



AN ONGOING CE PROGRAM
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School of Pharmacy

EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists will be able to:

- Describe FDA programs that accelerate access to and approval of new agents and how they differ from traditional FDA approval mechanisms.
- Identify the elements of Right To Try laws.
- Describe how Right To Try laws differ from FDA sanctioned programs.
- Discuss the benefits and risks for patients who may take advantage of Right To Try laws.
- Discuss how patient participation in Right To Try programs may affect pharmacists.

After participating in this activity, pharmacy technicians will be able to:

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- Identify the elements of Right To Try laws.
- Describe how Right To Try laws differ from FDA sanctioned programs.
- Discuss the benefits and risks for patients who may take advantage of Right To Try laws.
- Discuss how patient participation in Right To Try programs may affect pharmacists



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Law: Right To Try Laws: Do the Terminally-Ill Need the FDA?

ABSTRACT: The Food and Drug Administration (FDA) is responsible for regulating distribution of prescription drugs and biologics (agents) in the U.S. and manufacturers must receive approval from the FDA before providing them to patients. Recognizing that approval is a lengthy process, the FDA has enacted programs to accelerate access to certain agents for the terminally ill. Patient advocates have sought efforts that go beyond FDA-sanctioned programs. As a result, 40 states have enacted "Right-To-Try" laws and the U.S. Congress also passed legislation in May, 2018. These laws permit terminally ill patients to request agents directly from manufacturers without seeking FDA approval if the agent has completed Phase I clinical trials. This continuing education homestudy examines these laws' main features. It also describes the positions advocates (patient autonomy and reduced red tape) and opponents (increased risk and impact on clinical trials) take with respect to Right To Try laws.

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INTRODUCTION

The federal government must allow unrestricted possession and use of unapproved medical products by patients when a physician has certified the patient has exhausted all other treatment options. To the practicing pharmacist, this may sound like the comments frequently expressed by a patient advocate or a non-mainstream therapist on a daytime TV "Doctor Show," but it is actually the core message of a bill passed by the U.S. Congress in 2018. Its purpose is to relax regulatory requirements for new therapeutic drugs and biologics (agents) for the terminally ill.¹ The Senate passed the bill in 2017 and the House approved the final version on May 22, 2018 by a vote of 250-169, 22 Democrats joining all

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228 Republicans in voting in favor.¹ As expected, President Trump signed the Act into law on May 30²; the issue had strong administration support, having been cited by President Trump during his 2018 State of the Union address. Vice President Pence signed a similar measure while Governor of Indiana.²

In his 2018 State of the Union address, Trump said, “We also believe that patients with terminal conditions should have access to experimental treatments that could potentially save their lives. People who are terminally ill should not have to go from country to country to seek a cure—I want to give them a chance right here at home. It is time for the Congress to give these wonderful Americans the right to try.”³

The new Federal law, which permits the use of new agents in certain circumstances without the need for Food and Drug Administration (FDA) approval (see Table 1), is the culmination of long-standing efforts at the state and grassroots level to expedite access to potentially life-saving, but unproven, therapies. Has the time come to loosen the FDA’s regulatory authority? This continuing education homestudy examines the features of these so-called “Right-to-Try” (RTT) Laws and discusses arguments raised by different sides of the issue. It will also review other programs that improve patient access to untested remedies and address the important, but difficult, role of pharmacists as gatekeepers in this new environment.

Drug Approval

As pharmacists and technicians are aware, the normal route to having a prescription drug become available to the public is a long, arduous, and expensive process, culminating in FDA approval of an agent for a specific use (although practitioners may prescribe an approved agent for non-approved [“off-label”] uses). The FDA’s approval mechanism is concerned with both efficacy and safety.⁴ A brief review of the normal drug approval route will help readers appreciate how programs that accelerate approval or access align with the existing process.

Existing Process

Before beginning the clinical trial phase of drug testing, the manufacturer must file an Investigational New Drug (IND) application showing the FDA the results of pre-clinical testing in laboratory animals and a proposal for testing in humans. The goal of Phase I of the clinical trial is to determine what the agent’s most frequent (short-term) adverse effects are likely to be and to gain preliminary information on its pharmacokinetic properties. This phase is usually conducted in healthy volunteers.⁵

If Phase I does not reveal unacceptable levels of toxicity, the agent moves to Phase II. In Phase II, the manufacturer or sponsor tests it on a small patient population—typically ranging from a few dozen to about 300 study participants—with the disease or condition the agent is intended to treat. The intent is to gath-

Pause and Ponder:

How many times has one of your patients died shortly before a breakthrough therapy was approved?

How did you feel?

