

# RIGHT TO TRY

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## HEARING

BEFORE THE

COMMITTEE ON  
HOMELAND SECURITY AND  
GOVERNMENTAL AFFAIRS  
UNITED STATES SENATE  
ONE HUNDRED FOURTEENTH CONGRESS

SECOND SESSION

CONNECTING PATIENTS TO NEW AND POTENTIAL LIFE SAVING  
TREATMENTS, FEBRUARY 25, 2016  
EXPLORING A RIGHT TO TRY FOR TERMINALLY ILL PATIENTS,  
SEPTEMBER 22, 2016

Available via the World Wide Web: <http://www.fdsys.gov/>

Printed for the use of the  
Committee on Homeland Security and Governmental Affairs



**RIGHT TO TRY—2016**

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# CONNECTING PATIENTS TO NEW AND POTENTIAL LIFE-SAVING TREATMENTS

THURSDAY, FEBRUARY 25, 2016

U.S. SENATE,  
COMMITTEE ON HOMELAND SECURITY  
AND GOVERNMENTAL AFFAIRS,  
*Washington, DC.*

The Committee met, pursuant to notice, at 10:02 a.m., in room SD-342, Dirksen Senate Office Building, Hon. Ron Johnson, Chairman of the Committee, presiding.

Present: Senators Johnson, Lankford, Ayotte, Ernst, Sasse, Carper, McCaskill, Heitkamp, and Peters.

## OPENING STATEMENT OF CHAIRMAN JOHNSON

Chairman JOHNSON. Good morning. This hearing will come to order.

I just want to thank all of the witnesses and everybody in the audience for attending what I think is a really important hearing. The title of the hearing is: “Connecting Patients to New and Potential Life-Saving Treatments.” We are going to be talking to Darcy Olsen, who has certainly been at the forefront of trying to pass—and successfully passing—legislation called “Right to Try” in States and trying to take a look at that on a Federal basis.

From a personal standpoint, I do not expect anybody to understand my story, but our first child, our daughter, Carey, was born with a pretty serious congenital heart defect. And, her first day of life, modern medicine saved her life with a procedure.

Eight months later, when her heart was the size of a small plum, they rebuffed the upper chamber of her heart. And so her heart operates backward today, but she is 32 years old and she has lived a perfectly normal life.

When we were going through that, the term “medical practice” always kept running through my mind, because I never thought of it in terms of what it really meant—medical practice—that there is nothing certain. There is no therapy, there is no procedure, and there is no drug that performs exactly the same with every person. Every person is different. And so, the advancement of medicine really does rely on the expertise of individual doctors working with patients, patients that should have the freedom to be able to try things, particularly, when we know the end result.

So this hearing is about allowing patients that freedom—and it is such common sense. Just let people try.

But then, when you start getting past the obvious conclusion—that, well, people should have the right to make these decisions

themselves—you start getting into the problems, the legitimate problems and concerns of whether it is the responsibility of the Food and Drug Administration (FDA) or the companies that are producing the drugs or the procedures—and there are legitimate concerns. It gets complex pretty fast.

But, at the heart of this issue, it really is about people. And I would ask that my written opening statement be entered in the record, without objection.<sup>1</sup>

We also have a binder of 200 letters submitted to this Committee in favor of us holding this hearing. I normally do not spend a whole lot of time on an opening statement, but I just wanted to read at least one letter. This comes from Tim Wendler of Waukesha, Wisconsin. He is the husband of the late Trickett Wendler, who I did meet back in 2014. She had amyotrophic lateral sclerosis (ALS). And Tim writes:

“My wife, Trickett Wendler, passed on March 18, 2015, after a 2-year battle with amyotrophic lateral sclerosis (ALS). When she was first diagnosed, we scoured the country to find the best doctors, medicine, treatments, etc. The only treatment drug prescribed for my wife was the exact same drug that was prescribed to her father over 20 years ago. Literally no progress. I will tell you that once we were out of options, our desire to transform the possibilities became the singular focus of our life. I have three small children with the hereditary gene that predisposes them to this intolerant disease. That is why it is infinitely important to provide patients with alternatives where none exist. The ‘Right to Try’ provides something that doctors, drug manufacturers, legislators, etc.—cannot provide: hope.”

Sadly, my wife did not have this option, but I write to you today to implore to you the importance of providing hope where none exists. I pray every day that progress is made to find a cure and that my children are not given the same drug that their mother and grandfather were given. But if none is made, I pray that my children will have the ‘Right to Try.’

Now, I read that one because, when I did meet Trickett, this was, quite honestly, shortly after I met you, Darcy, and was made aware of what you were trying to do with “Right to Try.” And without prompting, without being asked, I made the statement, “I know about this initiative, I am fully supportive of ‘Right to Try,’” and tears started streaming down her cheeks.

That has an effect. And the purpose of this hearing now is to put a face—a human face—so that we in Congress can make some intelligent decisions here—so that we can try and break through the legitimate concerns of whether it is the FDA or the drug manufacturers and give people, give patients the freedom and the access so that they have hope. And that is really what this hearing is all about.

I again thank the witnesses for very thoughtful testimony. It will be powerful testimony. And I just want to thank my colleagues for coming because I think that this is one of the most important hearings that we will hold.

With that, Senator Carper.

<sup>1</sup>The prepared statement of Senator Johnson appears in the Appendix on page 35.

**OPENING STATEMENT OF SENATOR CARPER**

Senator CARPER. Thank you. Thank you so much, Mr. Chairman. Thank you for bringing this together this morning. I appreciate your willingness to open a conversation about an issue that is important to all of us, especially to Americans that are seeking access to potentially life-saving treatment and new medical innovations for themselves or members of their families.

I want to thank young Jordan for bringing his Mom today to be one of our witnesses, so that she can tell your story. I want to thank Ms. Olsen, Mr. Morris, Dr. Gulfo, and Ms. Goodman for being with us, especially for those of you who are going to share your own stories with us today.

One of the things that the Chairman does as we start a hearing, before the witnesses speak, he swears in the witnesses—and this is going to be interesting to see how young Jordan, age five, handles that. It will be one for the books. Jordan, we are glad that you are here. All I can say is that when my boys were 5 years old, there was no way in the world that I would have put them at this table. I know—excuse me—six. My sheet here says five. But there is no way that I would have done that. [Laughter.]

They would have wrecked the hearing. But you seem to be very well behaved—better than some of us.

Today, we are going to hear from patients, we are going to hear from their loved ones, and we are going to hear from others about potential opportunities, hopefully, to improve access to medical breakthroughs and to life-saving medical treatments. These folks and their families have faced some of the most difficult and challenging circumstances and decisions that just about anybody could face, and they deserve our compassion and they deserve our understanding. And they certainly are going to get our attention, today.

Speaking as a dad, as a husband, as a brother, and as a son, it is important that we learn from our witnesses' experiences so that we in Congress can maybe work better together with the Executive Branch, with patient groups, with industry, and with other stakeholders to ensure that all Americans can gain access to safe and effective life-saving treatments as quickly as possible.

Simply put, the development of new medicines is, as we know, a long, complex, and risky process—an expensive process. For individuals with life-threatening conditions and for their loved ones, safe and effective treatments cannot come quickly enough.

As we will hear from some of our witnesses today, the path for patients and their physicians to access innovative, new treatments may not always be clear. Reforms may be needed to make sure that patients, their families, and their doctors have the information that they need to explore new treatment options.

The U.S. Food and Drug Administration, which is charged with ensuring that the drugs available to American consumers are safe and effective, has given an extraordinary level of attention to the requests of patients with life-threatening conditions. In fact, I am told that they have approved more than 99 percent of requests for emergency treatments.

Despite these high approval rates, I understand that the FDA believes that more can be done and that they are continuing, at the

FDA, to work to improve patient access to these experimental medical treatments.

I hope that we can help with some of those efforts and continue to work closely with the patients, with health care providers, with the pharmaceutical industry, and with the FDA to ensure that all patients and their families can access safe and reliable treatments as quickly as possible.

Again, we are delighted that you are all here, and it is just a real special treat to see young Jordan at 6 years old—Jordan, when is your birthday?

Chairman JOHNSON. May 15.

Senator CARPER. May 15. All right. Well, good, a day to remember. Thank you very much. Welcome, everybody.

Chairman JOHNSON. So almost seven—and, by the way, he is a great writer and a good speller—a lot further progressed than I was in kindergarten, trust me.

I do want to explicitly ask consent to enter those letters for the record<sup>1</sup> and I also want to let all of the Members know that we will distribute those to your offices as well.

As Senator Carper said, it is the tradition of this Committee to swear in witnesses, so if you will all rise and raise your right hand. Do you swear the testimony you will give before this Committee will be the truth, the whole truth, and nothing but the truth, so help you, God?

Ms. OLSEN. I do.

Ms. MCLINN. I do.

Master McLinn. I do.

Mr. MORRIS. I do.

Ms. GOODMAN. I do.

Dr. GULFO. I do.

Chairman JOHNSON. Thank you. Please be seated.

Our first witness is Darcy Olsen. Ms. Olsen is the president and Chief Executive Officer (CEO) of the Goldwater Institute in Phoenix, Arizona and the author of the book “The Right to Try.” She is a graduate of Georgetown University and New York University. She is also a recipient of numerous awards for her work in public policy, including a 2014 Bradley Prize. Ms. Olsen.

**TESTIMONY OF DARCY OLSEN,<sup>2</sup> PRESIDENT AND CHIEF EXECUTIVE OFFICER, GOLDWATER INSTITUTE**

Ms. OLSEN. Thank you, Chairman Johnson, Ranking Member Carper, and other Members of the Committee. Thank you for being here today.

As I was preparing my testimony for you on Monday, I received a call from an old friend of mine, who called to tell me that she had recently received an ALS diagnosis—or what a lot of people know as Lou Gehrig’s disease. And, although it has only been a few weeks since the diagnosis, her deterioration has been so rapid that they have already called in hospice to plan for those final days. And, as her physicians explained to her, ALS is 100 percent fatal, and there really are no treatments. And this goes, of course, Chair-

<sup>1</sup>The letters referenced by Senator Johnson appears in the Appendix on page 193.

<sup>2</sup>The prepared statement of Ms. Olsen appears in the Appendix on page 39.

man Johnson, to what you were saying. The same medicines that they were using 20 years ago are what they are using today.

But what Hazel's doctors really mean is that, in their toolbox of approved medicines, there is nothing left, because the truth is that right now, pending before the FDA, there are a dozen treatments to treat ALS and there is possibly even a cure. And in my book, "The Right to Try," I tell the story of a man named Ted Harada—and we call Ted "Lazarus" because he is the first known survivor of Lou Gehrig's. He was very fortunate to get into a clinical trial where he received a treatment that reversed his ALS symptoms. Today, it is 7 years later, and he is swimming with his kids, he is walking 5 kilometer (5k) races, and he has seen no decline at all in his respiratory function. Ted and 31 other Americans have been lucky enough to try this cutting-edge therapy. But, in the years since that clinical trial began, 24,000 other Americans with Lou Gehrig's disease have passed.

The problem is the FDA's extremely long and archaic process for approving treatments—especially for people with terminal diseases. It takes on average 15 years to bring one of these new drugs to market.

During the course of writing my book, someone who has become a friend of mine, Jenn McNary—she is the mother of two brothers with Duchenne's Muscular Dystrophy (DMD)—said to me, "By the time this drug that we need is on the market, we are going to lose an entire generation of boys." Fifteen years of delay at the FDA is an entire generation of boys lost. It is unethical not to give these boys a chance at life.

It is also unconstitutional. In America, today, terminal patients have the right to hasten their deaths through "Right-to-Die" laws, but they do not have the right to try to fight to live. So you can get drugs to die, but not if you want to save your life.

And that is why the Goldwater Institute designed what we call "Right-to-Try" laws. And, as of today, 24 States—including 7 of the home States that members of this panel represent—have adopted the "Right to Try." And that is passing on a 99–1 vote margin. Under these laws, if you have a terminal diagnosis and the FDA-approved treatments are not working for you, you have the right to try to save your life by taking some investigational medicines that are under study at the FDA, but may still be 10 years, or even 15 years, away from getting that final green light.

These "Right-to-Try" laws are not a panacea. They will not help every patient. But, at least they move us in the right direction. I know of 28 patients that are being treated under the laws at this time and I know that lives, in fact, are being saved.

There are two key reforms that you can move in Congress that will help millions access some of these life-saving drugs.

The first is that Federal law should clearly let doctors prescribe drugs to terminal patients after they have passed "Phase 1" safety testing. Terminal patients simply do not have time to wait for efficacy tests.

Second, an estimated 30 percent of the newest advances in medicine are first available overseas—as you will hear in Diego's story. These drugs, that have already received the green light from countries like Germany and Japan, should be available to patients here

in the United States. This would bring proven life-saving treatments to patients in America, now.

If you were on a sinking ship—or your spouse or your child—would you pass on the only available lifeboat because the government had not certified it yet?

As a society, we can and we should debate the best ways to make better and stronger lifeboats. But there is no argument for withholding the lifeboats that we do have from people who are drowning. So, please, help us loosen the ropes and let us get the lifeboats in the water.

Thank you.

Chairman JOHNSON. Thank you, Ms. Olsen.

Our next witness is 6-year-old Jordan McLinn, who brought along his Mom, Laura McLinn. Ms. McLinn is the owner of Indy Learning Center, founded in 2005, and the mother of three—including Jordan. She received her bachelor's degree in elementary education from the University of Indianapolis and a master's degree in education from Indiana University. She is a former junior high school and high school math teacher.

Ms. McLinn and Jordan.

**TESTIMONY OF LAURA MCLINN,<sup>1</sup> INDIANAPOLIS, INDIANA  
(ACCOMPANIED BY JORDAN MCLINN)**

Ms. MCLINN. Thank you, Chairman Johnson and Ranking Member Carper. I really appreciate you allowing us to be here today.

I am going to let Jordan just say a word here, and then, if it is OK, I am going to just send him out with Erica to play, but I want to make sure that he has a turn to speak here. Go quickly. What do you want to say?

Master MCLINN. Please say yes for the drug.

Ms. MCLINN. OK.

Master MCLINN. Watch this, Daddy.

Chairman JOHNSON. I think he is, Jordan. [Laughter.]

Thank you, Jordan. We appreciate it.

[Applause.]

Ms. MCLINN. About a year ago around this time, Jordan and I were in the State of Indiana, and we were testifying together for the “Right-to-Try” legislation, and Jordan stood there, and he said to them, “Please say yes.”

This year, he is a year older, and the things that I am going to tell you I do not, necessarily, want his ears to hear this time, so I want to start by just telling you how special Jordan is. You see him. He is six. He is running around here like he owns the place. He sat right up there in that chair. And, that is what he does. He is really smart. He plays. He hugs me. He climbs.

But, believe it or not, he is in a fight with the clock—and he is declining. At just 6 years old, he has Duchenne Muscular Dystrophy, just like you heard about earlier, about Jenn's boys. Jordan has the same disease. It is 100 percent fatal. Most boys live to be around 20. Some make it a little longer; some do not make it that long.

<sup>1</sup>The prepared statement of Ms. McLinn appears in the Appendix on page 88.

So, he is in the physical decline phase now, which means that he is losing function—and, with muscle disease, when that starts to happen, you just do not get that back. It is a little different from maybe cancer and some other diseases where, maybe when you are on your deathbed you can take a medication, and then, maybe, you can live a long, full life.

For Jordan, it does not work that way. We cannot wait 15 years and then give him these drugs that are coming up through the pipeline for him. There are exon-skipping drugs that are working, that exist. So, for the first time in the history of this disease, there is something that can help Jordan.

When I was in Ohio testifying for “Right to Try,” I actually talked with them about changing the language in their bill there because they defined “terminal” as, I believe, maybe 6 months or a year to live. Well, Jordan’s disease is terminal, and when he is at the point where maybe he has 6 months to live, it is going to be too late for him to receive the treatments that are existing, that are coming up.

So what I would like to say to you today is that Jordan—there is a drug there. Jordan needs it now. I do not know the best way for him to get that. When we testified for “Right to Try” and it was passed in the State of Indiana, we were given kind of a whole new layer of hope—kind of like a backup plan. But, ideally, we want Jordan to get this drug because the FDA approves it, because it works. We do not want them to wait 15 years to approve it because we do not have that kind of time.

Back in 2012, you passed the Food and Drug Administration Safety and Innovation Act (FDASIA). The President signed that into law in 2012. And prior to that, I am sure that you remember when acquired immunodeficiency syndrome (AIDS) was very scary and everyone was so afraid that so many people were going to die—and the FDA acted very quickly and they started approving things quickly. And they should have. And now you do not hear that much about it, right? Because there are so many drugs out there that are helping patients with human immunodeficiency virus (HIV) and AIDS.

Well, in 2012, the President signed FDASIA. FDASIA says that, “Hey, this should not just apply to something like that. It should also apply to rare disease.” So you gave the FDA the authority to say, “It is OK to do a smaller trial, it is OK to do accelerated approval, and it is OK to do that for these boys, like Jordan, that have rare diseases.” We might not find 500 people to do a trial for a disease like what Jordan has. There might not be that many patients out there. But, right now, at the end of May, the FDA has a decision to make about an exon-skipping drug. They are going to decide yes or no. They are going to say yes or no to Jenn’s sons, who are on this drug that you heard about earlier.

In this trial, there are 12 boys. So that is a small group, right? The FDA does not like that. But there are 12. There are 12 in this trial. The 4-year data showed that 10 of those 12 boys are still walking. In the external control group that had 13 boys—the same ages, with the same mutation, and receiving the same steroid regimen—one of the 13 is still walking after 14 years. That should tell

everyone in this room something, right? That drug is working for these boys.

But, we are not getting a good feeling right now from the FDA that we are going to hear yes at the end of May. We are hopeful. It is the right thing to do. They have the authority to say yes. You have given them that power. So, I am not asking even for any new legislation—although I believe in “Right to Try” and I think that there is definitely a place for that. It might not work for Jordan today, but there are lots of cancer patients and ALS patients that “Right to Try” works for. I believe in that.

But I also believe that the FDA needs to use the power that they already have been given, by you, to say yes and give accelerated approval to drugs that are working, that are safe, and that are effective. And boys like Jordan—all of these boys deserve that chance.

So I urge you to urge the FDA to use the tools and the power that you have given them to say yes.

Chairman JOHNSON. Thank you, Laura, and, obviously, we hope that they say yes.

Ms. MCLINN. Thank you.

Chairman JOHNSON. Our next witness is Diego Morris. Diego is a 15-year-old honor student at Brophy College Preparatory and previously a student and student body vice president at All Saints Episcopal Day School. He is also a cancer survivor and, at the age of 13, was honorary chairman of the “Right to Try” initiative in Arizona. Diego.

#### **TESTIMONY OF DIEGO MORRIS,<sup>1</sup> PHOENIX, ARIZONA**

Mr. MORRIS. Good morning, Mr. Chairman and Members of the Committee. Thank you for inviting me to testify. I am incredibly honored to be with you today.

Four years ago, I was a typical 11-year-old boy. I was playing two sports at the time—baseball and soccer. One morning, I woke up with pain on the outside of my left knee. I thought that it was just a typical sports injury. I continued to play in my games, and I did everything as usual for a few days. But the pain would not go away and it was causing me to limp. My mom took me to the pediatrician—and thank goodness my doctor knew immediately that something was not right. She sent me to an orthopedic surgeon the following day for an X-ray. The doctor told my mom that he believed I had osteosarcoma, a rare type of bone tumor, just by looking at my X-ray.

Everything happened quickly after that appointment. My parents consulted with many of their physician friends about what we should do next. My parents took the advice of our close family friends. He is a radiation oncologist and she is a pediatrician. They told my parents that I needed to have a biopsy as soon as possible at a premier research institution.

