental drugs that companies receive is not known.
- Right to try laws do not obligate a company to provide the drug being requested.
- When companies are willing to grant requests, the FDA then approves more than 99% of them.
- If a company is unwilling to grant access to an experimental drug, the FDA cannot override this decision.
- There are no substantiated cases of patients receiving experimental products because of a right to try law.
- Some right to try laws put patients’ hospice, in-home healthcare, and/or insurance coverage at risk.
- There is widespread support in mainstream and social media for right to try legislation. However, this enthusiasm does not appear evidence-based.

**Findings on “Right to Try” Laws and Pre-Approval/Compassionate/Expanded Access to
Investigational Medical Products
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Genesis and Spread of Right to Try Laws

The first so-called “right to try” law was passed in Colorado in May 2014. As of July 1, 2016, right to try laws have been signed in 31 states, and similar bills are under consideration in an additional eight state legislatures.

The right to try movement was instigated by a libertarian think-tank, the Goldwater Institute, which released a model right to try law and lobbied for its adoption by state legislators. Right to try bills have been introduced by both Republicans and Democrats, and they have passed with nearly unanimous support whenever they have come to a vote. The governors of California and Hawaii vetoed their states’ bills; a new bill was reintroduced in California.

Representative Matt Salmon (R-AZ) introduced a federal right to try bill in the U.S. House of Representatives in July 2015. In the U.S. Senate, Ron Johnson (R-WI) introduced the Trickett Wendler Right to Try Act of 2016 in early May 2016. Senate Bill 2912 is named after a woman from Johnson’s home state who was diagnosed with amyotrophic lateral sclerosis (ALS); she died in March 2015. Johnson’s bill has 24 co- sponsors, all Republicans.

Who Requests Pre-Approval Access to Investigational Medical Products?

For years, people have been making requests for pre-approval (or “compassionate” or expanded) access to investigational medical products (drugs, biologics, devices) outside of clinical trials under existing Food and Drug Administration (FDA) rules. In recent years, the FDA has approved more than 99% of the requests it receives.

Requests for access to an investigational medical product can be made by an individual, an individual’s physician, or even an individual’s employer (such as the humanitarian aid groups that sought compassionate use drugs for their employees who contracted Ebola). Most pharmaceutical companies prefer that a request come from the patient’s physician.

The total number of requests made to those companies developing products that can potentially be used for a “serious disease or condition” for which “there is no comparable

or satisfactory alternative therapy” (two of the FDA’s requirements for expanded access or compassionate use) is not known. Also unknown are the percentage of requests granted or denied by companies, or how many people actually receive and use an investigational medical product.

Requests often come from people with serious or chronic, but not terminal, diseases, such as irritable bowel syndrome and hepatitis C. Some requests are for adults; other requests are made

on behalf of children. Requests can, and do, come from all over the world. Some requesters are eligible for clinical trials; some are not. There are no available statistics that provide a breakdown of how many requesters are or are not eligible for clinical trials, nor is it known how many requesters are aware of the existence of or their eligibility for clinical trials (meaning, whether they are asking for expanded access because they do not want to be in a clinical trial or because they do not know a trial is available). Some requests come from people who do not want to participate in a clinical trial for fear of being randomized to a placebo group or to the standard treatment, which they deem inferior or otherwise undesirable. Some requests come from individuals who are unwilling or unable to relocate to the site of a clinical trial for which they are eligible. Some come from individuals who are ineligible to participate in a clinical trial solely on the grounds of age, not medical status or prior involvement in another trial.

There Are Many Types of Requests for Pre-Approval Access to Investigational Medical Products

Requests can be made for investigational drugs, vaccines, biologics, and devices.

Requests can be for investigational medical products that are very early stage, such as drugs in Phase 1 studies or even earlier, including products that have been tested only in animals or in vitro.

Some requests are for investigational drugs that are in short supply because of manufacturing issues. Others arise in the middle of humanitarian emergencies or rapidly spreading epidemics.

The phrase “compassionate use” is sometimes used to describe requests for medical marijuana/cannabis, but seeking this type of access is not analogous to requesting preapproval access to a commercially produced drug or device.