Table 1. Key Features of Federal Right-To-Try Law (2018)

- An eligible patient is someone who has been diagnosed with a life-threatening disease or condition.
- Patient must have exhausted approved treatment options and be unable to participate in a clinical trial.
- Patient must provide a physician with written, informed consent.
- Available therapies must have completed a Phase I clinical trial.
- No liability shall lie against a manufacturer, prescriber, or dispenser.
- Manufacturer may refuse to provide the agent to patient.
- The FDA may not consider adverse clinical outcomes to delay or adversely affect the review or approval of an agent.

er preliminary data on efficacy and to continue evaluating safety and short-term adverse effects.⁵

In Phase III, the studies are larger—enrolling up to 3000 participants—and are designed to gather additional information about safety and efficacy. These studies may enroll different populations and use wider dosage ranges. Usually, they are double blind (information about the agent is masked [kept] from study staff and participants to reduce or eliminate bias). The manufacturer may then file a New Drug Application (NDA) for FDA review. If the health benefits outweigh the risks, the FDA may approve the agent for sale in the U.S.⁵

In this process, the FDA serves a role to safeguard the public by mandating that marketed drugs provide evidence that they are reasonably safe and effective for their intended use. The drug approval process may take as long as 10 to 15 years from conception to FDA approval, creating estimated costs of \$1.3 billion or more per drug.⁶ As a reminder, only about one of 1000 drugs that have gone through pre-clinical testing become candidates for clinical trials in the U.S. and almost 90% of new agents fail in the clinical testing phase. In at least one analysis, 50% of agents that reach Phase III of clinical testing did not make it to the market.⁶ The problem is not unique to the United States; a recent study in the United Kingdom found that only 18% of drugs advanced from Phase II to Phase III. Clearly, completing Phase I is no guarantee of success.⁶

Expanding Access to Unapproved Therapies

While the FDA approval process seeks to ensure that marketed drugs are safe and effective, terminally-ill patients may not be willing—or able—to wait for the manufacturer and the FDA to complete the regulatory requirements summarized above. Patients and their families and patient advocacy organizations have lobbied for decades for greater patient control over medical decisions and supported speeding up access to potentially life-saving drugs.

One relatively recent development has been the so-called “Right-to-Try” movement. Victor Riches, President and CEO of the Goldwater Institute, a libertarian thinktank that has been active in the RTT movement, has said “There’s no more fundamental freedom than the right to save your own life. Right-To-Try guarantees that freedom by ensuring that patients, along with their doctors, are in control of the treatments they receive when facing a terminal diagnosis. Right-To-Try will open new paths to treatments for many patients who are currently out of options.”⁷ The Goldwater Institute developed model RTT legislation that served as the framework for many state and Federal initiatives described below.⁸

The Model Act has several goals, in addition to providing access to and use of experimental treatments for patients with advanced illnesses. These include:

- (1) establishing the conditions for use of experimental treatment
- (2) protecting health care providers by prohibiting sanctions solely for recommending or providing experimental treatment
- (3) clarifying health insurers’ duties with regard to experimental treatment, and
- (4) restricting some legal actions arising from experimental treatment.⁸

Most of these components can be found in typical state laws and will be discussed in more detail.

RTT advocates are just the most recent group to demand that the FDA’s methodical approval process needs modification. AIDS activists as far back as the 1980s called on the FDA to make experimental drugs (beginning with the antiviral drug AZT or zidovudine) more easily available. Larry Kramer, a prominent AIDS activist, wrote: “There is no question on the part of anyone fighting AIDS that the FDA constitutes the single most incomprehensible bottleneck in American bureaucratic history.”⁹ He also criticized the use of double blind clinical studies stating: “Double-blind studies were not created with terminal illnesses in mind,” and called on the FDA to make experimental AIDS drugs available on a compassionate use basis.⁹

FDA Programs

In response to these and other criticisms and recognizing that it may take years to demonstrate that a new agent has clinical benefit, the FDA has instituted several regulatory programs to accelerate drug approval and access to therapeutic agents. In 1988, the FDA issued new regulations to expedite the approval process for certain drugs, which was mirrored a program used to expedite zidovudine’s approval. Despite these efforts, zidovudine remained the only drug approved for AIDS until 1991.⁹

Currently, the FDA has four approaches to accelerating new agents’ approval¹⁰:

- Priority Review
- Breakthrough Therapy
- Accelerated Approval
- “Fast Track”

Programs that aim to make new agents available to the public sooner have many similar features and some differences. The interested reader can find more details in a U.S. Food and Drug Administration document called *Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review* available at <https://www.fda.gov/ForPatients/Approvals/Fast/default.htm>.¹⁰

Generally, these programs are designed for new agents that offer significant benefit compared to available therapies for serious medical conditions or where there is an unmet medical need. After approval, manufacturers are expected to conduct definitive confirmatory efficacy trials.¹¹

In some of the more recent programs, approval may be based on a “surrogate endpoint,” which is a marker such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to “predict clinical benefit.” A surrogate marker is not itself a measure of clinical benefit. Or, approval may be based on an “intermediate clinical endpoint” effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality.¹⁰ The FDA uses these endpoints as earlier results rather than waiting for traditional measures of clinical benefit. For example, the FDA may approve an anti-cancer drug based on evidence that it shrinks tumors instead of waiting to see if it actually extends survival for cancer patients. In this case, the FDA considers reducing tumor size a *reasonably likely predictor of* real clinical benefit.^{10,11}