Just 3 days after my trip to the pediatrician, we were on our way to St. Jude Children’s Research Hospital (St. Jude) in Memphis, Tennessee. We never stopped hoping that I did not have cancer. After a long week of different types of tests and scans, they per-

<sup>1</sup>The prepared statement of Mr. Morris appears in the Appendix on page 91.

formed a biopsy. We knew the surgeons would be looking at a quick type of analysis that they perform in the operating room. If the surgeons determine that it is cancer at that point, they go ahead and place a port in the patient's chest. When I had barely come out from anesthesia, I asked my parents, "Do I have a port?" They answered, "Yes." The three of us cried—and my life was never the same again.

After many conversations with physicians, we decided that I should start chemotherapy back in Phoenix. My parents came to the conclusion that, if I would receive the exact same pre-surgery chemotherapy in Phoenix, I should be home and in my own bed as much as possible, surrounded by the family and friends who love me. I received chemotherapy for 10 weeks at Phoenix Children's Hospital before returning to St. Jude for limb salvage surgery. I am so grateful that the surgeons were able to save my leg and completely remove the tumor. They inserted a significant titanium device in my leg, which partially replaced my femur and my knee.

After surgery, the analysis of the tumor indicated that the necrosis, or the amount of the tumor killed by the initial chemotherapy, unfortunately, was only 50 percent. The doctors were hoping to see at least 80 percent necrosis. This meant that I would have to have a very aggressive plan of treatment. I needed a total of 21 rounds of chemotherapy, with some of the strongest chemotherapy drugs.

Thank goodness that my parents' physician friends never stopped doing research on every available treatment for me. They told my parents about a drug called Mifamurtide. Mifamurtide is an immune therapy drug that has improved survival rates for children with osteosarcoma. My parents were excited about the drug, but they quickly realized that it was not approved in the United States. Mifamurtide was available in so many countries all over the world, they were astonished that it was not available in America. The trials for Mifamurtide had actually been started by physicians in the United States. My parents flew to Mexico City with our friend who is a pediatrician to see the results of Mifamurtide on their osteosarcoma patients. The doctors there showed them their findings and told my parents that I was welcome in their hospital to receive Mifamurtide.

The clock was ticking. In order to have Mifamurtide immune therapy, I had to start it at the exact same time as my post-surgery chemotherapy—just 10 weeks after undergoing surgery at St. Jude. My parents never gave up hope that they could get this treatment in the United States. They contacted our Congressman, the FDA, the drug manufacturer, and anyone who they thought could help us find a way. They even spoke with the lead physicians for the U.S. trials at the University of Texas MD Anderson Cancer Center (MD Anderson) and Memorial Sloan Kettering Cancer Center (Sloan Kettering). The doctor at Sloan Kettering explained Mifamurtide and answered all of my parents' questions. My parents told him that they were not looking for guarantees—just hope.

I will never forget my parents and their friends explaining to me and my brother that we were going to move to London so that I could have Mifamurtide treatment along with my chemotherapy. We were so upset with my parents, at first, but, ultimately, we ac-

cepted that this might help to save my life. Our entire family left our home in Phoenix, Arizona and moved 5,000 miles away.

My chemotherapy treatment was brutal, and I was in the hospital more often than not. My dad was always exhausted and hated not being with us. My mom was exhausted, too, going back and forth between the hospital and home to take care of my brother and I.

But, there is no place like home. I felt so isolated. I missed my friends, my home, my dog, and my school.

My family and I were very fortunate to have the resources to relocate to another country. Most people do not have that option. When my family and I returned to the United States, we all agreed that we would do anything to help other families to not have to go through what we did to get this treatment—or, worse, to not have a promising treatment at all. So, when the Goldwater Institute asked me to serve as honorary chairman of the “Right-to-Try” campaign in Arizona, I jumped at the opportunity. I am grateful to Darcy Olsen and the people at the Goldwater Institute for giving me the chance to do something positive with my terrible experience. I am grateful to be alive, and I am grateful to be here with your esteemed Committee today.

I hope and pray that we can make it easier for Americans to have faster access to critical medical treatment. Please help us give Americans a better chance to save their own lives and those of their loved ones. No guarantees—just hope.

Thank you very much.

Chairman JOHNSON. Diego, I have to just quickly ask now, have you been judged cancer-free?

Mr. MORRIS. Yes.

Chairman JOHNSON. For how long?

Mr. MORRIS. It has been about 3 years.

Chairman JOHNSON. OK. Thank you for your testimony.

Mr. MORRIS. Thank you.

Chairman JOHNSON. Our next witness is Dr. Joseph Gulfo. Dr. Gulfo is executive director of the Rothman Institute of Innovation and Entrepreneurship at Fairleigh Dickinson University, at which he is spearheading the Initiative for Patient-Centered Innovation. He is also visiting scholar at the Mercatus Center of George Mason University and the author of “Innovation Breakdown.” Dr. Gulfo received his Doctor of Medicine (M.D.) from the University of Medicine and Dentistry of New Jersey and his Master of Business Administration (MBA) from Seton Hall University. He was responsible for the approval of an antibody for prostate cancer, a bladder cancer drug, and a medical device for melanoma detection. Dr. Gulfo.

**TESTIMONY OF JOSEPH V. GULFO, M.D.,<sup>1</sup> EXECUTIVE DIRECTOR, ROTHMAN INSTITUTE OF INNOVATION AND ENTREPRENEURSHIP, FAIRLEIGH DICKINSON UNIVERSITY**

Dr. GULFO. I would also like to note that I submitted a fuller, written statement, a book excerpt, and other writing to the record that I would like to be submitted.

<sup>1</sup>The prepared statement of Dr. Gulfo and attachments appears in the Appendix on page 94.

Chairman JOHNSON. It will be entered. Thank you.

Dr. GULFO. Thank you very much.

Well, thank you very much for inviting me to participate in this hearing. As Chairman Johnson and my fellow witnesses eloquently explained, “Right to Try” is an especially important concern for patients and their families—particularly those for whom no approved options exist and who are terminally ill.

The “Right-to-Try” debate also vividly illustrates several foundational principles contained in my research about the proper role of the FDA for the 21st-Century medical ecosystem, which apply to patients at all stages of their disease—not just terminally ill or those with no good choices.

I have six brief points to make.

First, the FDA has substituted its statutory mission to promote health with a new, misperceived duty to protect health, virtually at any cost. When terminal patients have no other options, what is the FDA protecting when it prohibits access to experimental treatment? The potential harms of the FDA’s approach to protecting health are not limited to terminal patients, however. It has serious implications for all who suffer disease—and it is having a chilling effect on medical innovation.

Second, benefit versus risk is a private health decision requiring the consideration of the individual’s needs. The FDA’s reliance on the benefit versus risk to the average patient is not an acceptable substitute. “Right-to-Try” patients seeking experimental therapies have a right to make these decisions, and patients and their doctors know far more about their specific circumstances than the FDA ever could. Of course, the same is true for all patients at all stages of disease.

Third, the FDA’s restated mission to protect, rather than to promote health has necessarily made it judge new drugs and devices not on safety and effectiveness—as specified in the law—but, rather, on clinical utility, benefit versus risk, and long-term outcomes, including survival. This truly stifles medical innovation by necessitating larger and larger and longer and longer trials that are extremely expensive. The net result is that many compounds, which could possibly help patients, are not even developed—and many that are obviously safe, effective, and could be helpful actually fail in these kinds of trials because the studies are improperly structured. It is simply impossible to control for all of the variables that modulate long-term outcomes.

Fourth, increasingly the drugs that are developed, even by large companies, are geared toward narrow, niche, and orphan populations, where benefit versus risk is a low bar because there are no other products available. In 2014, 40 percent of all new drug approvals were for orphan claims. In 2015, the number jumps to 48 percent.

Fifth, the very fact that we are here, today, to discuss this magnificent movement is testimony to the sophistication of today’s medical ecosystem and marketplace. That which we may have needed the FDA to do just a few years ago is unnecessary today. With the Internet and rapid communications among patients and among physicians, knowledge is shared at a lightning pace. Patients have easy access to timely, high-quality information that al-

lows them to make excellent treatment decisions with their doctors. Today's reality could not have been anticipated 20-plus years ago, when the FDA began to move away from safety and effectiveness as the rightful basis for approval.

My final point is that medical innovation is fragile because most of it occurs in small start-up companies. I have been responsible for the development and approval of products for prostate cancer, bladder cancer, and melanoma. As such, I have worked very closely with all three of the FDA centers—drugs, biologics, and devices—in the development of novel products. The two things that start-up companies need the most are investment and regulatory certainty. Two companies that I ran no longer exist because the FDA changed the criteria for approval after we performed large studies that achieved all of the endpoints to which the FDA agreed before we started. In both circumstances, the FDA told us that safety and effectiveness were not enough—rather, clinical utility and evidence concerning long-term outcomes were required. This made investment disappear and rendered it impossible for us to launch the products and bring them to doctors and patients effectively after, ultimately, obtaining the approval with no new data in either case.

In summary, the need for the “Right-to-Try” movement is emblematic of the FDA’s “protect health at all costs” ideology. This has made the FDA assume a role that it was never intended to have—being arbiters of benefit versus risk, clinical utility, and long-term outcomes—and that has brought the FDA into private health decision-making. We need the FDA to return to its public health mission of promoting health by making approval decisions on the basis of safety and effectiveness.

Thank you.

Chairman JOHNSON. Thank you, Dr. Gulfo.

Our final witness is Nancy Goodman. Ms. Goodman is the executive director of Kids v Cancer, which she founded in memory of her son, Jacob, a victim of pediatric cancer. Her group focuses on encouraging pediatric cancer research and pediatric, rare disease drug development. Ms. Goodman.

**TESTIMONY OF NANCY GOODMAN,<sup>1</sup> EXECUTIVE DIRECTOR,  
KIDS V CANCER**

Ms. GOODMAN. Thank you, Chairman Johnson, Ranking Member Carper, and Members of the Committee for inviting me here today. I am honored to testify before you about how to connect patients, and children in particular, to new and potentially life-saving treatments.

I am the executive director of Kids v Cancer. But, more importantly, I am the mother of Jacob, who was a beautiful, normal, loud, difficult, and brilliant little boy at 8 years old, who was diagnosed with brain cancer. Jacob suffered 2 years of profound neurological impairments and unmanaged pain before he died at age 10.

I have been working at Kids v Cancer now since Jacob died 7 years ago, and, frankly, I do not even like speaking about him in public anymore. It is too raw. But, I brought a photo so that you can emotionally connect that way.

<sup>1</sup>The prepared statement of Ms. Goodman appears in the Appendix on page 187.

The fact is that the drugs that were used to treat Jacob were 40 years old, and so for this reason, I launched Kids v Cancer to focus on changing the landscape of pediatric cancer research and to make it possible for children to get access to novel treatments.

When Jacob was at the end stage of his cancer, I contacted eight separate companies, who were in the process of adult clinical trials for brain cancer drugs, to request access to these unapproved drugs for Jacob. Finding the right person to speak with was very difficult. Sometimes I contacted the CEO, others times the Chief Medical Officer (CMO) or the head of business development. For one company, it was a friend of my cousin. It was all very ad hoc. Of the eight companies, six did not ever respond to my request and made no determination. Two formally reviewed it and declined. And then, Jacob died.

So the purpose of the “Right-to-Try” laws is to help patients get access to drugs that they would not otherwise get access to. That is a serious problem, and it is a goal that I share. But I think that we need to take a broader approach to this problem, and that has been the focus of Kids v Cancer.

The fact is that children with cancer seek compassionate use access to drugs because there are almost no clinical trials available to them of these same unapproved drugs. Kids have to wait until drugs are approved, when they have cancer, before they get access to them in a clinical trial setting.

So our first step at Kids v Cancer was to incentivize companies to develop drugs specifically for pediatric cancers and other pediatric rare diseases. In 2012, Congress passed the Creating Hope Act as part of the Prescription Drug User Fee Act (PDUFA). That has created nearly \$800 million in incentives—at no cost to the taxpayer—for companies that get a new drug for pediatric rare disease approved by the FDA. The Creating Hope Act is doing what everyone hoped: stimulating companies to turn advances in science into treatments for pediatric cancer.

The medical challenges are hard enough to overcome. Kids with cancer should not be disadvantaged by the lack of economic incentives for companies to develop drugs for tiny markets. The Creating Hope Act is up for renewal as part of the 21st Century Cures Act passed by the House, and I urge the Senate to pass it as well. And I am also proud to say that several of the drugs developed for Duchenne Muscular Dystrophy are benefited and supported financially by this legislation.

Our second step with Kids v Cancer was to make new drugs being developed for adult cancers available for kids as well. In 2003, Congress passed the Pediatric Research Equity Act (PREA), which requires companies developing drugs for adults to conduct pediatric trials on such drugs where they could benefit children. The problem is that PREA has not kept up with the science. PREA only requires clinical trials if the children have the same “indication”—that is, if children have the same kind of cancer. But now, we know that children do not get breast cancer or prostate cancer, but the mechanism in these cancers might be evident in pediatric cancers such as neuroblastoma or medulloblastoma—the type of brain cancer that my son had.

We have proposed the Kids Innovative Drugs (KIDS) Initiative, a modest change to PREA that would update PREA to take into account these new scientific developments and ensure that drugs being developed for adults, which could have relevance to pediatric cancers, are tested on children as well. And I urge Congress to take up and pass the KIDS Initiative as soon as possible.

We are exploring other ideas related to eligibility for trials as well. For example, why do almost all adult cancer trials use 18 years of age as the minimum age of eligibility without any discussion of the scientific or medical rationale for this cutoff?

And that brings me to “Right-to-Try” laws. Yes, when it comes to seeking compassionate use access to unapproved drugs, the paperwork is onerous and the process is time-consuming. In response, Kids v Cancer is launching a “Compassionate Use Navigator.” We are working to better inform physicians on how to apply for compassionate use applications for their pediatric cancer patients with drug companies, the FDA, and their hospitals. We hope to provide point of contacts (POCs) for drug companies. We will post the FDA’s new, expanded access form and we will work with the Institutional Review Boards (IRBs) of the hospitals where the children are treated. We will offer to counsel physicians, personally, on specific applications. In addition, we will collect information about the efforts and the outcomes of pediatric cancer compassionate use applications.

The “Compassionate Use Navigator” is not the whole solution to the challenge of connecting children with cancer to new treatments. However, it will give parents of dying children more time with their kids. It will lessen the burden that their physicians have as they apply for compassionate use applications. And, we hope that it will encourage more physicians of kids with cancer to apply for compassionate use.

In addition, Kids v Cancer supports the Andrea Sloan Compassionate Use Reform and Enhancement (CURE) Act to have drug companies make available to the public their policies on requests for compassionate use access, including the minimum criteria for approving requests and the time needed to make a decision. I urge the Senate to pass the Andrea Sloan CURE Act as part of the 21st Century Cures Act bill as well.

But, from my personal experience and from working with dozens of other families, my sense is that the fundamental problem is not the FDA, but, rather, it is the incentive facing companies. Even though the FDA approves virtually all compassionate use applications that it receives, and even though it has indicated that an adverse reaction to a drug provided for compassionate use will not adversely affect a company’s application for that drug’s approval, companies remain risk averse—and they would rather not provide such drugs.

But, even if one could change that, the results would be one-off anecdotes. We cannot afford to take an ad hoc approach to addressing pediatric cancers and pediatric rare diseases. We need to address the lack of access that seriously ill children have to novel, unapproved drugs not only by one-off compassionate use applications, but also in clinical trials. That is why initiatives such as the Creating Hope Act and the KIDS Initiative are so important—they

give companies compelling economic reasons to create new drugs for kids and require them, where appropriate, to study pediatric uses of drugs that are being developed for adults. And that makes it easier for children to get access to drugs that they need to survive and live happier, healthier lives.

We need more, however, than anecdotes. We need to change the landscape of pediatric cancer, and we need to ensure that children with rare diseases—life-threatening diseases—like Jacob, Diego, and Jordan, will have access to new and potentially life-saving treatments.

Thank you.

Chairman JOHNSON. Thank you, Nancy. Obviously, we are sorry for your loss.

I do want to go right to you—and possibly Dr. Gulfo will also answer the question. Why is it that kids are not involved in clinical trials? I mean, how else do you test these things? You kind of asked the question. Do you not have the answer? Do you have suspicions? Or, maybe, we will push it over to Dr. Gulfo to answer that question.

Ms. GOODMAN. I have my theories as well as to why companies are reluctant to undertake pediatric clinical development. First of all, the markets are small. It is very tough to develop a drug for a very rare disease, whether it be pediatric medulloblastoma or Duchenne's Muscular Dystrophy. Accrual rates are small. It is just challenging to put a drug together, and what that means is that the drug that you develop has to really be very good—and that is difficult.

Chairman JOHNSON. So, is that a company decision or is that an FDA decision?

Ms. GOODMAN. That is a business decision.

Chairman JOHNSON. A business decision. So, there is no law that prevents children from being involved in clinical trials?

Ms. GOODMAN. Well, that is correct. And for that reason, Congress passed the Creating Hope Act in 2012.

The second reason that I think it is difficult is that companies maximize return on investment (ROI) over the long run through blockbuster drugs, and undertaking a pediatric trial is just a distraction for them if their goal—for which they have fiduciary responsibility to shareholders—is long-run return on investment. There are two laws that Congress has passed to address this problem. One is PREA, which I discussed, and the other is the Best Pharmaceuticals for Children Act (BPCA). The problem with PREA is that it does not apply to cancer. PREA requires companies to undertake certain pediatric trials and BPCA does provide a carrot, an incentive for companies to provide such trials.

The challenge with BPCA is that it is entirely optional. Companies do not have to undertake these trials until the time that it makes the best business decision, the most sense for them, from a business perspective—which is the very end of their exclusivity period. So the National Organization for Rare Disorders (NORD) has estimated that that is 9½ years after approval of the drug for adult indications.

Chairman JOHNSON. Dr. Gulfo, do you have anything to add to that?

Dr. GULFO. Yes, I will add. Cancer is a disease of the elderly. I mean, I teach cancer biology, and in order to accumulate the mutations that you need, you need to live a long time. So, I could not agree more with what Nancy said. So, it is a very small market for pediatric cancers. I think that that is a critically important thing. The other is that—

Chairman JOHNSON. But, I just want to—because, one of the things in your testimony that you talked about was the innovation occurring in orphan diseases—limited use targeted. So, can you explain that for me?

Dr. GULFO. You took the words out of my mouth. As we continue to see companies going for these ultra niche claims, you are going to get to the population sizes for pediatric cancer. So, I actually think that we are going to see more of that.

It is also very hard to do studies in children—very hard. The level of approvals that you need and the way that they are looked at—the way that they are looked at by the IRBs and things, it is very difficult because you have patients who are young and who could, potentially, live a very long time. So, it is harder to do. The market is not there. But, I agree with you, as this progress is pushed to more and more niche claims, you will see more and more childhood cancer studies.

Chairman JOHNSON. With my questions, I am really going to be talking about the impediments. I think that I said earlier “legitimate”—I will say “understandable” problems. And I thought that your testimony was really pretty interesting. Part of the problem has been things, like congressional hearings, where we call members of the FDA up here, and if it has not been perfect—let us face it, life is full of risk. There is no such thing as a risk-free society. Members of Congress beat up on the FDA, and so, they become even more risk averse. So, I want to concentrate on that.

Darcy, I do want to talk to you, though, because you talked about Ted Harada, but you mentioned 31 other people with that same exact drug. I am afraid that I know what the result was for the other 31. Did they pass?

Ms. OLSEN. To my knowledge, most of them actually did quite well.

Chairman JOHNSON. So, they extended their life, but, I mean, have they all passed or—

Ms. OLSEN. No. No, they have not all passed.

Chairman JOHNSON. OK. So we have more than one Lazarus then.