Role of the FDA

Before the FDA will consider a request for pre-approval access to an investigational medical product, the requester (normally the patient’s physician) must contact the entity developing the desired product (the “sponsor”). If the sponsor is willing to provide access, the physician must submit an application (Form FDA 3926) to the FDA for

consideration. If the sponsor is unwilling to provide access, the FDA has no authority to override this decision.

The FDA is not the obstacle to accessing pre-approval products that right to try proponents allege it to be. The FDA approved more than 99% of pre-approval access requests in the last reporting year (October 1, 2014–September 30, 2015).

In emergency cases, the FDA has special provisions to process requests for pre-approval access within hours and frequently does so. By law, the maximum amount of time that the FDA can spend evaluating any request is 30 days.

The claim that it takes 100 hours to complete the FDA paperwork required to request pre-approval access is often made but is not true. It is a misuse of the amount of time estimated to fill out the form for a full Investigational New Drug (IND) application, required when a new compound will first be tested in humans (prior to beginning a Phase 1 clinical trial). Embedded in this form was a short section that needed to be completed by physicians requesting to use a drug pre-approval, and this required only a fraction of the effort needed to complete the entire form. Additionally, in many cases the drug's sponsor will help requesting physicians fill out the paperwork.

In response to the persistence of the 100-hour claim, the FDA released a new form (Form FDA 3926), which is estimated to take 45 minutes to complete. The form requires the same information as did the previous form, but the extraneous information has been removed. It is much clearer than the previous long-form IND, and it is less confusing for physicians to complete.

The FDA very rarely penalizes a drug company if its product causes an adverse event during pre-approval use. The agency recognizes the inherent risk in providing investigational products to a very sick population, and it believes that the few times such action was warranted—0.2% of cases over the last four decades—were due to severe, avoidable harms stemming from administration of a drug. The FDA has reviewed this matter and will be releasing a peer-reviewed article about it.

The FDA has stated repeatedly that it will be reasonable in dealing with adverse events that occur in the context of compassionate use. However, it has not put this in print. Investors may still be concerned if a death or serious adverse event happens to a person to whom a company has granted compassionate use.

States do not have the authority to preempt federal control over the process of drug, device, or vaccine development, with the exception of providing relief from legal liability, as liability is a state issue. The constitutionality of state right to try laws is exceedingly dubious.

Failures of State Right to Try Laws

Right to try laws do not obligate a sponsor to provide an investigational medical product to those asserting their “right to try.”

To date, there is no evidence that anyone in a state with a right to try law has obtained anything under that law that would have been unattainable under pre-existing federal regulations. The Goldwater Institute disputes this, but it has not provided any evidence in support of its claims.

The majority of right to try laws focus on the terminally ill, although about a third of them also apply to those in a “permanent state of unconsciousness” and one applies to those in a persistent vegetative state.

Right to try laws vary from state to state in how they define “terminal illness.”

Some states' laws put patients' hospice coverage, home healthcare coverage, and/or insurance benefits at risk. By trying an experimental treatment while in hospice, coverage could be forfeited.

Right to try laws may open a door to crackpots and shysters looking to take advantage of terminally ill people, a huge problem in the stem cell field even before the passage of right to try laws.

Right to try laws offer no financial help to patients seeking access to investigational medical products, although one state, Utah, did establish a private foundation to address this concern.

Under right to try laws, a company may or may not decide to charge for its investigational product, and health insurers may or may not decide to reimburse such costs. However, under FDA regulations, a sponsor can charge only for its costs, and there are few examples of a sponsor charging anything at all for a medicine provided under expanded access/compassionate use. The Texas right to try law requires that pre-approval drugs be provided for free.

Right to try laws vary from state to state in whether the patient must obtain a second opinion of a terminal diagnosis or the experimental treatment plan as well as in who is qualified to provide that opinion.

Oregon's right to try law excludes minors. Three states' laws exclude in-patients.

There are currently 31 states with right to try laws, and these laws differ from state to state; however, there is no guidance for physicians about which law to follow in cases of conflicts. For example, if a patient lives in South Dakota but seeks care in North Dakota, which state law ought to be observed? If a hospital is located in Arkansas but is part of a network based in Delaware, which state law ought to be observed? If the patient and doctor are in Tennessee but the experimental product they wish to try can be administered only in Texas, which state law ought to be observed?