Results from accelerated approval have been mixed. According to the FDA’s analysis of oncology and hematology drugs, the use of the accelerated approval programs has increased during the past 25 years. Products have been brought to the market years before confirmatory trials are typically completed, with only a small number failing to verify clinical benefit.¹² Another published analysis however, concluded that the goals of accelerated approval were not being met.¹³

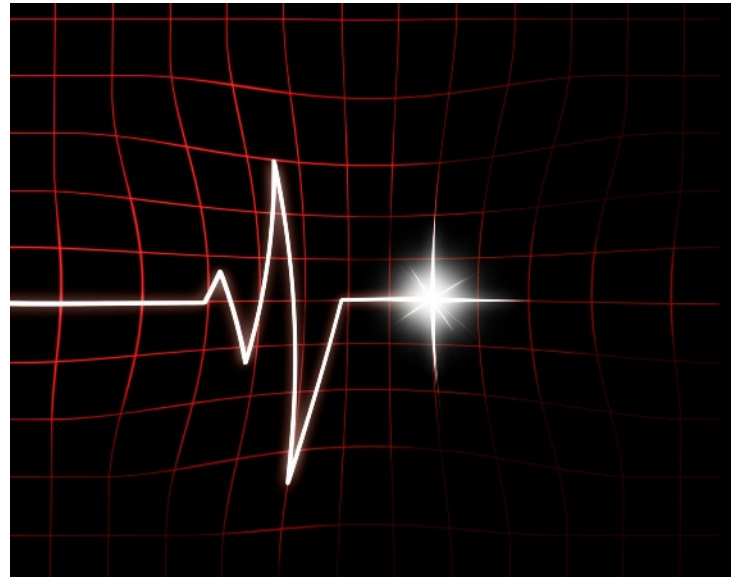
Pathways to Access

While programs designed to speed the approval of new agents may bring beneficial therapies to the market more quickly, RTT advocates seek access prior to approval. The FDA has developed pathways to expand the availability of drugs while they are still in the pre-approval stage. These are sometimes referred to as “compassionate use” programs.

In 1987, the FDA introduced the Treatment IND to permit access to drugs for AIDS before all clinical efficacy trials had been completed.⁹ The FDA has implemented additional regulatory strategies over the past 30 years. Typically, patients may receive investigational drugs before formal product approval if they have a serious or life-threatening condition and there is no satisfactory alternative therapy.¹⁵ The FDA defines a serious disease/condition as “a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease... will progress ... to a more serious one.”¹⁴ An immediately life-threatening disease or condition is a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.¹⁴

For all FDA-approved expanded access programs, patients may be eligible for treatment if they meet all the following conditions¹⁴:

- The patient and a licensed physician are both willing to participate.
- The patient's physician determines there is no comparable or satisfactory therapy available to diagnose, monitor, or treat the patient's disease or condition.
- The probable risk to the person from the investigational product is not greater than the probable risk from the disease or condition.
- FDA determines there is sufficient evidence of the safety and effectiveness of the investigational product to support its use in the particular circumstance.
- FDA determines that providing the investigational product will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval.
- The sponsor (the manufacturer or the patient's physician in the case of a single patient expanded access request) submits a clinical protocol describing the treatment plan consistent with FDA's statute and applicable regulations for IND's.
- The patient is unable to obtain the investigational drug under another IND or to participate in a clinical trial.



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The physician must first contact the manufacturer and then file an application to the FDA. The FDA claims that treatment may begin 30 days after they receive the application and that in an emergency, the approval time may be as short as 24 hours.¹⁴ When the agent is investigational, Federal law requires that its use be reviewed by an Institutional Review Board (IRB) or Ethics Committee. These entities will review an informed consent document to ensure patients are aware of potential risks and are willing to accept the level of potential risk associated with the drug. However, significant unknown risks may exist.¹⁴

The FDA recognizes that even if the patient meets these criteria, there may still be obstacles to gaining access.¹⁴

- The physician may not be able to obtain expanded access because of the patient's medical history or the risks associated with taking an investigational agent.
- The physician may not be willing to manage the use of an investigational agent.
- The company that makes the agent is not required to offer it outside their clinical trials, and it may be unwilling or unable to do so.
- The company may not have enough of the agent available for all patients requesting expanded access. Some companies establish a lottery system to determine which patients will have treatment access. Others make the decision on a case-by-case basis.

Right-To-Try Laws

If the FDA approves most requests and does so within 30 days of receiving an application, why are additional efforts necessary? The FDA estimates that between 2010 and 2014, it approved more than 5000 requests under these expanded access pathways.¹⁶ Proponents of RTT counter that the FDA only received 1757 requests in 2016, far below the number of people who could potentially benefit. While the FDA has enacted a number of different programs to accelerate patient access to agents undergoing clinical trials, many regulatory barriers remain. RTT laws go far beyond the FDA's earlier reforms.