Ms. OLSEN. Yes, we do.

Chairman JOHNSON. OK.

Ms. OLSEN. And so, for that particular treatment, they are in Phase II and III. They are doing all kinds of tests. But even someone like Ted—it is interesting, when you talk about wanting to get into clinical trials, Ted actually no longer qualifies for the next clinical trial. So, if the treatment wears off for him, he could still die from—

Chairman JOHNSON. And he had access to this when?

Ms. OLSEN. About 7 years ago. But now, he is disqualified for the next—

Chairman JOHNSON. I cannot imagine having a family member with ALS, knowing that 7 years ago somebody was surviving this, and not having access to it. I mean, Doctor, can you explain that? Can anybody explain? Again, I am not beating up on anybody. Please explain why something that could be that great a breakthrough, in a disease that we all know the end state of, is not made available. Why don't we just rush that? Please explain that.

Dr. GULFO. I cannot. I mean, are the trials still ongoing?

Ms. OLSEN. Yes.

Dr. GULFO. And he does not meet the entry criteria?

Ms. OLSEN. Yes.

Dr. GULFO. Right, so the entry criteria would need to be amended for him, and there is a mechanism in place for compassionate use in order to do that. But, I think that what people are asking here is, why do we need to go through so many hoops?

Chairman JOHNSON. Ms. McLinn, you were talking about some drugs that really address—maybe not specifically your son's condition, but certainly would tie into a potential cure as well. Talk about that, the impediments to compassionate use. What are you finding to be the barriers?

Ms. MCLINN. Well, first of all, it does apply to Jordan, and it is kind of confusing, but the drug that is up for accelerated approval is a drug that 13 percent of boys with Duchenne are—they can benefit from this drug. The drug that Jordan needs is the very next one in the pipeline. In fact, it works the same way. The chemical backbone is the same. It is made by the same company. But we need approval for this one in order for Jordan's to move forward.

Chairman JOHNSON. And it just addresses a different part of the gene? Is that the—

Ms. MCLINN. That is right.

Chairman JOHNSON. So how many children—how many young boys—has this actually helped, to date, that have had—and how do they get access to it? Was it through a clinical trial? Was it through compassionate use? Was it a one-off?

Ms. MCLINN. Only through a clinical trial, not through compassionate use at all. So, there were 12 boys in the original trial for the drug that skips Exon 51, but they are now doing confirmatory trials. I cannot give you an exact number, I am sorry, but there are a lot more boys now who are receiving that drug.

Chairman JOHNSON. Is it tens? Is it hundreds?

Ms. MCLINN. Hundreds? Hundreds.

Chairman JOHNSON. Hundreds—but there are thousands with the disease.

Ms. MCLINN. Oh, yes. Yes. And the thing is that 1 in 3,500 boys have Duchenne, and so, within that 1 in 3,500, 13 percent of boys can take this drug that I was speaking about—that the FDA is going to say yes or no to. And then, 8 percent of boys have the mutation that Jordan has and 8 percent have another mutation. And then, it just keeps going down the line there. But we are talking still about a lot of boys that are waiting on this treatment. It exists. And I will tell you that there are boys in Europe who are receiving the drug that Jordan needs. I know one of them, personally. He is jumping. That does not happen. Jordan cannot jump. This

does not happen in this disease. These drugs are working. So, there are boys on this drug in Europe—just not here, yet.

Chairman JOHNSON. So just real quickly, before I turn it over to Senator Carper, Dr. Gulfo, is there any rationale for not—I mean, again, is there any rationale for not allowing parents, and their children with this disease, to have access to this drug now?

Dr. GULFO. Well, there is rationale not to approve it, but—until there is proper evidence. Now, my whole testimony is about defining what “proper” is, OK? But having them have access—absolutely, they should have access to it. These children, as you said earlier, their diseases are terminal. It is terrible.

Chairman JOHNSON. But, again, I do want to get the other—the companies, themselves, are concerned about having an adverse result—

Dr. GULFO. Absolutely.

Chairman JOHNSON [continuing]. In a nonclinical trial, or whatever, and having that affect the ability to—and we all ought to be concerned about that, because, if there is a drug that could be helpful and it gets, basically, kiboshed because of one of these compassionate use—

Dr. GULFO. Right. So, why would the company do all of the things that you need to do to show that it is safe to give to the child in that case, OK, when it is just pure risk? Because if an adverse event were to happen—and adverse events happen—it will directly impact the development program and hurt many other children. I mean, you look back at it, this could really hurt the availability of this drug for many others. So, I could not agree more with what Nancy said—although the right things are said, it is not in practice. There was a company whose product was put on clinical hold because of an adverse event that happened in a compassionate use setting. The company’s name is CytRx. And that just should not happen—and that sent the message throughout the whole industry that there the risks involved in trying to be good citizens.

Chairman JOHNSON. “Catch-22” is running through my mind here, as we are talking about this.

Dr. GULFO. Yes.

Chairman JOHNSON. Senator Carper.

Senator CARPER. Mr. Chairman, one concern that I think that we are hearing here, today, is about a lack of access to information about which programs are available to help people who are facing these life-threatening conditions. Since the FDA is not with us today to provide information on how their current processes work, I just want to ask unanimous consent for the fact sheet<sup>1</sup> that I have here, on patient access to investigational therapies, from the FDA, be included in the hearing record.

Chairman JOHNSON. Without objection.

Senator CARPER. Thank you.

Thank you all for joining us today. It is wonderful testimony. And, Ms. McLinn, I walked back into the anteroom, behind me, to get a cup of coffee, and there spread out on the floor were all kinds of toys and a little boy having a good time with Erica, who is 22

<sup>1</sup>The fact sheet referenced by Senator Carper appears in the Appendix on page 209.

years of age. And, I had a nice chat with them, and he seems to be in good hands, with you and with Erica.

I have a question for the whole panel that I am going to ask you to think about—and then I am going to come back and ask it at the end—but I am going to telegraph my pitch. Then I am going to ask Nancy Goodman a couple of questions, and then we will come back to the whole panel. But, the question that I want you all to think about, in the meantime, is that there seems to be a general consensus that there are some improvements that are needed in the current process that patients use to gain access to clinical trials and to unapproved drugs. And, here is what my ask is: What actions do you think that Congress should take—that Senator Johnson and myself and our colleagues should take—either through legislation or through partnering with the administration, to improve patient access to new and potentially life-saving treatments? So think about that. And, while you are thinking, I am going to ask Ms. Goodman a couple of questions.

Ms. Goodman, in your testimony—I think that it was at the end of your testimony—you noted that you do not necessarily believe that the FDA is a fundamental problem for those trying to gain access to new treatments but, rather, there are challenges that companies who are developing these new treatments face when they receive requests from an individual patient. Could you just elaborate on this for a moment? Does the FDA assist individuals who are trying to contact companies and seeking medical treatments? Go ahead, please.

Ms. GOODMAN. So, I think that it is best that I just answer this from my personal experience. I am not an FDA expert nor have I worked at a drug company.

When I was applying for compassionate use access for Jacob, the two companies who declined our requests stated that they had not started drug development in children and that they were just concerned about what the implications of the pediatric trial would be.

At that time, I was like any other parent with a terminally ill kid. I did not know a lot of people at the FDA. I did not know how to contact people. Since that time, however, I have formed Kids v Cancer, and I am grateful that I do have an opportunity to speak with people at the FDA. And, I have to say that, though the systems could be better developed, I have found officials at the FDA to be very interested in helping families gain access to compassionate use access to drugs.

For example, a year and a half ago, there was a little boy, Josh Hardy, who was seeking access to an adenovirus drug on a compassionate use access basis. It was a matter of life and death for him. The entire pediatric cancer community rallied around him. There was social media and traditional media. Kids v Cancer was not the leader, but we did participate. And, ultimately, my understanding is that the reason that he got access to the drug is that an official at the FDA heard a story on the Cable News Network (CNN) and she called the CEO of the relevant company and said, “What is going on?” And she offered to craft, with the CEO, a solution.

So, my personal experience is that they are really very interested in helping—and we need to give them the support and, maybe, the

legislative authority to do more. To that extent, I support the Andrea Sloan CURE Act, which would do that.

Senator CARPER. All right. Thank you.

Changing gears just a little bit here, I think that you launched something called the “Compassionate Use Navigator” through Kids v Cancer.

Ms. GOODMAN. That is correct.

Senator CARPER. Could you just walk us briefly through how that navigator works for patients and for their families?

Ms. GOODMAN. Absolutely. So, the “Compassionate Use Navigator” will be launched in April, and so, I want to talk to you about our plans. The first steps that we are building now on our website are a lot of information for physicians, so that they just have an easier time understanding what it is that they need to do to undertake a compassionate use application. It is very difficult for physicians, even, to figure out the necessary steps right now. We will be talking with them first about, for example, how to find a point of contact in the company to reach. If they have difficulty doing that or if they would like our assistance, we will take that responsibility, and we will do our best. We will help them write the letter to the company. We have an excellent person who we just brought on board, Elena Gerasimov, who will be reviewing the letters and providing support. Doctors may be wonderful scientists and weak writers. That should not be a reason that a kid does not get a drug.

Then, we will be working with the physicians as they approach the FDA. We will be posting the FDA’s short form on our website and working with the physician—and we intend to use that form when we approach the FDA.

And then, third, the IRBs of the hospitals need to be involved. Sometimes, the IRBs are slow. I have found that whenever I call the IRB officials and leave a nice voicemail on their machine, they decide within about 30 minutes.

So, that is what we intend to do, and then we intend to document all of our experiences, so that the whole community that is interested in this issue will have some information about what is happening with respect to compassionate use applications in the pediatric sphere.

Senator CARPER. All right. Well, thank you. I am—

Ms. OLSEN. Senator Carper, I do not mean to be rude and interrupt, but could I just shed a slightly different perspective on compassionate use?

Senator CARPER. Sure, please.

Ms. OLSEN. I really appreciate what Nancy is trying to do with compassionate use, because it speaks to a fundamental problem, which is that the FDA says that they approve 99 percent of requests, but that is because you basically have to get to the top of the Himalayas to be able to present your request. The truth is that less than 1 percent of patients who are terminally ill in this country will ever get through the compassionate use program.

There is a principle at stake as well, which is that you should not have to beg the Federal Government for permission to save your life. This is America, and compassion should be the rule, not the exception to the rule. And, in working on my book, we interviewed Janet Woodcock, is head of Center for Drug Evaluation and

Research (CDER) and is acting director of CDER's Office of New Drugs (OND), and asked this question to the FDA: "Do you think that it would be a good thing if tens of thousands of patients with terminal illnesses were able to access these investigational medicines that we are talking about?" And, the first words out of her mouth were, "It would be another burden on the health care system."

A little bit of a different perspective. In Europe, they have tackled this. For 25 years, they have had compassionate use. They have it writ large. The problem in America is that companies do not have an incentive to participate. They have overcome that, in Europe, by granting provisional access, so say for these DMD drugs where they have trials going, they open it up to all of the kids, and then they monitor, in real time, what is going on so that they get better data. The kids get access right away, the companies can charge a nominal fee, and they have an incentive to participate because the regulatory steps become more clear.

So there is a way to do this. We are 25 years behind.

Senator CARPER. Thank you.

Just very briefly, Ms. Goodman, would you like to respond to that—to what Darcy has said? Just very briefly.

Ms. GOODMAN. So I do not have experience with the European system, and I will defer to Darcy on that. And, my only question is: What environment could we create where companies truly would be comfortable if they put a kid on a trial and the child died? Even if a company did not have to report that adverse event to the FDA, it gets reported in the newspapers. I think that the company would still be concerned. So, I do not know as much about this piece of it as Darcy does, but I am not sure that I understand, from the company's perspective, how this really takes care of their concerns. And so, that is why, from my vantage point—at Kids v Cancer we have focused, first, on process with respect to compassionate use—it is only part of the answer—and, second, getting companies to start developing more interesting drugs in the first place. I just want to give an example.

In the cancer space, there is a new kind of drug called PD-1 inhibitor drugs. It looks like these might be curative for patients with melanoma. It is very exciting. And, if you do combination therapies, the response rates are 70 percent in adult trials. It is really very exciting.

There are 220 PD-1 inhibitor trials that are listed on "clinicaltrials.gov." This morning, I went to take a look at how many are available for kids right now that are open for enrollment. Three. How many are combination therapies? None.

So, I just want to provide this as an example of how, from my perspective, I think, the goal is to create reasons for companies to start pediatric trials—get the denominator as big as possible.

Senator CARPER. All right. My time has expired, and maybe we will have a second round, and I can ask—

Chairman JOHNSON. We will.

Senator CARPER [continuing]. That question that I telegraphed a few minutes ago. Thank you.

Chairman JOHNSON. Senator Ernst.

**OPENING STATEMENT OF SENATOR ERNST**

Senator ERNST. Thank you, Mr. Chairman. And, thank you to all of you for—many of you traveled a long ways to get here. We are glad to have you with us today.

Earlier this morning, I hopped on Facebook—and I was checking it out—and this is a picture of one of my best friend's sons, and he was diagnosed with leukemia several years ago. And he has just taken the last of his chemotherapy pills. He has gone through quite an extensive treatment over the past number of years. And so after church on Sunday, we are all going to celebrate the fact that he is still with us. Fortunately, his family was able to use approved drugs and treatments. There are many families that do not have access to those drugs. So, we are lucky. And there are a lot of families that are not as lucky.

And so, this is an important topic—and I know all of you have struggled with this issue, and we will continue to struggle with this issue, I think, as we work through this particular situation.

Diego, it is great to have you here.

Mr. MORRIS. Thank you.

Senator ERNST. It is great to have you here.

So we have spent a lot of time visiting about this, and I was astounded when I got the statistic—it came from the Energy and Commerce Committee during the House's consideration of the 21st Century Cures Act, and that statistic is that 95 percent of rare diseases have no recognized treatment—so, Nancy, what you were speaking on just a little bit ago. And, I think that we all agree that gaining access to treatments is important and discovering those treatments is important. And, I do hope that our colleagues on the Senate Health, Education, Labor and Pensions (HELP) Committee can continue working on this and parallel medical innovation legislation that helps us to streamline processes, so that we can cut some of the red tape to get to these cures and to make sure that we are not hampering innovation that is available out there.

For this panel, it is an important time, as we have seen development of new technology, and drugs that can cure illnesses and improve the quality of life. And, although, today, we have spent a lot of time talking about the FDA's regulatory processes, especially for children, we also need to think ahead as well. And so, I would like to just step out there a little bit ahead. When we do have those life-saving treatments in place and they are FDA-approved, can any of you speak to ways that we can break down the regulatory burdens that exist at the Centers for Medicare and Medicaid Services (CMS) that affect how quickly our Medicare recipients can start receiving these therapies? There seem to be barriers, not just for our youngsters, but also for those toward the end of life. Is there anyone that can speak to that? Dr. Gulfo, you look like you are thinking very hard about it.

Dr. GULFO. Yes, I am. I am not an expert in that area, but to my understanding, Medicare patients cannot be denied approved drugs for approved claims.

Senator ERNST. For approved—

Dr. GULFO. So, the issue is the approved claims part of it. Now, in pediatric cancers, there is a tremendous amount of off-label use. I think that it is as high as 60 percent, because the drugs get ap-

proved for adults—like PD-1 inhibitors are approved for adults—and then it will be tried in pediatrics off-label. So, I think that that is something that you could look at—that, if approved drugs are used on-claim, they cannot be denied. It is when they are used off-claim, I think, that that could be an issue to look at.

Senator ERNST. Very good. Any other thoughts? I know probably not your specific area, but—

Ms. GOODMAN. Senator Ernst, I think that that is an excellent question, and, again, with respect to children, one challenge is that, when drugs are approved, that is when pediatric oncologists have the opportunity to undertake pediatric trials. And then, the problem is that, because these are rare-disease drugs, the way that they get developed is by companies looking forward to the premium pricing of these drugs—and they price them very high. And then, pediatric oncologists cannot afford to buy them to undertake pediatric studies.

So, again, they have to wait until companies decide to provide them a clinical supply of the drug for free—and that decision occurs when it is the right business time for that company—not when it is the right time for the kids. That is why we only have three PD-1 inhibitor trials for all pediatric cancers at this time. It is not the right business time for these companies to undertake these trials. And, again, that is why we are asking Congress to take up the KIDS Initiative to reform PREA, so that there are certain times when, if it is appropriate, companies should undertake pediatric trials.

Senator ERNST. I appreciate that very much, and, again, my friend's son and my friend's family, they have been through a lot of stress already with approved drugs. I cannot imagine the stressors on families as they try and get into clinical trials and so forth. So, I appreciate it. I think that we need to have further discussion on how we streamline the process and make it easier for folks to get those life-saving drugs.

So, thank you, Mr. Chairman, very much. I appreciate it. And, thank you to all of our witnesses.

Chairman JOHNSON. Thank you, Senator Ernst.

As soon as Senator Ayotte comes back, I will turn it over to her, but I want to keep going back to the impediments. There was one—Nancy, you talked about, in one instance, you contacted the FDA, and that official at the FDA contacted the CEO and crafted a solution. As briefly as possible, what was the crafted solution? How did they break through? Because I would think that that would be sort of the model of what we are trying to work—

Ms. GOODMAN. Yes.

Chairman JOHNSON. I mean, it should not take a gargantuan public relations campaign to have an official at the FDA say, "Let us break through." So what was the key? In other words, what did the FDA allow a company to do, so that it was not risk averse to actually involve that person in a trial?

Ms. GOODMAN. The FDA suggested what is called an "expanded access trial" for that company. So, the FDA and the company crafted a new trial with 20 or 30 children—but it would be a clinical trial. The company would not only be obligated to report adverse outcomes, but could also collect efficacy data and submit that to the

FDA, too. And because it is a trial, the company has certain additional controls over how the drug is administered and who administers it. So, it was a solution that was good for both.

And, I think that the question of when we use expanded-access trials is really important—and also when companies should be required to inform the FDA that someone has come and asked for the drug. The fact is that companies do not have to report that information to anyone right now, and so, in this particular case, 300 people had asked the company for this drug. It is a drug to fight the adenovirus and other viral infections. And so, in this case, the drug really will keep people alive or not based on whether it is provided. And the FDA did not know.

Chairman JOHNSON. Well, I am quite sympathetic with private sector businesses having kind of an adverse reaction to what the FDA can do to them—and trial lawyers as well. There is an awful lot of incentive—or disincentive for doing this, and that is what we are trying to break through. What are the impediments?

Darcy, do you have a comment?

Ms. OLSEN. Yes, I would just like to add—I mean, I feel like some of this conversation about the FDA is like, saying, “Let us put some fresh paint on an old jalopy,” and what we need to be doing is getting people to the moon. And to Senator Ernst’s question, for the elderly, but also for pediatric medicines, I mean, the simplest straight line is to adopt reciprocity with Europe. I mean, 30 percent of the advances are out overseas. It is—in Diego’s case, that saved his life. The medicine that saved his life—Europe’s like gold prize for the greatest advance in childhood medicine—and it has been over 20 years and it is still not approved here. This DMD drug is approved in Europe.

I mean, for goodness’ sake, why is our market just this? Why do we not open it up to these countries? This child, that you were talking about, would have had access to those things. They are proven. They are proven, they are tested, and they are on the market.

So, that is what we need to be talking about. Let us get to the moon. That is your real answer.

Chairman JOHNSON. To me, that sounds like a no-brainer. Let us take the first steps here that are just so incredibly common sense. What has been the resistance to it, though? I mean, it is just so common sense. Why have we not done that?

Ms. OLSEN. Well, that is a good question. I do not know all of the politics. There is a bill, S. 2388, right now that allows for reciprocal improvement—or, excuse me—approval.