Industry Concerns About Requests for Access to Pre-Approval Investigational Medical Products

The number of requests submitted to the FDA has increased over the last several years; in 2014, requests rose by 92%. The number of Change.org online petitions in support of individual requests has increased over the last several years.

Many companies developing investigational medical products have no publicly available policy or website for requests for pre-approval access to investigational products.

Social forces such as social or mainstream media campaigns or pressure from a celebrity/politician/shareholder have been used to influence or pressure companies to grant access to investigational medical products.

Many companies are concerned that adverse events in a compassionate use context will count against the drug when it is being evaluated for approval by the FDA.

Pre-approval access requires much effort on the part of the industry sponsor, and some companies are unwilling to provide their products outside of clinical trials due to factors including lack of experience, concerns about the organizational, logistical, or financial impact, or fear that pre-approval access would harm their clinical trials.

There is no systematic tracking by the FDA of patient outcomes after receiving access to pre-approval products.

Given their position as “sponsors” of investigational drugs, as well as the FDA’s annual reporting requirements, companies are more likely than individual doctors to report outcomes, including adverse events, to the FDA.

The FDA does not routinely audit those involved in compassionate use to ensure that they have reported adverse events and/or outcomes.

Requests for pre-approval access to investigational medical products are not always handled consistently by either the sponsor or the FDA.

While some companies are worried about the handling of requests for pre-approval access to investigational medical products, others, such as Johnson & Johnson and mytomorrows.com, are seeking to innovate in this area.

Institutional Review Boards (IRBs) and Pre-Approval Access to Investigational Medical Products

Once a company and the FDA agree to allow pre-approval access to a specific investigational product, the requesting physician must then obtain approval from an institutional review board (IRB) at the facility at which the product will be used.

In states with right to try legislation, IRBs have no definitive guidance on implementing the laws.

IRBs vary in how they perceive, handle, and process requests for pre-approval access to investigational products. Currently, there are no best-practice guidelines that IRBs can follow. IRBs almost always approve requests, but they can sometimes slow the process of getting drugs or devices to patients.

Media and Pre-Approval Access to Investigational Medical Products

Many editorials and stories in the mainstream press support the adoption of right to try legislation without acknowledging the serious limitations and questionable constitutionality of these laws.

Although individual stories about terminally ill individuals are a prominent feature of reporting on pending right to try legislation, there is a dearth of reporting on the impact of enacted right to try laws on the terminally and chronically ill. Likewise, there is a dearth of reporting about patients' positive experiences with either the FDA or company sponsors.

Many editorials have conjoined the issues of "right to try" legislation with so-called "right to die" legislation, instead of reporting on these separate issues on their own merits.

Much reporting has used language that makes it sound as though right to try laws automatically guarantee patients access to investigational medical products, such as language claiming that "Under this new law, patients *will have access* to new drugs..."

Reporting frequently fails to mention that many right to try laws stipulate that patients who try pre-approval products may lose access to hospice, home healthcare, and/or insurance benefits.

The discrepancies and inconsistencies of state right to try laws are rarely addressed. Federal efforts have received little attention and almost no critical assessment.

International Policies on Pre-Approval Access to Investigational Medicine Products

In 2014, the World Health Organization (WHO) declared, in the context of the Ebola outbreak in West Africa, that "provided certain conditions are met...it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential

treatment or prevention." This was a significant departure from decades of ethical norms about when investigational products should be used in patients or potential patients. Unapproved agents were used in a number of countries to treat Ebola patients. Unapproved vaccine was used to try to stem the tide of pandemic flu. Doses of cholera and, most recently, yellow fever vaccines smaller than what was approved have been used in efforts to stretch vaccine supply during humanitarian emergencies. The Wellcome Trust (UK) has provided some guidelines for reviewing requests for compassionate use in humanitarian emergencies.

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Suggested Resources

NYU Langone Medical Center Working Group on Compassionate Use and Pre-Approval Access website. Accessible at: <http://www.med.nyu.edu/pophealth/divisions/medical-ethics/compassionate-use>

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