The first attempt at the Federal level was a bill entitled "Compassionate Freedom of Choice Act" introduced in 2014.¹⁸ This sweeping measure would have allowed "the manufacture, importation, distribution, and sale of investigational drugs and devices intended for use by terminally ill patients who execute an informed consent document." It would have prevented the FDA "implement[ing] or enforce[ing] any provision of law preventing or restricting, the manufacture, importation, distribution, or sale of an investigational drug or device intended for use by a terminally ill patient,"¹⁸ effectively cutting the FDA out of the process entirely.

As of May 2018, prior to the passage of the Federal Law, 40 states had enacted RTT laws (See Table 2) and measures have been introduced in the 10 others.¹⁹

No two state RTT laws are exactly the same²⁰ but several components are common to nearly all states.^{15,20} The laws generally permit patients to request an investigational agent that has not been approved by the FDA directly from the manufacturer if: (1) the patient is terminally ill; (2) the use of the product is recommended by a physician; (3) patients have considered all other treatment options before requesting access to an experimental product; (4) the patient provides informed consent; and (5) the product is in active clinical trials and completed Phase I (Federal Law also requires Phase I completion¹). Most states have provisions for parents or guardians to give consent for minor patients. Many states also require that patients be unable to participate in a clinical trial.

Under most state laws, product manufacturers and physicians receive liability protection against claims arising from adverse events caused by the investigational product, and medical licensing boards are prohibited from taking disciplinary action against a physician for recommending an investigational agent.^{15,20} Manufacturers may charge for the product, and health insurers are not required to cover the agent's treatment costs. However, the RTT laws do not require a manufacturer to fulfill a patient's request for the investigational product.^{1,15,20}

The definition of an eligible patient varies slightly among the states, usually referring to a patient who has a terminal illness or a disease or disability that will soon result in a state of permanent unconsciousness from which recovery is unlikely.²⁰ A few states use the term "advanced illness" while California refers to "immediately life-threatening disease." Similarly, states vary on the time course of the risk of death, ranging from imminent to two years.²⁰ Under the new Federal Law, an eligible patient is one "who has been diagnosed with a life-threatening disease or condition," defined as "where the likelihood of death is high unless the course of the disease is interrupted."¹

Colorado was the first state to implement an RTT law in 2014²¹ and many states follow their guidelines. The patient must receive a "recommendation" from a

Table 2. States that have Enacted Right-To-Try Laws

- Alabama
- Arizona
- Arkansas
- California
- Colorado
- Connecticut
- Florida
- Georgia
- Idaho
- Illinois
- Indiana
- Iowa
- Kentucky
- Louisiana
- Maine
- Maryland
- Michigan
- Minnesota
- Mississippi
- Missouri
- Montana
- Nebraska
- Nevada
- New Hampshire
- North Carolina
- North Dakota
- Ohio
- Oklahoma
- Oregon
- Pennsylvania
- South Carolina
- South Dakota
- Tennessee
- Texas
- Utah
- Virginia
- West Virginia
- Washington
- Wisconsin
- Wyoming

physician to be eligible for the agent and the physician must also attest to the informed consent document, which has specific requirements. The patient must also have “considered all other treatment options” currently approved by the FDA and “been unable to participate in a clinical trial for the terminal illness within one hundred miles of the patient's home address... or not been accepted to the clinical trial.” Most states have a requirement that the patient is unable to participate in an ongoing clinical trial, but the details vary.²⁰

Many states have some troubling issues dealing with insurance.²⁰ Laws in at least 16 states state that patients may become ineligible for hospice care upon beginning treatment with an experimental therapy and six may deny home health care. Four states (Colorado, Connecticut, Oklahoma, and West Virginia) warn that undergoing treatment with an experimental therapy obtained under RTT may cause patients to lose their health insurance, and that coverage can be denied for as long as six months after the experimental treatment ends. Utah allows insurers to deny coverage for treatment for harm caused by use of the investigational product, and Nevada advises patients that “future benefits” may be affected by use of an investigational product.²⁰

Oregon's law has many unique elements.²⁰ It requires physicians to refer patients for further evaluation if they suspect their judgment may be impaired by a psychological or psychiatric disorder. The statute also requires physicians to inform patients that the investigational product they seek may be available to them through the FDA, and it bars one of the two required witnesses to the informed consent from being entitled to any portion of the patient's estate. Oregon also requires physicians to file records documenting both adverse events and positive outcomes, cost of treatment, and patient demographics and makes these data publicly available, so that other health care providers and potential patients have access to information on the agent's benefits and risks. It is the only state to require that the investigational medical product be in at least Phase II of clinical testing. Oregon is also the only state to require that hospice eligibility be determined solely by a patient's prognosis and treatment goals, not by whether the patient is receiving, or has received, a drug via RTT.²⁰ Texas bars manufacturers from charging for experimental drugs and individual states have other unique elements.²⁰

Pros and Cons

As noted above, RTT laws have many supporters including current lawmakers in Washington, DC. Generally, supporters contend that the FDA's slow, cumbersome approval process causes life-threatening delays and cite the concept of patient autonomy. Proponents of the RTT movement contend that it empowers terminally-ill patients to make choices about their healthcare and gives patients the legal right to use investigational drugs years before they might otherwise be available



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on the market. One commentator⁹ has framed the argument as whether “the government or the individual, in consultation with doctors, has the right to determine what level of risk is acceptable where it comes to using a medication that may, or may not, be effective in a last-ditch, life-or-death situation.” Colorado's statute²¹ includes the statement that “Patients who have a terminal illness 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 is the intent of the general assembly to allow for terminally ill patients to use potentially life-saving investigational drugs, biological products, and devices.”