Chairman JOHNSON. Who is opposed to it? Literally, because I cannot imagine any human being taking a look at any one of these instances—whether it is Jacob, whether it is Jordan, or whether it is Diego—and not doing everything possible, on an individual basis. And yet, then collectively where is the resistance? Where is it coming from?

Ms. OLSEN. My understanding is that the FDA wants total control over all of the drugs in the U.S. market. And, they want to do the regulatory process from beginning to end—even if that means an additional 15 or 20 years of studies. I think that that is where the problem is. And, when the lead official tells you that access to

these experimental medicines would be another burden on the health care system, I think that that gives you some insight, that sometimes—

Chairman JOHNSON. Are they talking about costs? That it is going to cost us money to save people's lives? Is that what you take from that comment?

Ms. OLSEN. Yes, it is about cost and systems instead of patients. And so, I think that that is the short answer. That is where the opposition comes from—but Congress can fix that.

Chairman JOHNSON. Dr. Gulfo, I want you to comment on that, but also I want to go to your sixth point—because it is true. Innovation is fragile.

Dr. GULFO. Yes.

Chairman JOHNSON. Where are the breakthroughs going to come from? Listen, I believe in the National Institutes of Health (NIH) and the Center for Disease Control (CDC). Government can fund basic science and research. But, I also believe in the private sector and in innovators—individuals coming up with an idea. I supplied packaging in the medical device industry. There are so many practicing surgeons or physicians that have a concept and the idea for a medical device, and it is that little moment of enlightenment, "Oh, if I could only do this."

So, we have to foster that. We cannot crush that. So, just speak to what I was just talking about. Where is that impediment? Where is the resistance to something that is so common sense—to take those first steps? And then, talk a little bit more about the fragility of innovation.

Dr. GULFO. Sure. So, I could not agree more with what Darcy is saying about reciprocity. The FDA is afraid of companies shopping for the least regulatory-burdensome market and that that would be automatically approved in the States. So, it is nationalistic thinking there.

Chairman JOHNSON. Well, is it nationalistic or is it the agency wanting control?

Dr. GULFO. Yes, I am sorry. Agency.

Chairman JOHNSON. OK.

Dr. GULFO. The other thing that I will say is, I could not agree more with Darcy as well—look, I believe in a strong FDA. I think that we need an FDA. But, it takes 100 hours for a compassionate use process to be undertaken by a doctor. So the FDA came out and said that they are going to reduce that to—

Chairman JOHNSON. 100 hours of a doctor's time.

Dr. GULFO. Yes, 100 hours.

Chairman JOHNSON. Of the practicing physician trying to save lives—it is taking him 100 hours.

Dr. GULFO. Right. So, the FDA said, "We will have a new policy; they can do it in 45 minutes." It has not been implemented. So, if the FDA were so helpful in the example that Nancy gave, and you have the guidance document written, why is it not implemented? I know that you know a lot about that.

Ms. OLSEN. It has been a year, so it has taken them a long time to do that. But, I think the whole conversation about compassionate use is slightly misguided because it is not just Laura's son that needs compassionate use. It is every single boy who has DMD.

Right? We need to bring these things to market. We need to get them to market faster. That is what Europe's compassionate use system essentially is. It is called "provisional access." So, once they go through safety testing and a little bit of efficacy testing, these drugs would be available in the United States. And because people could buy them, the companies would not be trying to give them away after spending \$1.5 billion to develop them. So, they have more incentive to participate. And that is the problem in this country.

Chairman JOHNSON. And your point also was just one of freedom.  
Ms. OLSEN. Yes.

Chairman JOHNSON. We are in America. This should be the land of the free and the home of the brave. It should be up to patients—not the government to tell you what you can and cannot do—past a certain threshold. And, again, with what you are trying to do, you certainly have certain threshold levels of approval, either within the FDA clinical trial process or in terms of approval overseas.

Ms. OLSEN. Correct, yes. So there is still basic safety with the "Right to Try," and overseas it is safety plus a little bit more, but there—instead of getting access at 15 years, you might get it at two, three, or four, when you are getting some results, because people—they do not have time to wait. And I think that Laura's point on that—we cannot wait until Jordan is 18. He needs that, today, to live a full life. And there are solutions. A lot of these things are available overseas, and so, we need to think a little bit bigger than just making it a little bit easier for people to apply for compassionate use. Compassionate use should be the rule in this country. Do we want to be a country where we have the right to die when we are terminally ill? Fantastic. But what about those who want to fight?

Chairman JOHNSON. Dr. Gulfo, as I recall—as I interpreted your testimony—the FDA was really set up almost with the presumption of approval, correct? I mean, if it is safe, basically, we are going to presume to allow doctors—physicians, who are pretty highly trained, are concerned about their patients, and are probably more concerned about an individual patient than somebody here in Washington, D.C.—that they have that ability to do so. Can you speak to that?

Dr. GULFO. First of all, I am flattered that you read my written testimony because that is exactly right. The law is set up for the FDA to not approve if—not approve if. So, the bias in the writing of the law was that we want innovative drugs, we want to promote health, and we want to—

Chairman JOHNSON. But over time—

Dr. GULFO. So, it should be a reason not to—not a reason to promote. It should be a reason not to. It is like, when I played baseball, I was pretty good. My father said, "You are pretty good, but a pretty good hitter you go up to the plate saying, 'I will swing if it is a strike.' And, a really good hitter goes up to the plate and says, 'I am swinging unless it is a ball.'" And that is what we want. We want the FDA swinging unless it is a ball. OK? And so that is what we want.

Now, for little companies, back to your point—yes, the engines of innovation. I do not run little companies anymore, but to add some-

thing that can just be pure risk, to do something that could put us on clinical hold, and to want to give a dying child something if we did not do all the kinds of work we are supposed to do to do that and did not get the right IRB approval and the whole bit, we are setting ourselves up for ruining the company—ruining the prospects of the product going forward. So there are tremendous disincentives to companies to try to help where they can.

Chairman JOHNSON. Because we have not mentioned this yet, but, right now, we are talking about the disincentives for, maybe, having the FDA, really stop the approval process. We have not even talked about the trial lawyers and the liability issues here as well, which, Laura, I want to kind of go back to you. I would imagine that you would sign any waiver of liability toward any company, correct?

Ms. MCLINN. Of course I would.

Chairman JOHNSON. I would. Have you ever met a family member who would not?

Ms. MCLINN. No.

Chairman JOHNSON. So the liability issue should be really off of the table, correct?

Ms. MCLINN. Correct.

Chairman JOHNSON. By the way, is it largely? Does it really end—no, it is not.

Dr. GULFO. No.

Chairman JOHNSON. OK. Nancy, I know that you wanted to weigh in on one of these issues.

Ms. GOODMAN. Well, thank you, Senator. Look, I think that you are asking exactly the right questions. And the piece of it that, again, I want to focus on is that drug development takes a long time. It takes 10 years or more. And, the question that we have been asking is: Once we know that there is an interesting drug under development, how do we get more patients that are dying on that drug? That is a very important question.

But, I want to go back to the first question, which is: How do we get companies to develop more exciting drugs? The Creating Hope Act, which we put together, creates financial incentives for companies to do that. It is going to markup on March 9 in the HELP Committee, and I hope the Senate will consider reauthorizing it on a permanent basis. Companies need long-term assurances that this incentive will be there for all 10 years of its development. I am concerned that a short renewal period will not create the proper incentive.

Chairman JOHNSON. The free market provides an awful lot of incentives. Doctors, themselves, want to create the cures. I am not sure government is going to be able to dictate a proper incentive better than what the free market actually does. So, from my standpoint, how do we get rid of the impediments? How do we reduce the disincentives? Because I think that there are plenty of incentives, just from a standpoint of humanity and compassion and doctors trying to cure disease and stuff. That is a huge incentive. And the question is—it does not take 10 years to really develop a drug. You can have a breakthrough. You can come up with the chemistry of it. The reason that it takes 10 years is the approval process and, now, the \$2.6 billion is the latest cost.

Dr. GULFO. It is really about what I said about shifting the standard. When the standard is truly safety—we do not want to give toxic stuff, right? And, we want to know how you can administer the drug safely. And, effectiveness. Effectiveness should be the activity of the drug—the pharmacodynamic activity. The FDA has taken that to unrealistic endpoints. They want to see survival endpoints. They want to see these endpoints that take tremendous trials and tremendously long follow-up. And to me, that is the real problem. Again, I could not agree more with Darcy. I wrote an editorial about this. The answer to “Right to Try” is getting drugs approved faster. That is the answer.

Chairman JOHNSON. So, let me ask, in terms of a company, is there any legitimate disincentive, other than having an adverse effect and having the FDA just say, “OK, this drug is ended,”—or the trial lawyers? I mean, if you are doing a scientific study and you are doing a clinical trial and all of a sudden you are starting to provide this drug for people that are not in this very controlled study, is there a legitimate scientific concern about harming the results of the trial, in terms of the information that you are getting?

Dr. GULFO. Actually, the answer is that there is no benefit to doing it, because I cannot dose enough of these one-off patients to get a claim in that. Right? So you need large—to do a study, you need a lot of patients. OK? So the companies pick breast cancer or they pick prostate cancer—a great example. However, it might be a drug that is focused on a particular mutation where the same mutation is shared with some childhood cancers. What would be great—and I would love to see us get there—is if we are not approving drugs on the basis of cancer type, but we are approving drugs on the basis of the genotype of the cancer. And then, they could be instantly applied in other places. Then you could do a basket approval. You could bring all sorts of patients, age groups, and certain disease types into one trial. FDA is not there yet.

Chairman JOHNSON. Well, I will turn it over to Senator Ayotte, but, first, would it be advantageous for clinical trials, for gathering information, and for approving safety and efficacy, if you just had more of these drugs available to people who want to use them? Or would that actually harm your ability to get information? Do you know what I am asking?

Dr. GULFO. The more that are available, the more that are approved, and the more that are in the hands of the doctors, the more discoveries that we get.

Chairman JOHNSON. OK.

Dr. GULFO. The more where a doctor observes, “Wow, when I give it to this patient”——

Chairman JOHNSON. That would be my assumption, so OK, good.

Dr. GULFO. Yes.

Chairman JOHNSON. Senator Ayotte, if you are ready.

#### **OPENING STATEMENT OF SENATOR AYOTTE**

Senator AYOTTE. Thank you. I want to thank you, Chairman and Ranking Member. And, certainly, thank all of you for being here today. Before I left, I got to hear almost all of your testimony, and it was very compelling and so important.

I have had constituents that—there was a young girl who passed away from a rare form of cancer, and her family came to me and certainly wanted the opportunity for compassionate use through the FDA—and really they got the runaround. It was very difficult. And, as you think about the difficulty that—all of the other things that families are dealing with under those circumstances.

I know that there has been a lot of discussion today about the incredible work that you are doing, Ms. Goodman, trying to help families navigate this issue. But, it seems to me that the FDA—does anyone have a sense of when the FDA—they put out this draft a year ago to make this process more simplified and to make it easier for families, because there is such a runaround. And you are all so engaged in this. Have you heard anything from the FDA—Doctor, I saw you shake your head—about what they are waiting for? This is a year. We are talking about families that are struggling and every minute matters to them. And so, it is really troubling to me that they have not issued final guidance. Does anyone have a sense—have we heard anything on this?

Dr. GULFO. I know just what you are talking about. It was an effort, to reduce the 100 hours that it takes to put in an application, into a 45-minute process. And we are all waiting with you. It is written. I believe that a draft guidance document was written, and it has not been implemented. But, I think that Darcy knows more about that than I do.

Ms. OLSEN. I just know who you can talk to at the FDA—who is in charge of that. It is Dr. Peter Lurie. They promised over a year ago that they were going to make it a 45-minute process, and, I think that, for people who work in this field, it is not a big surprise that they have not finished that form.

But I will say this: Even once that form is finished, it is not going to solve all of the problems. It will be a little bit easier, but, we attached it to my testimony—just issued an investigational report on the compassionate use process which really goes through the disincentives that the companies face and why they do not participate. And that will not change just with a shorter form. That is going to require some of the bigger reforms, like they have done in Europe. And, of course, reciprocity would be very helpful to get drugs here today.

Senator AYOTTE. I hope—

Chairman JOHNSON. Really quick, Senator Ayotte, just so you—

Senator AYOTTE. Yes, I hope that we can follow up on that.

Chairman JOHNSON. No, we have already—as part of this hearing, we sent out an oversight letter asking that specific question, along with other things. So, we will certainly—as soon as we get feedback from the FDA, we will give you the answer.

Senator AYOTTE. Good. I hope so, because this is really just awful. I appreciate what you have said today, and, Ms. Olsen, you really put it well. How are we taking this decision-making away from families who are in a position where it is a life-or-death situation for them? And what are we trying to protect them from by not allowing them to make their own decisions? It is really hard to understand. I understand if it is not a situation where there is a life-or-death situation, but let us face it, if we all put ourselves in the

shoes—if we put ourselves in your shoes, Ms. McLinn—it is hard to do, but, I know that, as a mother, I would want to fight and do everything that I could, and I would not want to leave any stone unturned when it came to my son. And, I happen to have an 8-year-old, Jacob, by the way, and so I am hoping that we can take this issue up in this Committee, because I think that you deserve more focus on research—that is critical, and that is something that obviously I am very supportive of. We need more focus, though, on the things that we know are working—to give you access to—and the fact that, Diego, you had to move and your family had to move overseas to get drugs that have been available overseas—you are right, not every family can do that. But, you should not have to do that.

So, we have to be able to do something about it. Honestly, it is common sense and we need the FDA to also start putting themselves in the shoes of the people who they are there to serve. The FDA is there to serve all of us. The FDA is there to make sure that people can be protected, but not from themselves. It is about letting them make decisions. I hope that we can come up with a really strong, bipartisan consensus with some of the feedback that you have given us today.

And, I want to thank all of you for coming here. This has been incredibly moving, and you have really distilled this down to some concrete actions that we can take as Senators that can make a difference. So, we look forward to working with you on all of that, and we are so glad that you have come here today. Thank you.

Chairman JOHNSON. Thank you, Senator Ayotte. Senator Carper.

Senator CARPER. Given what Senator Ayotte just said, I may have missed this, but, while you were out of the room, I have been in and out of the room, too. We are trying to do the rest of our schedules and be here to listen to the testimony. But, the question that I asked—remember, I telegraphed a question. I said that I am going to telegraph my pitch. The question that I was going to ask was: What do you think that those of us who are sitting over here on this side of the dais can do, either through legislation or, maybe, through partnering with the Administration, to improve patient access to new treatments or to new therapies? And, if you could just briefly address that for me, that will pretty much be it. Do you want to go first, Ms. Olsen?

Ms. OLSEN. Thank you, and I—

Senator CARPER. Give us a short to-do list—one thing, maybe, one thing. And we will ask everybody to just give us one good idea.

Ms. OLSEN. OK. Reciprocity, which we talked about, with European countries, and since I prepared for your first question, which was 2—

Senator CARPER. Go ahead.

Ms. OLSEN. For these drugs that are being developed for people with life-threatening, terminal illnesses, we need provisional access, which means that, as soon as they know that something is working, they let people go ahead and put it on the market and study it, until it gets the final green light. That will solve the problem of companies not participating.

Senator CARPER. OK. Thank you.

Ms. MCLINN. Thank you for asking this question. I wanted to come here today and tell you guys exactly what you could do to help Jordan—to help my son—and that is all I have thought about since I was invited to come here to testify. And, the truth is that I do not know and I cannot give you an exact answer, and that is really hard for me to say because I am used to problems just having—I am a math teacher. I am used to a problem just having a cut-and-dry answer.

Senator CARPER. My guess is that you are a pretty good teacher.

Ms. MCLINN. What is that?

Senator CARPER. My guess is that you are a pretty good teacher.

Ms. MCLINN. Thank you. But, yesterday, I had the opportunity, and I was actually in Speaker Ryan's office, and I spoke with his chief of staff. I told him, "In 2012, when the President signed FDASIA, that had a lot of support." And, I asked him, "Can you get the President of the United States to go to the Advisory Committee (AdCom) meeting and say, 'Hey, I signed this. The Congress said that we want you to do this. Can you do this?'" And I know that that is an outlandish request, but you asked what you can do. So, I would like to see a physical presence by Congress at an AdCom meeting, or with the FDA. I would like to see you speak with them, directly, and say, "We want you to use the tools that we have already given you. This is legislation that already exists." And, I want someone from Congress to stand up and say, "Will you please do this?"

Senator CARPER. All right. Good. Thank you.

Diego, before you speak, let me just say that we have a lot of witnesses before this panel. You are one of the youngest, and I want to say that you are one of the best. You did a great job.

Mr. MORRIS. Thank you.

Senator CARPER. Would you like to answer my question, please? Give us some good advice, please, before we adjourn.

Mr. MORRIS. I think that the compassionate use process needs to be expedited. Particularly, when I was going through treatment, the drug that I had in London needed to be taken while I was doing the chemotherapy. And, the compassionate use program would have taken far too long, so we did not even apply because we were advised that it would take too long. The process needs to be expedited, because, in some cases, it needs to be faster.

Senator CARPER. All right. Thank you, Diego. Dr. Gulfo.

Dr. GULFO. Yes, three things, I think, and I appreciate the question.

Senator CARPER. Sure.

Dr. GULFO. First, I think that the FDA has to feel loved. We all need to love the FDA, and not do fire-alarm, knee-jerk oversight, if you will, when things do not go well. So, I think that that does, as I wrote in my—

Senator CARPER. I call those "gotcha" hearings.

Dr. GULFO. Yes, OK. And so, even when the FDA gets it right—look at the case of Avandia. They still get beaten up for it, and that is just wrong.

Senator CARPER. That is a good point.

Dr. GULFO. And, that makes them retrench, and it is terrible.

That, combined with really letting them know that we want them to promote health, OK? Sure, protecting is a part of promoting, but we want them to promote health. We do not expect them to guarantee absolute safety for all patients and all drugs.

And, then, my third wish would be to get the FDA back to focusing on safety and effectiveness—not on these other outcomes.

Now, in my written testimony, I have a proposal for that. You can have four categories of the nature of the evidence, and one of the categories could be those longer-term outcomes. Fine with me. But, I think that if you get the FDA back to promoting and focusing on safety and effectiveness, and not getting the heck beat out of them when things go wrong—because things do go wrong—I think that we could do a lot.

Senator CARPER. Great. That is great advice, thank you.

And, Nancy, one more, please?

Ms. GOODMAN. Thank you, Senator Carper.

The first solution, again, is that we need to reauthorize the Creating Hope Act, so that companies have incentives to develop pediatric rare disease drugs, and I hope that the Senate will move on that.

Second, when companies are developing drugs for adults, we need to give companies incentives and requirements for them to just test them in kids, and update the Pediatric Research Equity Act, so that it protects children with cancer.

And, maybe, we would ask companies to explain why they have minimum ages—a minimum age of eligibility for their adult trials at 18. Maybe, ask them to explain whether there are medical and scientific rationales for not lowering it, so that kids with terminal illnesses can get access to these drugs.

And, finally, it is only a partial solution, but it is a very important one. I think that it would be terrific if Congress could pass the Andrea Sloan CURE Act to start improving the compassionate use process.

Thank you.

Senator CARPER. OK. Thank you.

Mr. Chairman, Cole, I am going to ask you to come over here just for a second. For a number of years, a young man from Delaware named Cole Hamstead has come to Washington. He brings his Mom with him every time. Laura and Cole have been a vital part of the work of the National Hemophilia Foundation (NHF). He is 10 years old and a wonderful young man. And, I showed a picture to your son, to Jordan over here, of Cole 3 years ago with me and explained to Jordan that, in that picture, Cole was then just the same age that Jordan is today. In response, Jordan was nice enough to offer to let Cole play with his toys as sort of a sign of welcome.

Ms. MCLINN. Good job, buddy.