The lead author of the federal law, Wisconsin Senator Ron Johnson, has said the law “gives patients with a life-threatening condition... a right to hope” and cautions the FDA that “It is not meant to grant FDA more power or enable the FDA to write new guidance, rules, or regulations that would limit the ability of an individual facing a life-threatening disease from accessing treatments.”²²

The Goldwater Institute claims that fewer than 3% of terminally ill patients have access to investigational drugs through clinical trials and that the FDA grants compassionate use exceptions to only about 1200 patients per year. The Goldwater Institute maintains that the “entire regulatory and financial structure of the drug industry is so loaded with disincentives that treatment

under compassionate use is rare by design” and, as a result, “Many patients run out of time before they can qualify for the exemption or complete the process.”²³ The Institute also points out that a bad outcome under the FDA’s Compassionate Use program could derail the approval of an otherwise promising new agent and could be especially damaging to small biotech firms with limited resources.²³ Significantly, the new Federal Law prevents the FDA from using “a clinical outcome associated with the use of an eligible investigational drug ... to delay or adversely affect the review or approval of such drug.”¹

Another concern is the FDA’s bureaucracy. RTT advocates claim that it takes an average of 100 hours for a physician to complete the FDA form for compassionate use.²⁰ Then patients have to wait for the FDA to evaluate and respond to the request. Eliminating the FDA from the process would shorten the amount of time needed for patients to begin treatment. Proponents have also suggested that easing the burdensome regulatory requirements for new agents could reduce the costs of drugs and biologics.²³

RTT opponents, on the other hand, generally frame their objections around several areas: the risks caused by removing the FDA from the process; that RTT is unnecessary; that RTT will interfere with clinical trials and hinder a broader distribution of therapeutic agents; that 40 different state programs do not accomplish their intended goals; or that it is a slippery slope to generally weakening FDA oversight. Opponents include some prominent patient advocacy groups such as the American Cancer Society and the American Lung Association.²⁴

In a joint statement issued while Congress was considering RTT legislation, four former heads of the FDA expressed their opposition to the bill.²⁵ The statement was signed by Robert Califf and Margaret Hamburg, who served as FDA commissioners under Barack Obama, and Mark McClellan and Andrew von Eschenbach, who served under George W. Bush. The statement read, in part, “There is no evidence that either bill [Senate or House version] would meaningfully improve access for patients, but both would remove the FDA from the process and create a dangerous precedent that would erode protections for vulnerable patients.”²⁵ Note that the current FDA Commissioner, Scott Gottlieb, has said that he is “comfortable” with the bill and that he is prepared to implement the law “in a way that achieves Congress’ intent to promote access and protect patients.”²⁶

The NYU Langone Health Working Group on Compassionate Use and Pre-Approval Access, a medical ethics and patient advocacy group, has also opposed the RTT efforts. It argues that RTT efforts are based on “myths” that removing the FDA from the process would give patients access to drugs faster.²⁷ They assert that all drugs obtained through the RTT programs could have been obtained through the FDA’s expanded access programs and that the FDA’s expertise during the approval process



can help physicians make better informed decisions and protect patients from harm. Another commentator reached a similar conclusion when comparing the proposed Senate version of RTT with existing FDA regulations, concluding that the two processes are almost exactly the same except that the FDA is removed from the equation with RTT, resulting in a greater risk for fraud and abuse.²⁸

RTT opponents dispute the notion that the FDA’s approach is slow, claiming that the FDA reforms first enacted in 2009 have simplified patient access to drugs in clinical trials.²⁹ They maintain that using the new form, FDA-3926, and its accompanying guidance documents and instructions,³⁰ a physician can complete the request in 45 minutes with a 99% approval rate.^{15,29} In fiscal year 2017, the FDA received 1,842 applications for expanded access to experimental agents and approved 1,831.²⁶ Moreover, in nearly 10% of cases, the FDA has made recommendations on dosing and other safety-related issues, often on the basis of confidential information that would be inaccessible to a practitioner who bypasses the FDA.¹⁶ They also point out that only 10% of drugs completing Phase I trials are ultimately approved and that this success rate is halved for some categories, i.e., oncology.^{16,31} In other words, nine out of 10 drugs which would be available to patients under RTT after Phase 1 would eventually prove to be unsafe or ineffective or both.