Senator CARPER. These are two brave young men, courageous young men, who face adversity in their lives and have found, through the help, love, and support of a lot of other people, some good. And, I just want to say, to those of you who continue to lead a good fight—and to those who have taken adversity, Nancy, in the loss of your own son—to make sure that good things happen for a

lot of other young people in our country, thank you. You are doing the Lord's work. God bless you.

Ms. GOODMAN. Thank you.

Senator CARPER. Thank you.

Chairman JOHNSON. Thank you, Senator Carper.

Again, I want to just thank all of the witnesses. I think that this has been a wonderful hearing—powerful testimony. I appreciate your taking the time and answering our questions.

I am going to—I think, with consent—we are going to have an honorary Chairman close out the hearing. So, I am going to switch chairs. I wish that I had a little bit of a fancier sign. And, I have a couple of things to say. I am going to switch chairs here, and then we will let you gavel it out.

Senator CARPER. Mr. Chairman.

Chairman JOHNSON. I have to say a few magic words here.

This hearing record will remain open for 15 days until March 11, at 5 p.m. for the submission of statements and questions for the record.

This hearing is adjourned.

[Jordan McLinn bangs gavel.]

Chairman JOHNSON. There we go. Thank you.

[Applause.]

[Whereupon, at 11:43 a.m., the Committee was adjourned.]



## A P P E N D I X

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**Chairman Ron Johnson Opening Statement  
“Connecting Patients to New and Potential Life Saving Treatments”  
Thursday, February 25, 2016**

*As submitted for the record:*

Good morning and welcome.

I would bet that each us of here today has been affected by a personal story of a loved one or friend who is fighting a life-changing or terminal illness. Many of us have felt that sense of desperation—of urgency—when we learn that we or someone we love is fighting for their life.

I vividly recall the moment that I learned that my infant daughter had a serious heart condition. When she was born, a doctor saved her life by conducting a procedure on her heart. And eight months later, after seven hours of open heart surgery, my daughter’s life was saved thanks to the miracles of modern medicine.

We all should be thankful that we are living in an era of unprecedented innovation and improvement in the ways that we treat serious and life-threatening diseases. It is a credit to the dedicated researchers, the pharmaceutical industry, medical device makers, and doctors who have brought us so many life-saving treatments.

The question that I want to ask today is: How can we do more to ensure that all patients, including those facing terminal illnesses, have access to potentially life-saving treatments? What artificial, regulatory barriers are keeping patients from trying and experimenting with new medicines and therapies when all others have failed?

Back in 2014, I met with a brave woman, Trickett Wendler from Wisconsin, who was fighting ALS. Sadly Trickett passed away last year, but her spirit and her fight are the reason I am passionate about this issue — because I know that today, and every day, millions of Americans are fighting similar life-and-death battles to save themselves and their loved ones.

Over the past year, we have seen an unprecedented bipartisan movement across the country adopting laws that are aimed at allowing patients, doctors and drug companies to use investigational medicines to try to save terminal patients’ lives. These laws have passed with nearly unanimous bipartisan support.

I recognize that the Food and Drug Administration (FDA) faces a challenge striking a balance between protecting public safety and granting access to new drugs. But we must always keep an eye on how we can improve the regulatory process, asking what incentives the system places on regulators and the industry, and what we can do to empower individuals to make choices for themselves.

As the Senate considers whether to move forward on FDA reform legislation, we need to hear from the experts and, more importantly, the patients about what we should do to improve the regulatory process to give more patients a chance to save their lives.

Finally, we recently learned our friend and colleague Claire McCaskill was diagnosed with breast cancer. Fortunately her prognosis is good and she is in good spirits. I know the thoughts and prayers of this committee are with her.

Thank you all for being here today. I look forward to your testimony.

**Statement of Ranking Member Tom Carper  
“Connecting Patients to New and Potential Life Saving Treatments”  
Thursday, February 25, 2016**

*As prepared for delivery:*

Thank you, Mr. Chairman, for calling this hearing today. I appreciate your willingness to open a conversation about this issue that I know is a very critical one to Americans seeking access to potentially lifesaving treatments and new medical innovations for themselves or members of their family.

I also want to thank our witnesses, especially Ms. Laura McLinn, Mr. Diego Morris, and Ms. Nancy Goodman, for their thoughtful and insightful testimony, and especially for their willingness to share their personal stories with us.

Today, we will hear from patients, their loved ones, and others on potential opportunities to improve access to medical breakthroughs and life-saving medical treatments. These individuals and their families have faced some of the most difficult and challenging circumstances and decisions anyone could face. They deserve our compassion and our understanding.

Speaking as a father, husband, brother, and son, it's important that we learn from our witnesses experiences so that we in Congress can work together with the Executive Branch, patient groups, industry, and other stakeholders to ensure that all Americans can gain access to safe and effective lifesaving treatments as quickly as possible.

Simply put, the development of new medicines is a long, complex, and risky process. For individuals with life-threatening conditions and their loved ones, safe and effective treatments cannot come quickly enough.

As we will hear from some of our witnesses today, the path for patients and their physicians to access innovative new treatments may not be clear. Reforms may be needed to make sure that patients and their families and doctors have the information they need to explore potential new treatment options.

The U.S. Food and Drug Administration (FDA), which is charged with ensuring that the drugs available to American consumers are safe and effective, has given an extraordinary level of attention to the requests of patients with life-threatening conditions. In fact, they've approved more than 99 percent of requests for emergency treatments.

Despite these high approval rates, I understand that the FDA believes more can be done and is continuing to work to improve patient access to these experimental medical treatments.

I hope we can help with those efforts and continue to work closely with patients, health care providers, the pharmaceutical industry, and the FDA to ensure that all patients and their families can access safe and reliable treatments as quickly as possible.

I want to close by thanking the witnesses and their families again for their willingness to share their stories and put forward possible solutions to these challenging issues.

**Testimony of Darcy Olsen**

**President**

**Goldwater Institute**

**Phoenix, Arizona**

**Before the**

**United States Senate**

**Committee on Homeland Security and Governmental Affairs**

**“Connecting Patients to New and Potential Life Saving Treatments”**

**February 25, 2016**

Chairman Johnson, Ranking Member Carper, other Members of the Committee, thank you:

As I was preparing my testimony for you on Monday, I received a call from an old friend of mine. “Oh Hazel! How are you?” “Not good,” she said, “I was just diagnosed with ALS.”

Only weeks after the diagnosis, her deterioration has been so rapid that she can no longer dress herself. She has already met with Hospice. After all, her physicians told her, “There really are no treatments for ALS.” But what Hazel’s doctors really mean is that there are no *FDA-approved* treatments available. The cruel truth is that there are a dozen treatments in the FDA’s pipeline to treat ALS right now.

In my book, *The Right to Try*, I tell the story of a man named Ted Harada.<sup>1</sup> We call Ted “Lazarus,” because he is the first known survivor of ALS. No one would call an ALS diagnosis lucky, but Ted was fortunate to get into a clinical trial where he received a treatment that reversed his ALS symptoms. Today, seven years after his diagnosis, he swims with his kids and completes 5k races. He’s shown no decline in his respiratory ability at all. Ted is one of 32 Americans who were lucky enough to try this cutting-edge therapy. But in the years since the clinical trial began, 24,000 people in the United States have died from ALS.

Why should only 32 Americans with ALS have a chance to try to save their lives? And what about the millions of Americans with other terminal illnesses? Why are so many people dying when promising treatments exist?

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<sup>1</sup> Olsen, Darcy. *The Right to Try: How the Federal Government Prevents Americans from Getting the Lifesaving Treatments They Need* (New York: HarperCollins, 2015), 1-19.

The problem is the FDA has a very archaic process for approving treatments, especially for people with life-threatening diseases. It takes an average of 15 years to bring a new drug to market.<sup>2</sup>

What does 15 years mean?

80 percent of oncologists and neurologists say the FDA's lengthy process has hurt their ability to treat their patients with the best possible care.<sup>3</sup> During the course of writing my book, the mother of two boys with DMD said to me, "By the time this drug is on the market, *we are going to lose an entire generation of boys.*"

It is unethical not to give those boys a chance at life.

The right to try to save your own life is the most personal right we have. It is unethical and unconstitutional for government to deny patients that right. In America today, terminal patients have the right to hasten their deaths through Right to Die laws, but they do not have the right to try to fight to live. You can get drugs to end your life but not to save it. I think most of us would agree there's something desperately wrong with that.

That's why the Goldwater Institute designed what we call Right to Try laws. As of today, 24 states, including 7 of the home states that Members of this panel represent, have adopted the Right to Try. Under these laws, if you have a terminal diagnosis and the FDA-approved treatments aren't working for you, you have the right to try to save your life by taking

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<sup>2</sup> Biopharmaceutical Research Industry, *2015 Profile*, <https://s3.amazonaws.com/goldwater-media/pdf/PDF+8+PhRMA+page2.pdf>, Executive Office of the President, President's Council of Advisors on Science and Technology, *Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation* (Sept. 2012), <https://s3.amazonaws.com/goldwater-media/pdf/PDF4White+Housepage38%237.pdf>.

<sup>3</sup> Olsen, *The Right to Try*, 187.

investigational medicines that are under study at the FDA but may still be ten years away from a green light.<sup>4</sup>

We designed Right to Try laws conservatively. Patients must have a terminal illness. Their doctor must support this choice – and determine that no other government-approved options are available. The treatment must have passed Phase I of the FDA clinical trial process and remain in the clinical trial process. These laws simply extend to terminal patients who are out of time and options the same permission to use investigational treatments as those who are fortunate enough to be enrolled in clinical trials.<sup>5</sup>

Right to Try laws will not help every patient in need, but they are a powerful step in the right direction. We know that people are being treated under the laws at this time and that lives are being saved thanks to those treatments.

In addition to state Right to Try laws, there are two key reforms that Congress should adopt this year to connect patients to new and potentially life-saving treatments.

First, federal law should allow doctors to prescribe – and manufacturers to sell – drugs to terminal patients after they have passed Phase I safety testing on a provisional basis. Terminal patients don't have time to wait 12 or 15 years for efficacy testing. This would put treatments and medicines, like those that saved Ted Harada's life, in the hands of dying patients today. Provisional approval would also allow data to be collected on both the benefits and risks of a

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<sup>4</sup> In just two years, Right to Try has passed in 24 states, often near unanimously and with bipartisan support. The current Right to Try states are: Alabama, Arizona, Arkansas, Colorado, Florida, Illinois, Indiana, Louisiana, Michigan, Minnesota, Mississippi, Missouri, Montana, Nevada, North Carolina, North Dakota, Oklahoma, Oregon, South Dakota, Tennessee, Texas, Utah, Virginia, and Wyoming.

<sup>5</sup> Right to Try Model Legislation, <http://scienceblogs.com/insolence/files/2014/10/GoldwaterInstituteRighttoTryModel.pdf>.

new drug in the actual full patient population rather than a tiny subset available to a select few in clinical trials.

Second, Congress should allow for reciprocal approval of treatments approved in advanced nations. An estimated 30 percent of the newest advances in medicine are first available overseas. Drugs that have already received the green light in countries such as Germany and Japan, for example, should be made available to patients here in the U.S.<sup>6</sup> This would bring countless proven, life-saving treatments to patients in America *now*.

The main concern I heard in writing *The Right to Try* was that some treatments could be dangerous. But as Ted puts it, “ALS is 100% fatal. It’s not a big risk for a guy with a fatal disease.”

If you were on a sinking ship, would you pass on the only available lifeboat because the government hadn’t certified it yet? No, you’d say, “Put the lifeboat in the water!”

As a society, we can and should debate the best ways to make better, stronger lifeboats. We can and should figure out the best ways to pay for lifeboats and make sure we have more of them. But there is no argument for withholding the lifeboats we do have from drowning kids.

We should all keep in mind the people, like my friend Hazel, who are facing their last day as we debate these issues. They don’t have time to wait.

Let’s get the lifeboats in the water.

Respectfully submitted,

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<sup>6</sup> For an example of a bill that would permit reciprocity, see S 2388, “Reciprocity Ensures Streamlined Use of Lifesaving Treatments Act of 2015,” <https://www.congress.gov/bill/114th-congress/senate-bill/2388/text>.

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**APPENDIX: INVESTIGATIVE REPORT****DEAD ON ARRIVAL: Federal “compassionate use” leaves little hope for dying patients**

By Mark Flatten

You are dying and have no hope.

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

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

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

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

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

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

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

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

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

Formally known as expanded access, compassionate use is meant as a way to treat dying patients with medications that are still being tested in clinical trials and are therefore not otherwise available.

Compassionate use must be requested by the patient’s doctor, endorsed by the company that makes the drug, and approved by officials at the FDA.

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

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

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

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

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

It is a system of all risks and no rewards.

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

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

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

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

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

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

Most fail.

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

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

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

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

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

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

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

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

Drug developers get no direct benefit from compassionate use.

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

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

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

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

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

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

### **LOADED WITH DISINCENTIVES**

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

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

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

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

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

That includes Dr. Arthur Caplan, director of the division of medical ethics at the New York University Langone Medical Center.

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

#### **‘SUCCESSFUL PROGRAM’**

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

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

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

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

The FDA does not track those numbers.

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

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

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

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

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

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

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

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

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

**TOO MUCH TO BEAR**

Nick Auden does not exist in the FDA's statistics.

No drug company would allow its product to be used to save him, so no formal application ever reached the FDA to approve or reject.

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

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

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

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

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

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

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

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

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

Then came the complications.

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

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

In July 2013, Auden's brain tumors were considered stable, and he was finally accepted into a Merck trial. By then he had spent almost seven months trying to qualify for the testing—about the same amount of time he was initially told most patients like him could expect to live.

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

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

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

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

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

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

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

#### **WALL STREET WATCHING**

What investors were hearing was much different.

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

Wall Street took notice, with the price of Bristol-Myers and Merck shares increasing more than 3 percent in a single day following the oncology conference, the *New York Times* wrote in an extensive article about

the new miracle cure in June 2013. Billions of dollars in potential sales were at stake for the company that got its drug approved by the FDA first.

That was particularly galling, Amy Auden said.

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

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

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

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

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

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

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

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

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

“It beggars belief that people still have to deal with the illness and then fight to get the drug too, which is proven safe,” she said. “Unless you are going through something like this, you don’t know what the system is. But the system was so frustrating that I can’t believe it was allowed to exist like this.”

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

#### **JUDGMENT CALL**

Just asking for compassionate use is a logistical nightmare.

Dying patients must first convince their doctors to make the application. Patients cannot petition the FDA directly.

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

What counts as "serious" is a judgment call by the FDA. Federal regulations say a serious condition is one that substantially affects day-to-day functioning, and includes such factors as whether it is likely to cause death and whether the disease is likely to progress without treatment.

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

#### **LOGISTICAL NIGHTMARE**

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

Most drug companies do not have policies on compassionate use, or at least do not make them easily accessible. A review of more than 100 companies developing multiple potential cancer treatments shows that fewer than 20 had compassionate use policies clearly posted on their websites. That number includes

companies whose websites say their medicines are *only* available through clinical trials. Those that did post compassionate use policies tended to be the largest companies, not the smaller ones which are developing most of the innovative treatments that might offer the best new hope for those near death. The doctor must agree that there are no other viable treatments available, and that the risks of administering the unapproved medication are outweighed by the risks of the disease.

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

All of that goes into the 100-hour estimate.

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

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

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

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

The next step is to get approval by the Institutional Review Board at the hospital or medical clinic where the patient will be treated. IRBs are internal panels that weigh the ethical considerations of treating people

with medicines that have not been approved by the FDA. They usually meet infrequently, adding weeks to the approval process.

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

### **TRIAGE**

"Of course there is triage," said Razelle Kurzrock, director of clinical trials and the Center for Personalized Cancer Therapy at the Moores Cancer Center at the University of California, San Diego.

"The number of patients that we would give compassionate use drugs to would probably be much, much higher if the bar for compassionate use was not so high."

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

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

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

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

Even with her level of expertise, assembling the information and filling out the FDA form would take about 50 hours, including the first round of phone calls and other research needed to find out if there was

any point in seeking approval, Kurzrock said. For a front-line physician, the 100-hour estimate could even be low.

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

The FDA disputes that it takes 100 hours to fill out the application, even though that number appears on the form itself. The paperwork the FDA uses to apply for compassionate use was designed for a drug company applying to run clinical trials, not for individual physicians wanting to treat a single patient. Many of the fields in the existing form do not have to be filled out by doctors applying for compassionate use, according to Klein of the FDA. The new form, once it receives final approval, will limit the application to the eight appropriate fields.

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

### **ROADBLOCKS**

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

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

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

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

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

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

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

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

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

#### **BAD OUTCOMES**

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

Good news doesn't help.

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

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

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

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

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

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

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

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

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

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

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

### **RISKY BUSINESS**

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

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

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

That adds time, expense, and investor uncertainty.

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

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

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

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

Representatives of CytRx would not agree to an interview.

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

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

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

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

### **NERVOUS INVESTORS**

Investor nervousness can kill a company.

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

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

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

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

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

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

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

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

#### **MIRACLE CURE**

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

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

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

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

Doctors again requested brincidofovir. Chimerix again refused.

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

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

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

Private security was hired to protect company officials.

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

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

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

About three weeks later, Moch was forced to resign.

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

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

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

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

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

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

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

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

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

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

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

#### **'SAFER THAT WAY'**

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

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

"It would be very hard to explain to investors why you were going ahead and doing this kind of risky behavior when you were already losing money and you were trying to put every bit of effort at the company into getting the trials completed so that you can have positive cash flow," Buenger said. "To the extent that the stock price is already struggling and you start getting the hint of something that might make investors nervous, I think it is a place that becomes very, very strange territory."

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

Companies also face risks when they refuse to participate in compassionate use. Chimerix was besieged with negative publicity when it refused to provide Josh the treatment that ultimately saved his life. Rightly or wrongly, the company was seen as putting profits ahead of saving a child's life. That explains why there is such vehement opposition from the drug industry to disclosing the number of compassionate use requests they receive and reject. Buenger said.

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

#### **'SAVING MY LIFE'**

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

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

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

Her doctors at MD Anderson first raised the prospect of compassionate use.

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

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

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

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

The company refused.

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

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

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

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

#### **'SPOILED, PETULANT BRAT'**

Things turned ugly when Bienaime responded directly to Sloan supporters.

In one email, he decried "a sorry illustration of the risks associated with politics and lobbying taking precedent (sic) over science."

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

A third and apparently internal email that reached a Sloan supporter discussed the need to hire a public relations agency.

The company was more reserved in official statements to the media.

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

She did not say whether BioMarin had ever sought approval.

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

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

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

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

Sloan responded well at first. But she developed pneumonia, which her body was too weak to fight off.

She died on January 1, 2014.

“A company took a chance on her. They gave her the drug and it worked,” Wittenburg said. “That is wonderful. It is sad that she did not get it in a timely manner because of the rigmarole of the system. We were all clumsy and cumbersome at navigating the system because nobody really totally knew what you needed to do.

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

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

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

### **BALANCING THE RISKS**

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

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

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

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

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

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

The risk-averse culture at the FDA puts those two missions in conflict, according to critics who say agency officials are more worried about approving an ineffective drug than getting real cures to patients. If the FDA approves a drug that does not work or has unforeseen side effects, the agency risks a barrage of negative media stories and congressional hearings punctuated by anecdotes from patients who were harmed. Failing to approve an effective drug may mean more people will die for lack of treatment, but those deaths are harder to quantify, and will not happen until sometime in the future.

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

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

### **RISK AVERSION**

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

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

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

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

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

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

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

They were also required to report adverse reactions to the FDA.

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

Then came the AIDS crisis of the 1980s.

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

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

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

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

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

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

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

#### **PHASES OF TESTING**

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

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

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

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

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

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

Adverse events in any phase of the trial must be reported to the FDA, which at any time can halt the trials, require the protocols to be rewritten, or impose additional screening, testing, or monitoring requirements. After all clinical trials are completed, a final New Drug Application is filed with the FDA, which spends months, sometimes more than a year, to decide if there is sufficient data to declare the drug safe and effective. Only then can a new medicine be made available to doctors for prescription, and sold for use in patients.

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

#### **HITTING A BULLET**

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

With everything riding on clinical trials, drug companies do everything they can to ensure trials are completed as quickly and predictably as possible. They select patients based on rigid criteria regarding health, age, stage of disease and other conditions to remove as many variables as possible that could lead to unforeseen reactions. Companies also select test subjects most likely to show positive results, since

gaining approval for a single condition is all that is needed to take drugs to market for either the targeted disease or any off-label use doctors later deem fit, said Walker of the Abigail Alliance.

“They are literally trying to hit a bullet with a bullet when they design a clinical trial,” Walker said. “They try to pick a very narrow population of patients that they believe gives them the greatest chance of hitting a very small statistical target at the lowest cost and in the shortest amount of time to get that very first indication.”

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

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

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

Fortunately she did, and was approved for treatment.

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

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

#### **‘YOU’RE IN A SLAUGHTER’**

Just such a blip could kill Mike DeBartoli.

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

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

What doctors eventually told him could not have been worse.

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

ALS is 100 percent fatal.

There is no cure or effective treatment.

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

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

There was nothing doctors could do.

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

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

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

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

Drug companies want people who are "pure" so they can get the test results they need to get their products approved, DeBartoli said. Those unlucky enough to fall outside the statistical models are left to die.

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

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

**‘HORROR STORY STUFF’**

DeBartoli still has another worry: placebos.

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

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

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

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

No one from PhRMA would agree to an interview.

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

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

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

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

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

#### **BARRIER TO ENTRY**

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

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

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

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

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

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

#### **NEW BUSINESS PLAN**

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

Twenty years ago, big pharmaceutical manufacturers were in the drug development business from start to finish. They had their own scientists who would develop a new product, and would run their own clinical trials through all phases and apply for final FDA approval before manufacturing and selling their drugs. That proved to be an inefficient way of doing business because of high failure rates in early stages of testing, Pauly said.

So rather than inventing their own new cures, most big companies now favor allowing the early research and testing to be done at smaller firms that will invent the new product and take it through sufficient testing in clinical trials to show it is both safe in humans and more effective than existing treatments. Once that has been proven, and there is a strong likelihood the new drug will be approved and turn a profit, the big companies will buy the patent rights or the company itself.

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

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

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

There are exceptions.

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

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

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

#### **BELLS AND WHISTLES**

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

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

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

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

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

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

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

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

“In some ways, the fundamental question is why would a profit-seeking firm do compassionate use at all? The answer, in large part, is because they want to curry favor, produce a good reputational effect. But that’s a luxury that many small firms really can’t indulge in. Nobody’s going to remember their brand name anyway. For the most part, a good reputation is more important for a Merck or a Pfizer than it is for XYZ Pharma.”

#### **OBVIOUS RISKS**

The current structure of the drug industry and pressure from investors does make it tough for small companies developing promising new products to treat patients through compassionate use, said Robert Erwin, president of iBio, Inc., a small firm developing treatments and vaccines using plant-based proteins. Money is always tight. There is always the fear that if something bad happens, it could harm the clinical trials or scare away investors, Erwin said, adding he believes those fears are overblown. Executives at small companies also tend to play it safe because that's what investors expect. Their natural inclination is to say no.

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

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

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

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

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

#### **HIDDEN REWARDS**

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

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

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

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

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

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

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

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

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

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

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

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

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

### **RIGHT TO TRY**

Changing that risk and reward equation is not easy.

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

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

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

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

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

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

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

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

Insurance companies are not required to pay for the care.

No approval is needed from the FDA.

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

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

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

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

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

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

### CHANGING THE EQUATION

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

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

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

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

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

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

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

### WEIGHT OF EVIDENCE

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

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

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

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

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

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

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

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

#### **RAISING THE REWARDS**

Griffith's concept is not new.

A similar approach was endorsed by the FDA's own science and technology subcommittee in 2007, and, on a more limited basis, by the President's Council of Advisors on Science and Technology in 2012.

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

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

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

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

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

Details of various proposals vary. Some would allow provisional approval only after Phase 2 testing.

Others would allow only drugs that have received an expedited designation from the FDA to be available to patients.

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

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

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

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

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

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

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

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

Calling their plan "real-world evidence," Strategy& recommends allowing drugs to be prescribed normally after basic safety and effectiveness have been established, sometime during traditional Phase 2 testing. Data collection would continue, but instead of expensive, lengthy, and highly structured Phase 3 testing, data would be generated by monitoring the much larger population of patients in the real world. That would reduce the time it takes to bring a new cure to market by about five years, and cut the cost by about 60 percent, according to Strategy&.

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

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

### **ONE LAST SHOT**

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

The current system is a death sentence, he said.

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

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



Laura McLinn &amp; Jordan McLinn

Testimony for the HSGAC Hearing – Connecting Patients to New and Potential Life Saving Treatments

Thursday, February 25, 2016 10 a.m.

Hello. My name is Laura McLinn and this is my 6 year old son, Jordan McLinn. I will let Jordan say hello and he might want to say something else into the microphone. His ears are a little more, "mature" now so after he speaks I will let him put his headphones on and play on his iPad probably. ☺

You may recognize Jordan from a special Christmas wish he was granted in 2014. His story went viral after I put together a resume for him to be "hired" at a local fire station. The response was overwhelming as he started getting job offers, patches, shirts, letters and other gifts from fire departments all across the nation. He had a couple of interviews in our home state of Indiana and then found two job offer letters in his stocking on Christmas morning. He started going to "work" on a regular basis...eating meals at the firehouses, washing the firetrucks, fixing taillights and taking part in special trainings. He has even worked with the firefighters at some Nascar races in Charlotte, NC. At just 5 years old he was welcomed into a very special family...the firefighter brotherhood. Jordan is living out this dream as a child instead of at the normal adult age. Let's talk about why...

Jordan was diagnosed with Duchenne Muscular Dystrophy just a few months before his 4<sup>th</sup> birthday. It came as complete shock to everyone. The disease is 100 percent fatal. To look at Jordan now, you might not even realize he is any different than most energetic, active kindergartners. He is super smart, "runs" and plays with his friends, has more faith than anyone I've ever known and absolutely loves life. The reality, however, is that his muscles are slowly wasting away and without a miracle he will lose his ability to walk very soon. Jordan is missing some exons on his dystrophin gene so his body is unable to produce this very important protein. As a result, he is getting physically weaker every day. Most boys with Duchenne are in wheelchairs before age 10 and do not live past their twenties. Many do not even make it to twenty years old. Duchenne affects 1 in 3,500 boys. Without a miracle Jordan will lose the ability to walk, climb, dress himself, feed himself and he will even lose the ability to hug me. Many of you in this room are parents. I don't have to tell you how heart wrenching this diagnosis is. I also don't have to tell you how fast these childhood years go by for us parents. Jordan is in a race with the clock for his life but there is tangible hope at our fingertips...

For the first time in the history of Muscular Dystrophy there are promising treatments coming up through the pipeline. There are boys who are receiving exon-skipping treatments through clinical trials and it is working to slow the progression of the disease! These boys are walking, playing soccer, riding bikes as teenagers because of the exon-

skipping drugs they are receiving through these trials. This is unprecedented, unheard of in the natural course of this disease. These exon-skipping drugs have no safety issues and they **are working**. Unfortunately, Jordan and many other boys may not get access to these treatments in time if we have to wait for the standard FDA approval process. Knowing that something exists that is safe and effective gives us hope but it also rips our hearts out because he's not able to get it yet. Jordan is already starting the decline phase of this disease at just 6 years old. He is getting tired faster, he often cries at night because his body hurts, he can't keep up with his friends, he is starting to fall more frequently, he can't do the things they are doing at recess and he doesn't understand why. We do not have time to keep waiting. With muscle disease once you lose function, there is so much damage and it's hard to regain any of that which is lost. This treatment is not just a pill he can take at some point in his future and then be okay all of a sudden. He needs it NOW, before he declines further. I want to see my son grow up. I want to see him be part of the first generation of boys to survive this. And that IS possible. Now, let's talk about the barriers and most importantly some solutions for how to make this happen...

Last spring, Jordan and I helped get the Right to Try Law passed in the State of Indiana. Jordan bravely stood in front of state lawmakers and told them to, "Please say yes". And they did. It passed unanimously in the house and senate. Our family and Jordan's firefighter family was there with Jordan when the governor signed it into law. It was a very special day for us because we felt like we had a new hope, kind of a back-up plan in case Jordan couldn't get the treatment through a trial or even better through accelerated approval. "Right to Try" basically says that if you have a terminal illness and a drug exists that could potentially save your life, you have the right to try it before it gets approval from the FDA. It has to have made it through a couple of important phases with the FDA showing it is safe. You can check out more about "Right to Try" and Jordan's story in Darcy Olsen's book, [The Right to Try](#) that was released last November. Jordan is featured in the chapter, "We are the 99 percent." Even though Jordan legally has the "Right to Try" now, the drug company has to be willing to give or sell him the drug. At this point, they are not open to doing that... for reasons that are understandable but not really okay for us at the same time. Maybe the drug companies are afraid to get sideways with the FDA and risk their billion dollar investment. I don't know. Unfortunately people die in the meantime because no company really knows what the FDA will do and the FDA is not really transparent about it. Therefore, the drug companies choose to be cautious. Patients deserve the, "Right to Try" to save their lives though when options are there.

I'd also like to talk about another pathway that can help Jordan. Back in 2012 Congress passed and President Obama signed the Food and Drug Administration Safety and Innovations Acts (FDASIA). FDASIA gave the FDA the backing and support they needed to more broadly grant accelerated approval for safe and efficacious therapies for rare or severe diseases that meet an unmet medical need, just like the exon-skipping drugs I've been talking to you about today... drugs for rare disease like

Duchenne. FDASIA mandates that the FDA include the patient voice in their review process. Sometime in the next few months there will be patients testifying in front of an FDA adcom panel and asking the panel members to endorse the approval of an exon-skipping drug that has shown to be safe and efficacious in clinical trials. Now... we want to see the FDA use the tools in FDASIA to grant accelerated approval to potentially life-saving treatments, starting with eteplirsen, Sarpeta's exon-skipping drug that could potentially be approved by the end of May. We need to hear a YES to this safe and efficacious therapy from the FDA in May. While this mutation-specific therapy will not be able to treat Jordan's mutation, future exon-skipping therapies will. We must start by approving these therapies as soon as possible, because Jordan does NOT have the time to wait.

Please, in order to help Jordan and all other boys living with Duchenne, encourage the FDA to use the tools you have given them to expedite life-saving drugs to patients. FDA has the flexibility and resources needed to approve these life-saving therapies, and they must use them in order to save children's lives. Additionally, if you are willing to stand with us at that adcom meeting and remind the FDA to use the tools you have given them, remind them to listen to the patients on the drug and the patients who want access to the drug, our family and the entire Duchenne community would be eternally grateful for your support.

**Statement of Diego Morris**  
**“Connecting Patients to New and Potential Life Saving Treatments”**  
**February 25, 2016**

Good morning Mr. Chairman and members of the Committee. Senator Johnson, thank you for inviting me to testify. I am incredibly honored to be with you today.

I am grateful to have the opportunity to explain my story and tell you why I am dedicated to the Right to Try movement.

Four years ago I was a typical 11 year-old boy. I was playing two sports at the time, baseball and soccer. One morning I woke up with pain on the outside of my left knee. I thought it was just a typical sports injury. I continued to play in my games and did everything as usual for a few days. But the pain would not go away and it was causing me to limp. My mom took me to the pediatrician and thank goodness my doctor knew immediately that something was not right. She sent me to an orthopedic surgeon the following day for an X-ray. The doctor told my mom that he believed I had osteosarcoma, a rare type of bone tumor, just by looking at my X-ray.

The orthopedic surgeon sent us down to the lower floor for an MRI and my mom called my dad and asked him to come right over with my little brother, Mateo. My mom told me much later that she felt sick when she saw a technician running out the door. She knew he was running up to tell the surgeon of my results.

Everything happened quickly after that appointment. My parents consulted with many of their physician friends about what we should do next. My parents took the advice of our close family friends, he is a radiation oncologist and she is a pediatrician. They told my parents I needed to have a biopsy as soon as possible at a premier research institution.

Just three days after my trip to the pediatrician we were on our way to St. Jude Hospital in Memphis, Tennessee. We never stopped hoping I did not have cancer. After a long week of different types of tests and scans they performed a biopsy. We knew the surgeons would be looking at a quick type of analysis they perform in the operating room. They look at something called a frozen section during surgery to determine if a person's tumor is cancerous. If the surgeons determine it is cancer at that point, they go ahead and place a port in the patient's chest for treatment. When I had barely come out from anesthesia, I whispered to my parents - I asked them "do I have a port?" and they said "yes". The three of us cried and my life was never the same again.

After many conversations with physicians, we decided I should start chemotherapy treatment back home in Phoenix, Arizona. My parents came to the conclusion that if I would receive the exact same pre-surgery chemotherapy in Phoenix then I should be close to home, in my own bed as much as possible, surrounded by friends and family who love me. I received chemotherapy for ten weeks at Phoenix Children's Hospital before returning to St. Jude for limb salvage surgery. I am so grateful the surgeons were able to save my leg and completely remove the tumor. They inserted a significant titanium device in my leg which partially replaced my femur and my knee.

After surgery, the analysis of the tumor indicated that the necrosis, or the amount of the tumor killed off by the initial chemo, unfortunately was only fifty percent. The doctors were hoping to see at least eighty percent necrosis. This meant that I would need to have a very aggressive plan of treatment. I needed a total of twenty-one rounds of chemotherapy, with some of the strongest chemo drugs.

Thank goodness my parent's physician friends never stopped doing research on every available treatment for me. They told my parents about a drug called Mifamurtide, or MTP. MTP is an immune therapy drug that has improved survival rates for children with osteosarcoma. My parents were excited about the drug but quickly realized it had not been approved in the United States. MTP was available in so many countries all over the world, they were astonished it was not available in America. The trials for MTP had actually been started by physicians in the U.S.! My parents flew to Mexico City with our friend who is a pediatrician to see the results of MTP on their osteosarcoma patients. The doctors there showed them their findings and told my parents I was welcome in their hospital to obtain MTP.

The clock was ticking. In order to have MTP immune therapy I had to start it at the exact time I started my post-surgery chemotherapy - just ten weeks after undergoing significant surgery at St. Jude. My parents communicated with physicians in several countries and, after reviewing the facts of my case, every oncologist determined I fit the criteria and welcomed me at their hospital. My parents never gave up hope they could get MTP in America. They contacted our Congressman, the FDA, the drug manufacturer, and anyone they thought could help us find a way. They even spoke with the lead physicians for the US trials at MD Anderson and at Sloan Kettering. The doctor at Sloan Kettering explained MTP and answered all of my parents' questions. He told them there are no guarantees with MTP. My parents told him they weren't looking for guarantees - just hope. My dad asked the doctor one last question. He asked whether if (God forbid) the doctor's child or grandchild had osteosarcoma, would he take them out of the country in order to get MTP? He responded that he would indeed travel for MTP. Little did I know that we were about to make a very significant move in record time.

I will never forget my parents and their friends explaining to me and to my brother that we were going to London so I could have MTP treatment along with my chemotherapy. We were so upset with my parents at first but ultimately accepted the fact that this treatment might help save my life. Our entire family left our home in Phoenix, Arizona and moved 5,000 miles away. My dad commuted between Phoenix and London for nine months and my mom, brother and I lived with family in England. Throughout my MTP treatment and chemotherapy my parents continued to look for ways to get this treatment at home but it was just not possible.

My chemotherapy treatment was brutal and I was in the hospital more often than not. My dad was always exhausted and hated not being with us when I had to be rushed to the hospital for emergencies. My mom was exhausted too, going back and forth between the hospital and home to take care of me and my little brother. We were blessed to have relatives in England who insisted we stay with them. Many relatives were amazing to us, and showed us so much love and kindness.

But there is no place like home. I felt so isolated. I missed my friends, my home, my puppy and my school.

My family and I were very fortunate to have the resources to relocate to another country to get this potentially life saving treatment. Most people do not have that option. When my family and I returned to the United States we all agreed we would do anything to help other families not have to go through what we did to get treatment, or worse - not to have a promising treatment at all. So when the Goldwater Institute asked me to serve as the Honorary Chairman of the Right to Try campaign in Arizona I jumped at the opportunity. I am grateful to Darcy Olsen and the other people at Goldwater for giving me the chance to do something positive with my terrible experience. I am grateful to be alive and I am grateful to be here, with your esteemed Committee today.

Mr. Chairman, members of the Committee, thank you for giving me the opportunity to tell my story. I hope and pray we can make it possible for Americans to have easier, faster access to critical medical treatment. Please help us give Americans a better chance to save their own lives and those of their loved ones. No guarantees - just hope. Thank you very much.

**United States Senate Committee on Homeland Security and  
Governmental Affairs**

**Title:** Connecting Patients to New and Potential Life Saving Treatments

**Description:**

This hearing will focus on identifying possible barriers that prevent patients from accessing new and potentially lifesaving therapies, often in the face of terminal or debilitating conditions. We will hear from patients and experts about the steps Congress can take to reduce impediments and help connect willing patients and potential medical innovations.

**Witness:**

Joseph V. Gulfo, MD, MBA  
Executive Director, Rothman Institute of Innovation and Entrepreneurship  
Fairleigh Dickinson University  
Visiting Scholar, The Mercatus Center, George Mason University

Thank you for inviting me to participate in this hearing. I hope that my testimony proves useful to the Committee.

**Introduction and Problem Statement**

The Food and Drug Administration has been charged by Congress with a truly daunting responsibility with respect to drugs, biologics, and medical devices – to approve products that are safe and effective. The mission of the Food and Drug Administration (FDA), as stated in the Food, Drug and Cosmetic (FD&C) Act, is to:

“promote health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely fashion.” This includes “ensuring that . . . (B) human and veterinary drugs are safe and effective; (C) there is reasonable assurance of the safety and effectiveness of devices intended for human use.”

**Safety and effectiveness** are the sole criteria that FDA is to use in determining which new products should be approved. In addition, Congress implied urgency to this function by using three key words – *promptly, efficiently, and timely* – and called for the FDA to be forward-looking – *promote health* – and not simply content with preserving the status quo.

However, we have seen progressive erosion of the safety and effectiveness cornerstone upon which FDA law has been built, and with that erosion, a loss of urgency to deliver safe and effective products to patients.

Safety and effectiveness are difficult enough to determine, and the FDA deserves our respect and admiration for the work that it performs along these lines. How much more

difficult and often impossible are other criteria and unrealistic expectations that have been wrongfully laid at FDA's doorstep?