The FDA provides detailed documentation of numerous clinical trials—for a wide range of products affecting different patient populations being treated for different diseases—where Phase II results inaccurately predicted safety and efficacy. This data cautions against undue reliance on Phase II studies and upholds the need for Phase III studies.³¹ For example, the drug torcetrapib, which blocks cholesteryl ester transfer protein, an enzyme that transfers cholesterol molecules from HDL to LDL, was touted by Pfizer as “one of the most important developments in our generation.” It performed well on measures of lipids in Phase II, but in phase III studies, it proved to be ineffective and active treatment had a higher risk of adverse cardiac events and death than placebo.³¹

These types of results raise the specter that if agents become generally available after early trials, they may have unknown and serious risks. Risks might include accelerated morbidity and death, especially in frail patients and those with serious complications, the kinds of patients most likely to request RTT and to be excluded from clinical trials. In addition, there is limited data available to guide health care practitioners in mitigating the risks.¹⁶ Clearly, some patients may be worse off after starting on an untested agent and as noted above, may become ineligible for insurance or hospice care as a result of using an RTT agent. (The Federal law is silent on this issue.)

Another concern raised by RTT critics is that permitting access to patients outside the clinical trial may compromise the clinical trials themselves, especially for rare diseases, and delay the development of evidence-based decisions about approval and use of new agents for a broader audience.³²

Some opponents believe that the RTT laws are not a solution. Critics, including at least one Congressperson, believe that RTT offers patients “false hope” since it fails to address the major obstacle to obtaining experimental drugs, namely resistance from manufacturers who can and do refuse requests.³³ One commentator has said that instead of “Right-To-Try” they should be characterized as “Right-To-Ask.”²⁹ He cites the example of Janssen Pharmaceuticals which has explicitly said that they will not evaluate right-to-try requests, “as those mechanisms do not provide for FDA input, which we consider critical for ensuring patient safety.” Janssen Pharmaceuticals encourages patients to use existing FDA expanded access programs.²⁹

Legal Precedence

Prior to the RTT legislative initiatives, patients attempted to use the court system to gain access.

An influential court decision is *Abigail Alliance for Better Access to Experimental Drugs v. Von Eschenbach*, decided by the DC Court of Appeals for the District of Columbia Circuit in 2007.³⁴ The case centered on the plight of Abigail Burroughs, a young woman who was diagnosed with squamous cell carcinoma of the

head and neck. She failed to respond to conventional therapies and did not meet the clinical trial entry criteria for two then-unapproved therapies, cetuximab (Erbix) and gefitinib (Iressa). Abigail’s father founded an alliance and sued the FDA to permit terminally ill patients to gain access to agents completing Phase I. (At the time, the FDA’s Compassionate Use program was limited to drugs completing at least Phase II.)

The DC Court of Appeals for the District of Columbia Circuit held that terminally-ill patients do not have a constitutional right to unapproved drugs. The jurists wrote, “We must conclude that, prior to distribution of a drug outside of controlled studies, the Government has a rational basis for ensuring that there is a scientifically and medically acceptable level of knowledge about the risks and benefits of such a drug. We therefore hold that the FDA’s policy of limiting access to investigational drugs is rationally related to the legitimate state interest of protecting patients, including the terminally ill, from potentially unsafe drugs with unknown therapeutic effects.”³⁴

Tragically, Abigail died prior to the court case, while waiting for newer treatments to become available; the FDA approved cetuximab in 2009 and gefitinib in 2015 (after an earlier approval was withdrawn).³³

PAUSE AND PONDER:

Stacy is a 47 year old mother of two and a long-time client of your pharmacy. She has an aggressive brain cancer and is responding poorly to her therapy. Her oncologist estimates she has six months to live. She heard on the news last night about a potentially promising new drug that has just completed Phase I clinical trials. She is looking for advice on acquiring the drug and has come to you.

What will you tell her?

Pharmacist Impact

Pharmacists are expected to provide counseling on medication use as part of their professional duties. Patients with life threatening illnesses may be particularly eager to seek advice and may be fortified by dubious sources. What can the pharmacist do if asked for information about an experimental treatment?

The pharmacist will often find it difficult, if not nearly impossible, to provide help for experimental therapies. If the patient obtains the drug after Phase I testing, there is likely to be no information available on therapeutic outcomes or safety, especially regarding long-term effects. Likewise, information on drug-drug interactions will be lacking. At best, there may be limited published data on drug mechanisms coming from pre-clinical or *in vitro* studies. However many of the most novel and promising investigational

agents will likely have unique mechanisms for which predictions of *in vivo* activity will be highly speculative. The limited amount of publicly available data will hinder health care practitioners' ability to recognize and mitigate the risks.¹⁶ In a related context, the lack of available information may impede the patient's ability to provide truly informed consent. The pharmacist should, however, be on the lookout for new and unexpected side effects in patients who are using experimental therapies. However, pharmacists should note that Federal and state RTT laws prevent the FDA from using adverse outcomes outside of the clinical trial to delay or adversely affect the review or approval of the agent.¹

Another potential concern is the risk of liability. The Federal measure, and most state measures, protect health care practitioners from liability for prescribing or dispensing an investigational agent if in compliance with the requirements of the law (unless there is willful misconduct or gross negligence). However, few if any pharmacists will dispense or prescribe these agents, since they are unapproved entities unavailable through normal channels. A pharmacist should, however, exercise extreme caution if he or she provides counseling or information on these agents.