The expectation from certain areas of society is that the FDA completely defines the clinical utility, clinical outcomes, and benefit-risk of new drugs, and vets all potential side effects for all people in all situations, even effects resulting from uses that are not intended and are not in conformity with approved labeling. Such an expectation is not just impossible to satisfy—it is entirely unreasonable. When we consider that conflicting studies continue to emerge about health outcomes related to coffee and red wine, which have been in use for thousands of years, we can see the absurdity of expecting the FDA to somehow anticipate, unerringly, all possible health outcomes from the use of new drugs.<sup>1</sup>

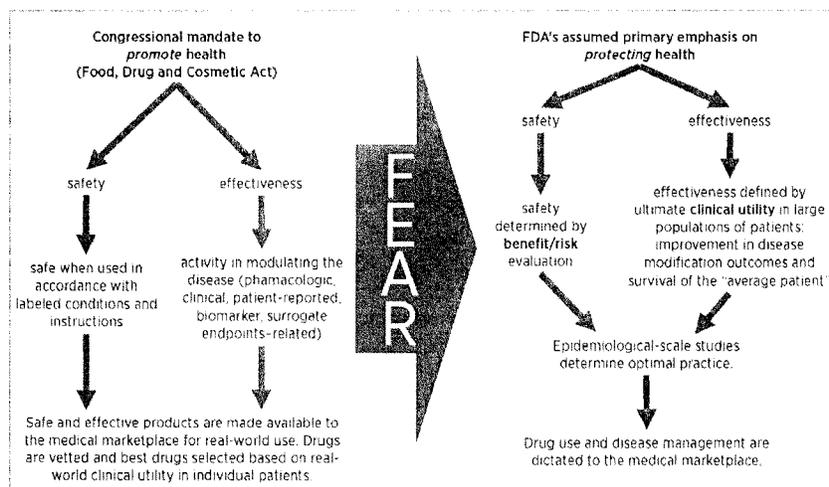
Due to fear and pressure from the media, members of Congress, and others, the FDA does not take as its starting point the view of doctors who are on the front lines of patient care and of patients. Instead, over the last 20 years, the FDA has become markedly more restrictive concerning new drugs, particularly through its efforts to anticipate clinical outcomes of drug treatment (as opposed to surrogate or intermediate endpoints, amelioration or reduction of signs and symptoms of disease, biomarkers, etc.).

As Figure 1 depicts, fear has caused a shift in FDA posture from promoting health to protecting health. With this shift, the safety and effectiveness standard has been dramatically changed - safety no longer applies to the use of the drug according to conditions of use contained in the label and effectiveness no longer means substantial evidence of disease activity. In the fear-based paradigm, safety is determined by projected benefit-risk and effectiveness requires proof of clinical utility, outcomes and survival.

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<sup>1</sup> Searches of the National Institutes of Health's PubMed research database for "coffee consumption" (<http://www.ncbi.nlm.nih.gov/pubmed/?Db=pubmed&term=coffee%20consumption>) and "red wine consumption" (<http://www.ncbi.nlm.nih.gov/pubmed/?term=red+wine+consumption>) turn up hundreds of studies.

**Figure 1. Fear-based shift in emphasis to protect health and associated changes in the meaning of safety and effectiveness**



The effect of the fear-based increased restrictiveness verges on telling doctors how to treat patients, as though the regulators are to prescribe drugs remotely from Silver Spring, Maryland. The FDA is applauded by many, particularly those who have misinterpreted the rise of an academic movement known as evidence-based medicine (EBM), when it purports to debunk medical practice on the basis of the humongous clinical trials that it requires drug companies to perform as a condition for approval.<sup>2</sup> And so the trend has been for the FDA to become more and more restrictive, protracting its pre-approval processes and now frequently requiring that additional controlled trials be done *after* approval.<sup>3</sup>

This fear stems from unreasonable expectations of perfection from certain segments of society. Fear of being blamed for the failings of approved products has caused the FDA to be too cautious in its reviews and approvals.<sup>4</sup> In a sense, the FDA has restated its mission from *promoting* health to *protecting* health—from permitting new safe and effective products that can advance health to demanding certainty that products will improve clinical outcomes and will not cause any harm. However, as drugs are small

<sup>2</sup> Matthew Herper, "Robert Califf Could Transform the FDA—the Right Way," *Forbes*, September 16, 2015, <http://www.forbes.com/sites/matthewherper/2015/09/16/robert-califf-could-transform-the-fda-the-right-way/>.

<sup>3</sup> Michael Dickson and Jean Paul Gagnon, "Key Factors in the Rising Cost of New Drug Discovery and Development," *Nature Reviews Drug Discovery* 3, no. 5 (May 2004): 417–29.

molecules designed to have an effect by binding to targets in the body, it is impossible to give assurance that no harm will ever occur.

Of course, protecting health is part of promoting health, however, the FDA has elevated “protecting” health as its main mission. Promoting and protecting health are two different postures – the latter looks to preserve that which currently exists while the former engenders optimism and belief in the advancement of scientific discoveries as a means of improving the health of Americans. Implicit in promoting health is an understanding that occasionally new products may not be found to be as desirable as we would like them to be, however, the only way to have genuine progress is to accept and deal with “bleeding edge” issues as we try to bring cutting-edge treatments and diagnostics to patients as soon as possible.

### ***The Primacy of the Safety and Effectiveness Standard***

The law reinforces the primacy of safety and effectiveness in FDA’s decision-making as evidenced in the language of C.F.R. Title 21, Chapter 1, Subchapter D, Part 314, Subpart D, Section 314.125(b)(2)–(5), which lists permissible reasons to refuse an application. Specifying reasons for refusal implies that approval is the anticipated (or hoped-for) outcome:

- (3) The results of the tests show that the drug is ***unsafe*** for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions.
- (5) There is a ***lack of substantial evidence*** consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

By listing the specific deficiencies for which approval can be withheld, as opposed to conditions that must be met for approval to be granted, the law clearly presumed approval to be the likely outcome. This makes sense because in order for review dossiers to be submitted, drugs (hereinafter inclusive of drugs, biologics, and medical devices) must first survive the low probability and roughly decade-long rigorous gauntlet of preclinical testing, early clinical development, and large late stage trials for sponsors to feel confident that the drugs meet the safety and effectiveness standard.

### ***Safety and Effectiveness Does Not Mean Clinical Utility, Benefit-Risk, Survival, or Comparative Effectiveness***

Notably absent in the law is any description of refusing an application on the basis of the FDA’s predictions as to how benefit-risk assessments will be made by an “average patient” and the patient’s physician. The agency has also departed from the statutory language by considering possible uses outside of the labeled uses. The law states that the FDA is to judge a drug’s safety, on the basis of “tests” and “investigations,” in the context of the “conditions of use prescribed, recommended, or suggested in its proposed

labeling.” This expressly does not include possible off-label uses.<sup>5</sup> Yet the FDA now asserts that it “must also consider how people will actually use newly approved drugs once they are marketed,” using “methods from social and behavioral science” to anticipate “cognitive and behavioral factors affecting human judgment and decision making in the context of health care delivery.”<sup>6</sup> It is now commonplace for FDA guidance documents to stray, not only from the statutes passed by Congress, but also from the FDA’s own rules. This is how the safety and effectiveness standards have been progressively eroded and changed over time.

Benefit-risk is a private health decision to be made by doctors and patients when weighing whether to use drugs that are safe and effective (public health decision) – see Table 1. Interestingly, the criteria of safety and effectiveness are relative to that which the sponsor claims in its proposed labeling, not in the absolute. All drugs have side effects – the FDA’s job is to label products appropriately so that they can be administered safely to patients for which they are intended. Benefit-risk is more of a labeling issue (relative to FDA’s responsibility) than it is a basis for approval, yet, benefit-risk has seemingly supplanted safety and effectiveness as the operating approval standard.

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<sup>5</sup> C.F.R. Title 21, Chapter 1, Subchapter D, Part 314, Subpart D, Section 314.125(b)(2)–(5).

<sup>6</sup> FDA, *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making: Draft PDUFA V Implementation Plan*, February 2013, 2.

**Table 1. Public Health Decisions (made by FDA) versus Private Health Decisions (made by patients and physicians)**

Health decision	Public	Private
Primary considerations	safety and effectiveness	benefit/risk
Main question	whether the drug under review can be labeled for safe use under conditions proposed by the drug sponsor	whether the likely benefits outweigh the likely risks of using the drug in the patient presenting to the physician
Responsibility	FDA	physicians in the medical marketplace
Inputs into decision	clinical trial results in regulatory filings	the personal profile of the patient under treatment, drug labeling, personal experience, literature, peer consultation
Contribution of drug intervention to the decision	determination of drug activity (pharmacologic, clinical, patient-reported, biomarker, surrogate endpoints-related) in modulating disease in the "average patient"	clinical outcomes of individual patients treated with the drug: improvements in survival, patient-reported outcomes, reduced morbidity, improved tolerability
Extenuating circumstances	conditions for which no other therapies exist	patient preferences

The use of benefit-risk opens the door for FDA to make determinations regarding clinical utility (proof that the treatment positively modulates disease outcome) and clinical benefit (proof that the effect of the drug enhances the patients' lives). This completely changes the nature of pre-approval clinical trials because in order to provide substantial evidence of clinical utility and clinical benefit, even larger health outcomes trials and comparative effectiveness studies are necessitated in the premarket drug approval process. Although "benefit-risk" sounds like a fine construct upon which to make determinations about the usefulness of new drugs, it is not (at least for the FDA). Rather, it ushers in consideration of a new drug's utility in clinical settings, which leads to a demand for data on hypothetical patient outcomes.<sup>7</sup> While clinical trials can readily show whether a drug is active in modulating disease parameters (lowering glucose levels, reducing pain, reducing tumor burden, etc.), however, even the largest trials cannot control for the myriad factors that affect ultimate outcomes (survival, reduction in end-organ complications, etc.). Choosing to base FDA decisions on benefits and risks implies that the FDA will take on the decision roles of physicians and patients, attempting to anticipate or predict their future choices. Requiring comparative

<sup>7</sup> The word *benefit* naturally leads to the question "to whom?" By contrast, the word *effective* naturally leads one to ask "for what?" Couching the matter in terms of *effectiveness* thus tends to promote a focus on what it is that the drug under study can or cannot do, while couching it in terms of *benefits* tends toward speculative imaginings about patient circumstances (e.g., constructs such as "the average patient") and other unbounded consideration of matters beyond the regulator's expertise and awareness.

effectiveness trials is a logical but unfortunate consequence of such an attempt because someone must choose *among* drugs. Requiring comparative effectiveness trials further adds to the cost and time it takes to develop new drugs. If required to better inform medical decision-making, benefits and risks, and comparative effectiveness, can and should be analyzed post-approval, in the medical marketplace. If certain payers demand comparative effectiveness trials, it need not be an FDA function to oversee such trials.

***Evidence Based Medicine Should Not Replace Private Health Decision-Making***

Despite incessant pleas from doctors and patients for more safe and effective products that might help when used appropriately, the FDA continues to raise the evidentiary threshold for permitting a new product—recasting premarket approval as a venue for the practice of evidence-based medicine to determine clinical utility, benefit, and health outcomes, pre-approval. This move is aimed at satisfying FDA critics, but it consumes precious time and resources, and it dissuades drug developers (and would-be developers) from pursuing projects.

The FDA has acknowledged the changes in its standards for product approval. In a March 10, 2015, opinion piece, two high-ranking FDA officials had this to say about the review process: “It is important to remember, however, that innovative therapies only save lives if they work properly. U.S. citizens rely on the FDA to ensure that the drugs they take are effective and that their benefits outweigh their risks. *Improving a patient’s life or lifespan must be central* to the concept of drug innovation.”

But the FDA is supposed to assure *safety and effectiveness of drugs*, not *life outcomes for patients*. A drug’s proposed label indicates the effect it is purported to have; safety and effectiveness are to be determined in the context of that labeling. The physician and the patient, acting in the medical marketplace, are to determine whether and when taking the drug will be conducive to improving a patient’s life. That we authorize physicians to prescribe drugs off-label is indicative of this division of labor.

Certainly, studies of life outcomes can be invaluable to informed decision-making by physicians and payers. But there are many and varied factors that contribute to disease development, progression, and response to therapy. It is far harder to produce good knowledge about life outcomes for patients than it is to produce good knowledge about a drug’s safety and effectiveness with respect to specific disease-related parameters.

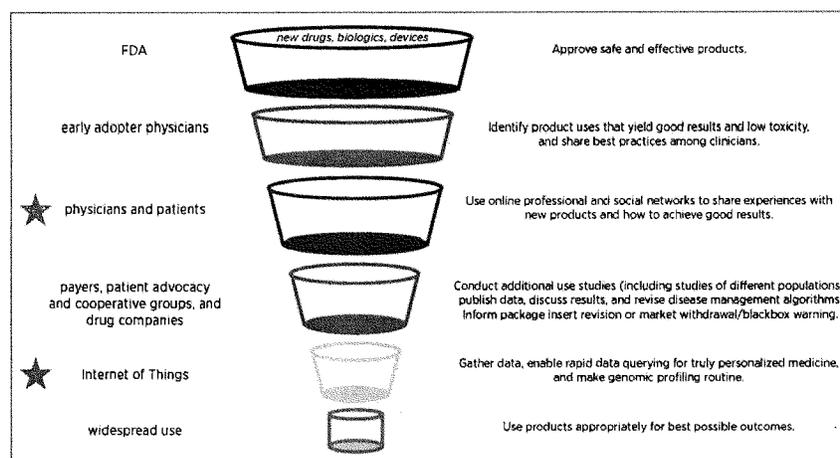
Moreover, the appropriate place to evaluate life outcomes is in the post-approval setting, by the medical marketplace. Trying to do so pre-approval, before a new drug has settled into practice, is not scientifically prudent. The myriad of real world factors that may modulate ultimate clinical benefit cannot be known or controlled in pre-approval studies, no matter the size, without informed data that become available only after a safe and effective drug has been in use for a period of time. Thus, the way that FDA currently approaches drug approval can actually mask clinical benefit. If clinical utility is used as the criteria for approval, many drugs that are safe and effective and could help patients will never see the light of day.

In fact, using life outcomes in clinical trials introduces a significant probability that a positive effect of the drug will be missed (false negative). The FDA cares more about reducing the chances of trials showing that there is a meaningful difference between treatment groups (new drug versus an alternative) when, in truth, there is no difference (false positive). In reality, patients (particularly patients with terminal illnesses) care more about trials missing a potential meaningful effect (false negative) - they would rather have more safe and effective products that could possibly help them than fewer products that are likely not inferior to other treatments.

***How is Precision Medicine Best Practiced?***

The other problem with the FDA's current approach is that it is directly contrary to the precision medicine movement. The FDA makes its determinations based on the responses of the average patient in clinical trials. While immediate- and near-term measures of effectiveness (reducing pain and tumor size, and increasing air movement in the lungs, for example) are appropriately evaluated by calculating average patient responses, clinical benefit is not appropriately assessed in this manner. Many patients may truly benefit from a drug, however, the benefit may not be seen in enough patients to pass the average patient hurdle. As long as the drug is safe and effective as per its labeled conditions of use, clinical benefit should be the domain of patients and doctors, not of the FDA.

In essence, the FDA, which should be the gatekeeper of safe and effective products that enter the medical armamentarium, has put itself in the position of judging which drugs are most beneficial. The funnel diagram in Figure 2 depicts the roles and responsibilities of medical marketplace constituents in the diffusion of new drugs and devices into practice. The law provides for the FDA to be at the top of the funnel and for the medical marketplace to decide from among the FDA-approved safe and effective products which are the most beneficial, therefore, which are used the most (bottom of the funnel). However, the FDA in demanding data from drug developers, pre-approval, to determine which drugs are most beneficial, is putting itself at the bottom of the funnel, as well.

**Figure 2. The Medical Ecosystem & Marketplace – Appropriate Roles**

At no other time in history have we been better equipped to perform real-world, large-scale outcomes and survival studies with regard to medical interventions, such as the use of safe and effective drugs and devices. There is no way that pre-approval studies of drugs and devices, in tightly defined patient populations under scripted medical management protocols, can produce the kind of evidence that is available through real-world data acquisition and the Internet of Things. What's more, in the post-approval, real-world setting, data that will enhance the selection of therapy for an individual patient can be made available in an unprecedented manner, which can truly drive personalized medicine.

### ***Patient Centered Development***

There has been a great amount of discussion centered around the goal of bringing the voice of the patient into the development of new products. In the PDUFA VI meetings in October 2015, a proposal for advancing the science of patient input (Patient Focused Drug Development and Patient Reported Outcomes) was discussed. As summarized in the meeting minutes<sup>8</sup>:

*FDA identified a need to bridge learnings from PDUFA V patient-focused drug development-type meetings to the development of methodologically sound fit-for-purpose tools to systematically collect key information about patients' experience including the burden of disease, and benefit as well as potential burden of therapy. To address this FDA proposed to use public workshops to*

<sup>8</sup> FDA-Industry PDUFA VI Reauthorization Meeting – Regulatory Decision Tools Subgroup October 7, 2015, 12:30am-2:30pm -

*develop a series of guidances focusing on recommended approaches including collection of comprehensive patient-community input, impacts that are important to patients, and the measurement of those impacts. FDA noted that the capacity for increasing patient engagement and review work would require increased staffing.*

These efforts have been fruitless to date and are unlikely to yield substantive change. Existing laws, rules, and guidance documents provide for the use of patient-reported outcomes, for example, pain scales and activities of daily living. The best way to bring the voice of the patient into development and approval decisions is to not presume to be capable of ascertaining the voices of individual patients. These efforts are likely to end up being representative of the fictional average patient. Patient preferences are highly personal and diverse and as such, the assumption that the FDA can make these decisions on behalf of patients is unsound. These decisions are appropriately made by patients and their physicians as they decide on which (and whether) available safe and effective products will be employed to help them, not by the FDA.

It is imperative that the FDA get back to focusing on safety and effectiveness as the pre-approval standards. The flow of new innovative therapies that can advance health is dependent upon all players in the medical marketplace performing their role, starting with the FDA making safe and effective products available. Acknowledging that medicine is more of an art than a science and that the FDA is not the lone participant in the medical ecosystem responsible for advancing the health of Americans is the first step.

### ***The Vicious Cycle that Erodes Safety and Effectiveness Standard***

As former FDA Commissioner Alexander M. Schmidt said in 1974: "In all of FDA's history, I am unable to find a single instance where a congressional committee investigated the failure of FDA to approve a new drug. But the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them. The message to FDA staff could not be clearer." Castigation and public embarrassment of the FDA when unfortunate issues with approved products emerge as they are used in larger real world populations is the first step of the vicious cycle that has eroded the safety and effectiveness standard.

Congressional oversight has been exercised more as a "fire alarm" than as "police patrol," in the words of McCubbins and Schwartz.<sup>9</sup> Congress has been deficient in "police patrol" oversight, that is, constant watchful vigilance to ensure that FDA laws are enacted dutifully. But, it has been quite aggressive in exercising "fire alarm" oversight in response to events like adverse reactions with medical products.

There have been many high-profile hearings on drugs including antidepressants, Vioxx, Rezulin, and Avandia. In all of these, the FDA is basically accused of inappropriately

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<sup>9</sup> Congressional Oversight Overlooked: Police Patrols versus Fire Alarms. Mathew D. McCubbins and Thomas Schwartz. *American Journal of Political Science*. Vol. 28, No. 1 (Feb., 1984), pp. 165-179

approving products that are unsafe. Of course, the issues are not so cut and dry. This kind of knee-jerk oversight, which provides great, significantly damages the cause of medical innovation.

The case of Avandia is particularly disconcerting – even when the FDA does the right thing, for example, approving an excellent drug that helps millions of patients, it is castigated and publicly humiliated. In 2007, a New England Journal of Medicine publication of a meta-analysis of 42 small clinical trials revealed an increased likelihood of significant cardiovascular toxicity in patients taking the drug, so the FDA restricted the drug's use in response to pointed criticism at a Congressional hearing. Here is what the FDA had to endure at a Senate hearing on the matter:

"This report poses several troubling questions for this subcommittee. Most obviously, if Avandia is unsafe, how did it ever get on the market in the first place? For that matter, why is it still on the market, right now? And what does the case of Avandia tell us about the FDA's current ability to conduct its drug safety responsibilities?"<sup>10</sup>

Subsequently, the FDA removed the restrictions from the label when the drug was shown **not** to cause increased cardiovascular problems, following a re-analysis of a very large prospective study, rendering the meta-analysis flawed. But the damage was done – the FDA changed the regulations to require larger and larger clinical trials and disease outcome endpoints for products that are intended for large chronic diseases, like diabetes. Knee-jerk oversight triggered by a flawed analysis had severe unintended consequences.