A Cautionary Note

One of the concerns about bypassing the FDA is that desperately ill patients will go to any lengths to obtain a heavily publicized, but unproven and potentially dangerous treatment. Andrew McFadyen, executive director of the rare disease patient group Issac Foundation, has warned that the proposed legislation is the first step to creating a "Wild West of medicine."³³

Similarly, Dr. Steffanie Strathdee, Associate Dean of Global Health Science at the University of California, San Diego has stated "Dying patients and their families are vulnerable; we could become victims to the likes of snake oil salesmen offering 'treatments' that could kill rather than cure."¹⁷ She has also warned against reducing the emphasis on clinical trials, stating "Treatments that work need to be monitored so their success can push forward randomized clinical trials that will decide if they work on a broader scale. And we need to know when treatments don't work, so that the deaths of these patients are not in vain and that their failures aren't repeated."¹⁷

Reviewing the experience with laetrile, touted as an anti-cancer drug in the 1970's, may reinforce concerns about relying on early results. Laetrile (also known by its unapproved name, Vitamin B-17) is a purified form of amygdalin, a cyanogenic glucoside found in the pits of many fruits and raw nuts and other plants.³⁵ At physiologic pH, it generates cyanide which is the purported active cancer cell agent. Laetrile use was legalized in 20 states and by 1978, more than 70,000 individuals in the U.S. were reportedly treated with it. The agent showed minimal toxicity in a



Phase I study,³⁵ so that if RTT had been in place, it would have been available to more patients. However, a Phase II study failed to show any therapeutic benefit and many patients exhibited signs of cyanide poisoning that was exacerbated by certain foods. Laetrile was never approved,³⁵ although it is still available through the Internet.

Summary and Final Comments

More than 100 years ago, the first laws regulating the distribution of drugs were passed. Over the years, the FDA has functioned as the Nation's oldest consumer protection agency, evolving to regulate the sale and distribution of food, human and veterinary drugs (both prescription and over the counter), biological products, medical devices, cosmetics, products that emit radiation, and tobacco products, items accounting for 20 cents of every dollar spent by consumers in the U.S.³⁶

Recent efforts to enact Right-To-Try laws at the state and Federal level are designed to eliminate most of the FDA's oversight of experimental agents for terminally-ill patients. Proponents of this movement cite support for patient autonomy and reducing the delay in access to potentially life-saving agents. Opponents cite the dangers of increased risks from unproven and untested remedies, interference with the clinical trial process, and lack of need due to recent FDA-sanctioned programs.

Pharmacists need to stay abreast and be involved in discussions and decisions about these changes, as they have potential to impact their role in health care. The impact will be greater if predictions that these changes in FDA oversight could become more commonplace are accurate, expanding beyond the needs of the terminally ill. The new "Wild West" of health care governed by patient autonomy will be in need of effective sheriffs. One question to consider is the cost-benefit of removing the FDA from the decision-making process by balancing ease of access to potentially life-saving agents against the loss of oversight and independent review. Pharmacists also need to stay abreast of FDA changes in response to the new Federal law and differences between the Federal law and the laws in their states.

Another concern raised about RTT is where to draw the line.¹⁶ If terminally ill patients have access to experimental agents with few restrictions, will demands from chronically ill patients follow?¹⁶ At the extreme, perhaps all patients whose treatment options are unsatisfactory may have a recourse to request novel, but unproven remedies.¹⁶

What could the future bring? Since the new bill prohibits the FDA from interfering with the “distribution” of experimental agents for terminally ill patients and distribution is not defined, it has been suggested that the RTT laws “could be a ‘camel’s nose’” for loosening the FDA’s ban on marketing unapproved agents,³⁷ particularly when coupled with the law’s liability protection for manufacturers.³³ The potential for Internet sales by willing and unscrupulous manufacturers is particularly chilling. Former FDA Commissioner Andrew von Eschenbach has suggested that the “FDA should approve drugs based on safety and leave efficacy testing for post-market studies,”³⁸ a dramatic shift in the FDA’s oversight. Similarly, the Goldwater Institute, a major driving

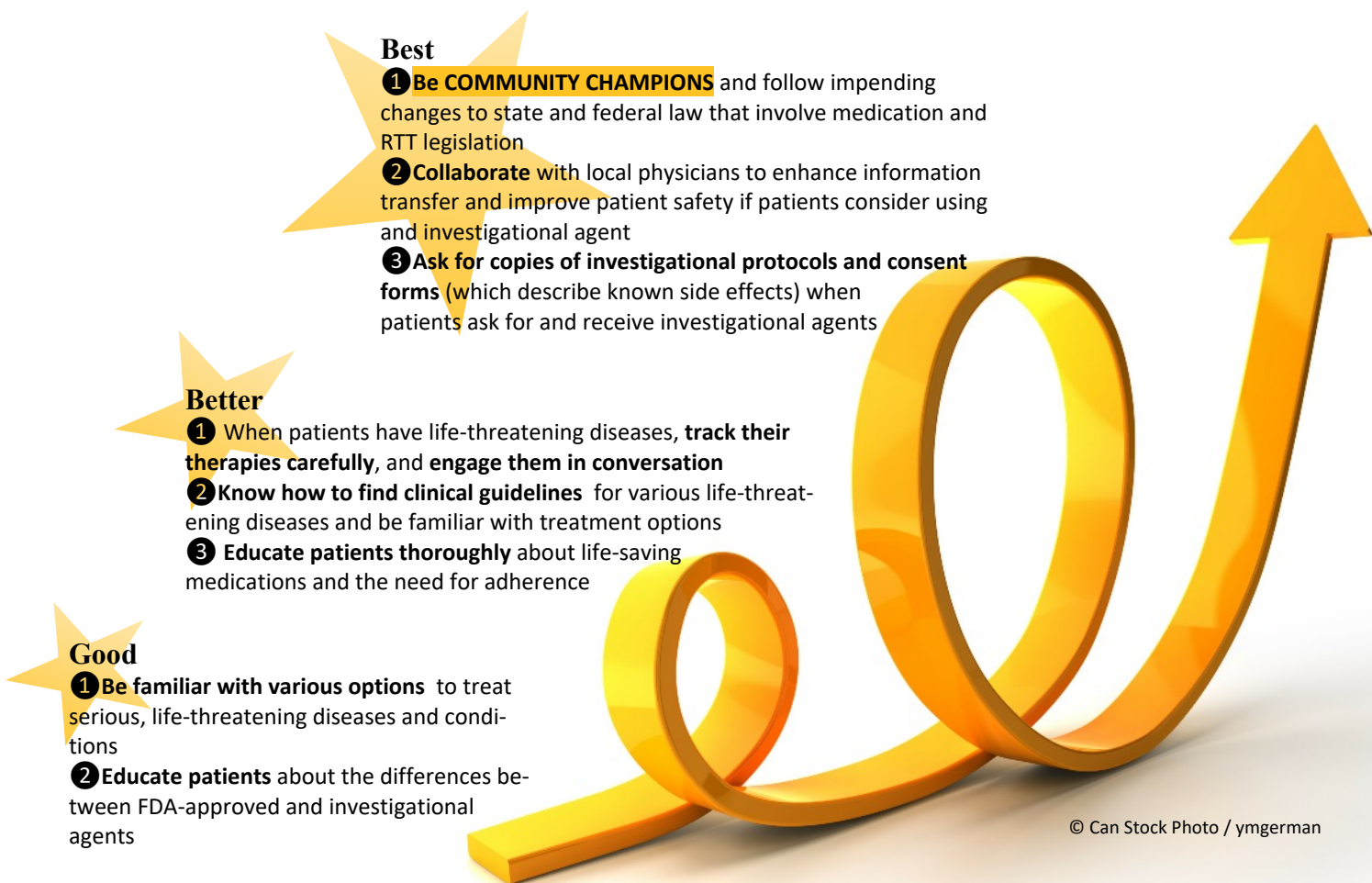
Pause and Ponder:

Do you know what it means for an issue to be a “camel’s nose”?

(Answer appears on page 12)

force behind the RTT movement, has recommended provisional approval of agents after Phase II allowing physicians to prescribe them to terminally ill patients (rather than requesting them from the manufacturer who can deny the request).²³ In their view, this approach would not only simplify the process of obtaining the drug, but could also provide additional benefits, since the manufacturer could recoup some of their investment by supplying the agents to pharmacies for ordinary retail dispensing and sale, and could also lead to insurance coverage. A lower standard of proof of safety and efficacy on unproven agents will place an increased burden on health care practitioners, including pharmacists.

Figure 2. Advancing Pharmacists and Pharmacy Technicians Role in Right To Try Laws



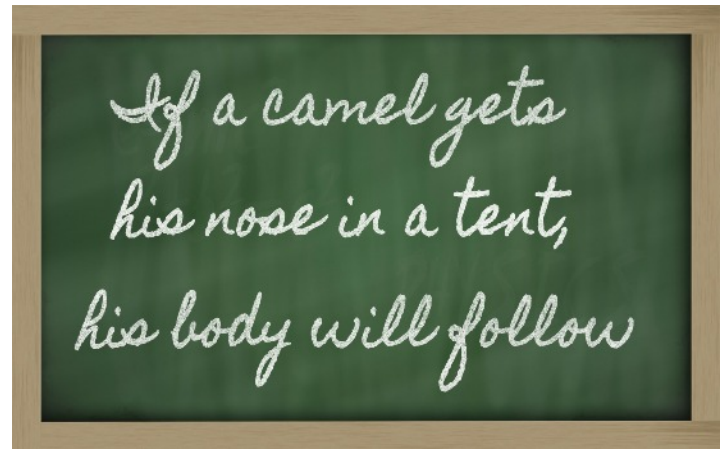
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A Camel's Nose



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This idiom is derived from the expression, “A camel’s nose under the tent,” meaning a small, seemingly innocuous act or decision that will lead to much larger, more serious, and less desirable consequences down the line. The term refers to an alleged Arab proverb that if a camel is allowed to get its nose inside of a tent, it will be impossible to prevent the rest of it from entering.