Sadly, Dr. Robert Califf, nominated to be the new FDA Commissioner, was in full support of erroneously demanding larger and larger trials in the midst of the Avandia saga – As Matt Herper of *Forbes* writes:

"In 2008, after Steven Nissen from the Cleveland Clinic had openly criticized Avandia, the GlaxoSmithKline diabetes drug, he proposed a new standard for studying diabetes medicines that would insist they be tested in clinical trials involving thousands of patients to see if they had any effect on heart attack rates. When Nissen mentioned the idea at an open public meeting, Califf was fast to back it."<sup>11</sup>

And, these sorts of unnecessarily large, expensive, and time-consuming studies have remained as the new standard – they were not walked-back when the case of Avandia was shown to be a false alarm. In December 2015, the FDA issued the following statement - "continued monitoring" of Avandia, Avandamet and Avandaryl had turned up "no new pertinent safety information" about the drug. So, the agency lifted the final layer of safety measures that it erroneously imposed. But, sales of the drug were crushed – as reported by FiercePharma, "The safety questions drove Avandia revenues down

<sup>10</sup> Medscape. Avandia and FDA Both Subject of Severe Criticism at Congressional Hearing. May 11, 2010

<sup>11</sup> Forbes. Robert Califf Could Transform the FDA – The Right Way. September 16, 2015

from a peak of \$3 billion before the controversy to \$183 million in 2011, just before generics hit the market.”

At the Senate HELP (Health Education Labor and Pensions) committee’s confirmation hearing for Dr. Califf on November 15, 2015, he doubled down:

Sr. Warren:” Do you agree with arguments to lower standards for FDA approval of drugs and devices?”

D. Califf: "I have never been a proponent of lowering standards for anything...I have been in favor of raising standards. In no case would I argue to lower the standard. I think I have been staunch in that regard."<sup>12</sup>

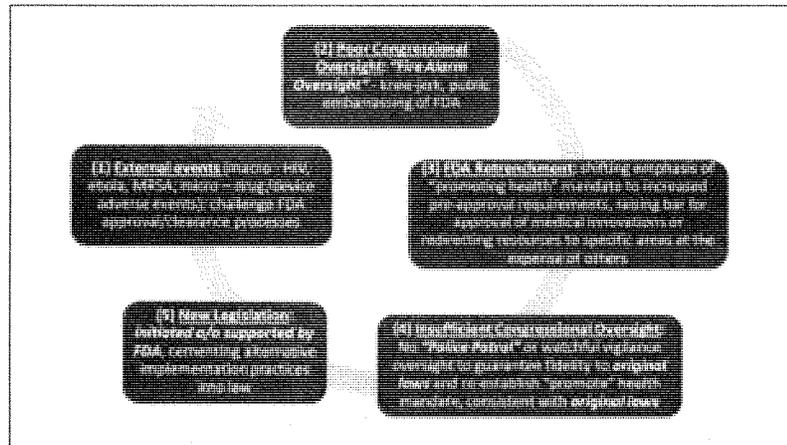
It is understandable that the FDA would recoil when it is attacked. The agency then protects itself from future attack by: (1) raising the bar for product approvals by moving away from the statutory criteria of safety and effectiveness and demanding proof of clinical utility, clinical outcomes and survival; (2) demanding larger and larger trials that cost tremendous amounts of time and money; (3) shifting its emphasis to pre-approval requirements versus a balance of pre-approval data and post-market controls and surveillance; and (4) preferentially approving products for niche diseases rather than those that affect millions of Americans. (See Figure 3, which depicts the Vicious Cycle.)

After FDA recoils in response to criticism and then issues new rules and guidance documents with alternative interpretations and implementations of the laws, Congress does not perform the appropriate police patrol oversight to re-direct the FDA back to its mandate, forcing the FDA to honor the letter and spirit of the laws. No, it does something worse – it actually passes more laws, for example, as part of each PDUFA (Prescription Drug User Fee Act) and MDUFA (Medical Device User Fee Act) reauthorization that takes place every five years, and in other legislation, like 21<sup>st</sup> Century Cures. This legislation, drafted in consultation with the FDA, then codifies the FDA’s new positions taken in response to inappropriate fire alarm oversight.

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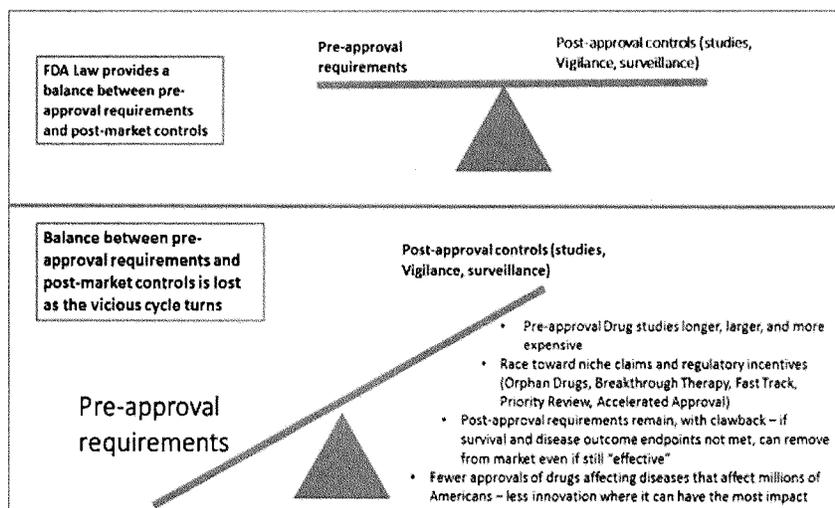
<sup>12</sup> BioPharma Dive. Senators grilled Obama’s nominee for FDA chief. Here’s how he responded. November 18, 2015

Figure 3. The Vicious Cycle the Progressively Erodes the Safety & Effectiveness Standard



The vicious cycle starts over again the next time unfortunate adverse events occur with drugs and devices that are on the market, which invariably happens. This is how regulation kills medical innovation and hurts patients. With each turn of the vicious cycle, the safety and effectiveness standard is further eroded along with the nature and balance of pre-approval criteria and post-approval controls. Figure 4 demonstrates how the balance of pre-approval requirements and post-approval controls is shifted with each turn of the vicious cycle. It also demonstrates how the nature of the pre-approval requirements and post-approval controls are modulated.

**Figure 4. Shift in balance and nature of pre-approval requirements and post-approval controls as the vicious cycle erodes the safety and effectiveness standard**



### ***Rise of Specialty and Orphan Drugs in Lieu of Drugs Treating Diseases with Large Populations of Patients***

A direct outcome of this vicious cycle is the rise of specialty pharmaceutical products intended for small populations of patients. In 2014, the FDA approved 41 new drugs – more than in any year since 1996, according to the agency’s numbers. In 2015, 45 novel new drugs were approved. Many have cited these statistics as proof that the agency is performing well, consistent with its mission since the 2014 total was more than double that of 2007. However, 40% and 47% of the drugs that were approved in 2014 and 2015, respectively, were for niche orphan diseases, that is, conditions affecting less than 200,000 patients per year. There were 467 requests for orphan designation last year by the pharmaceutical industry (~35% increase from 2013), and 293 drugs were granted orphan status by the FDA (13% increase).

Given these statistics, it becomes obvious that the industry’s focus on niche specialty drugs as opposed to drugs for diseases that affect millions of Americans is driven by the erosion of the FDA’s safety and effectiveness standard for approvals.

The FDA, following public ridicule in oversight hearings of drugs for diabetes and arthritis, has imposed new standards for approval – not only must drugs for diseases that affect millions of Americans (diabetes, cardiovascular disease, COPD, obesity, etc.)

prove clinical utility (as opposed to disease activity as embodied in the effectiveness standard), they must be studied in huge trials and either show an improvement in – or no deleterious impact on – survival and major adverse cardiac events. And, even at that, the FDA requires large and expensive post-approval studies to confirm the findings.

The FDA has imposed a de facto “better than the Beatles” standard, as well; basically, if the drugs are not shown to be more effective or safer than drugs already on the market (in large trials using the “average patient standard”) the FDA typically denies their approval. [This is very unfortunate because often, many patients experience benefit of a drug on an individual basis and the effect is lost when patient responses are averaged over the entire study population.] So, companies have increasingly foregone the development of drugs for these diseases and focused on rare diseases and conditions for which no other therapies exist. These qualify for Orphan Drug, Fast Track, BTB, Expedited Review, and Accelerated Approval, which provide substantial regulatory incentives (reduced review times, smaller trials, etc.).<sup>13</sup>

*...Add to that the benefit of lower R&D costs. Derek Fetzer, director, global strategic analytics/global strategic marketing & market access, at Janssen Pharmaceutical Services, says that this made it worthwhile for a big firm like J&J to make a move into the specialty arena: “Improving on the many good drugs on the market is a significant, technical challenge,” he observes. “This is because demonstrating smaller, incremental benefits actually requires more patients in a clinical study, from a statistical point of view, and thus is more costly.”*

*Compared to PCP-focused candidates (drugs for use by primary care physicians), specialty medicine clinical development can be not only less expensive but offer a nearer-term opportunity for cashing-in on an investment. Specialty medicine candidates typically are vetted by big pharma along the dimensions of demonstrating substantial innovation, where R&D efforts can require fewer patients and significant differences can be demonstrated over a shorter period of time.*

*There are regulatory rewards, too. The most prominent “X-factor” in new drugs—the FDA—displays more love toward products that aspire to occupy salient treatment voids as opposed to those gaining incremental yardage vs. existing therapy. Indeed, this is an essential element of FDA’s charter. “One central factor FDA takes into account in determining the speed of review of a new product application is whether it addresses an unmet medical need, hence potentially translating into shorter time to market,” says Wayne Pines, former FDA associate commissioner, who is now president of regulatory services and healthcare for APCO Worldwide. “A usual review is 10 months and a fast-track or priority review is six months or less.”*

<sup>13</sup> Specialty Pharma: Niches to Riches. Medical Marketing and Media, March 1, 2012.

And, these specialty products are very expensive for two reasons – the number of patients for which they can be used is small, and there is literally no competition, meaning no other drugs approved in these settings.

### **Getting the FDA Back to Safety and Effectiveness**

Unfortunately, better oversight alone cannot make up for the problems that have been caused by many turns of the vicious cycle. Therefore, legislation is necessary to essentially re-set the FDA back to the foundations that were established prior to the user fee era. This includes:

1. Restatement of **promoting health** as the FDA's principal function with respect to new products. The law states the following as FDA's mission - "to promote health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely fashion." The law is actually biased toward embracing medical innovation by assuming that new drugs that undergo the drug development gauntlet would be approved, **unless** the drugs (or applications) had certain deficiencies. This attitude and inclination is not embodied in many FDA regulations and guidance documents, as well as in new sections of the law that have been passed as part of reauthorization legislation. The law also provides for a balance between pre-approval hurdles and post-approval controls and makes clear that approval should not be denied in cases where questions about a drug or device could be answered in the post-approval setting via post-market controls (studies, vigilance, and surveillance).
2. Restatement of **safety and effectiveness** as the only requisite standards for approval of new products. (For devices, reaffirmation of reasonable assurance of safety and effectiveness, and least burdensome approach is needed.) Legislation needs to explicitly state that effectiveness is to be evaluated by the FDA in accordance with the labeling proposed by the sponsor and that the FDA is not to impose standards requiring demonstration of clinical utility for approval. The FDA can and should limit the claims based on the data – if there are no clinical benefit data in the application, then clinical benefit should not be claimed. Likewise, legislation that explicitly lists acceptable measures of effectiveness that can support approval – pharmacodynamics effects on disease parameters, clinical signs and symptoms, biomarkers, surrogate endpoints, patient-reported data, comparative effectiveness, clinical outcomes, and survival. A strong caveat that comparative effectiveness, survival, and disease outcomes are not needed to demonstrate effectiveness, but are needed to obtain claims that include these parameters is needed. The legislation should also state the approved label will contain the measures used to determine effectiveness and claims will be limited to the specific findings.
3. Congress can greatly help the FDA by providing for categories of approval according to the nature of the data used to provide substantial evidence of effectiveness, and if sponsors so desire to obtain additional, 'higher order' categories (for example, survival and disease outcomes), supplemental approval

applications can be submitted. Such a system might lay out four categories of approval, as in the following example:

Category 1. **Biomarker**—improvement in a biomarker known to be elevated or decreased in patients with specific diseases (for example, fasting blood glucose, hemoglobin A1c, CEA – carcinoembryonic antigen, CD4/CD8 ratio, PSA – prostate specific antigen, INR – blood clotting, LDL cholesterol, HDL cholesterol, etc.)

Category 2. **Clinical Signs and Symptoms**—reduction in pain, improvement in activities of daily living, tumor response (size, local control, improved progression-free interval); improvement in forced expiratory volume; improved walking distance; improved bone mineral density; improved treadmill performance and EKG findings (atrial fibrillation, pre-mature ventricular contractions), etc.

Category 3. **Disease Modification**—reduction in flares of diarrhea, reduced joint space narrowing; reduction in MS relapses; reduction in the use of other medications (steroids); reduction in development of deep vein thrombosis or pulmonary embolism; reduction in sickle cell crises; etc.

Category 4. **Clinical Utility/Outcomes**—improvement in survival, reduction on major cardiac events (myocardial infarction, heart failure, re-hospitalization), etc.

4. Provisions for Breakthrough Therapy Designation, Accelerated Approval, Fast Track, Priority Review and Accelerated Approval should be rescinded –with enforcement of the effectiveness standard defined in #2 above and with the FDA meeting its review time frames these programs will no longer be needed. [Orphan Drug designation and Qualified Infectious Disease Product should remain.]
5. Post-approval studies should be limited to amassing greater safety databases to inform labeling. Studies performed to generate evidence for higher order effectiveness claims shall not result in market withdrawal if higher order effectiveness objectives are not met. This is in contrast to the current regulations, which allow for rescinding product approval if drugs approved on the basis of surrogate endpoints (Accelerated Approval) are not shown to have improved disease outcomes and survival in post-approval studies.
6. Personalized medicine in the real world should be fostered, as well. Legislation should make clear which decisions are the domain of the FDA (public health) and those that are the domain of physicians, patients, and other members of the medical marketplace ecosystem (private health). FDA is responsible for safety and effectiveness. Clinical utility and clinical benefit often cannot be easily measured or analyzed in “average patient studies” because these can vary greatly from patient to patient. If sponsors seek claims that communicate clinical utility and clinical benefit, then, the sponsor must present data to the FDA that supports these claims in a meaningful percentage of patients, even if the exact profile of responding patients cannot be defined for labeling purposes, either demographically or genetically. Ideally, to further foster personalized medicine, the data from clinical trials should be made available to practicing physicians

who would then be able to query the databases to obtain knowledge of the effects of the drugs on patients given certain demographic and genetic profiles; this will aid physicians in their private health decisions.

Another recommendation is for Congress to refrain from using hearings as a venue to publicly embarrass and humiliate the FDA when products that have been approved are shown to have undesirable effects and toxicities when used in the real world in larger numbers of patients. This initiates the vicious cycle that stifles medical innovation which was previously illustrated in Figure 3.

It also sets an expectation in the eyes of the public for the FDA to be perfect when it comes to the review and approval of new products. We should not be conditioned to expect perfection, rather, we should be assured that proper mechanisms are in place to appropriately judge the safety and effectiveness of new products and to track them and rapidly report any issues that might emerge after approval. The FDA should then act, appropriately, either with revised labeling or other actions, including removal from the market in extreme settings. Congress would do well to reinforce to the public that the FDA is just one member of the medical ecosystem – physicians, medical societies, hospitals, cooperative research groups, drug companies, and clinical researchers have an important responsibility to disseminate information quickly and to educate medical professionals and the public. Placing blame at the door of the FDA is neither accurate nor conducive to fostering medical innovation.

### **Conclusion**

As Richard M. Cooper, Food and Drug Administration (FDA) Chief Counsel, said in 1978, "The perception that agencies are out of control arises from the fact that in being called on to make fundamental value judgments they have moved outside their accustomed sphere of activity, outside their expertise, and outside the established system of controls. This perturbation of the regulatory process will not be corrected until the regulatory agencies are relieved of the necessity of making judgments they are not equipped to make." The FDA was never intended, and is not equipped, to make value decisions for individual patients. These are private health decisions. Congress charged the FDA with a public health mandate to approve drugs that are safe effective for physicians to use in the care of their patients, on an individual basis.

The key to reducing the amount of time required for potentially life-saving and life-enhancing treatments to reach patients is to restore the FDA to its proper role in the medical marketplace, that is, to the role of gatekeeper with regard to the entry of safe and effective drugs into the medical armamentarium. It is in the medical ecosystem that the diffusion of drugs into practice takes place. The medical marketplace constituents (early adopters, medical consortia and societies, hospitals, doctors, payers, and patients) decide which safe and effective products are the most beneficial and which should be prescribed in widespread fashion. This occurs after using the products in the real world for a period of time; much more is learned about the clinical utility and potential benefits in day to day use than is possible during large clinical trials of highly selected patient populations.

Attempts to approve only those drugs that have shown clinical utility in massive randomized clinical trials prior to approval serve to deprive patients and physicians of safe and effective products that could ultimately be enormously beneficial to them. This also runs counter to medical practice, which is as much art as science and requires direct first-hand experience with drugs to determine which are most appropriate in the real world on an individual basis. Another unintended consequence is that drug developers will focus on developing drugs for niche indications that serve small populations where clinical benefit is obvious because no other treatments are available. This reduces investment and research and development in products aimed at diseases affecting large populations of patients.

Determining safety and effectiveness is a daunting responsibility that should not be encumbered with unrealistic expectations – the FDA cannot make perfect public policy decisions. Neither is it possible for the FDA to make private health decisions that are based on benefit-risk for individual patients. FDA's role is to provide information in the labeling – the parameters within which drugs can be administered safely to achieve the approved effects – that doctors and patients can use in their decision-making.

The FDA is not in it alone despite having been made to feel that it, indeed, is solely responsible for health and well-being of the American public. In order to be effective, the FDA needs the support, understanding, and confidence of the American public in fulfilling their crucial and proper role.

**Attachments:**

The Proper Role of the FDA in the 21<sup>st</sup> Century -- February 2016

FDA must focus on drug safety and effectiveness, not patients' life outcomes – The Hill, February 19, 2016

Meet FDA critic Joseph Gulfo, the Antonin Scalia of the life sciences – Boston Business Journal, February 18, 2016

COMMENTARY: Return FDA to its proper role – Courier Post, February 7, 2016

Appropriate oversight is needed to change FDA behaviors, not more laws – The Hill, December 22, 2015

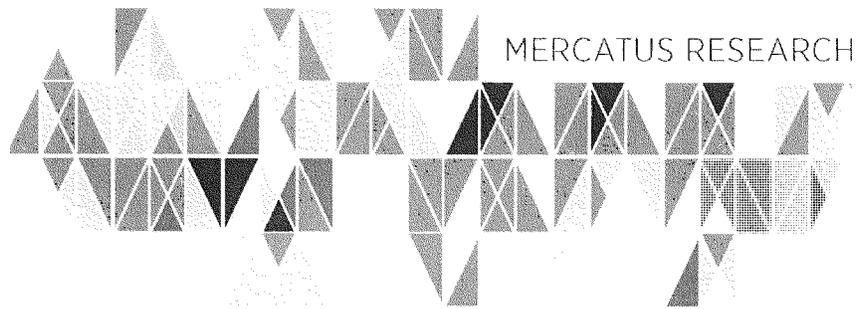
MI3 Alert - Congressional Oversight of the FDA – December 1, 2015

FDA 2014 Approvals – The Message Behind the Numbers – The Hill, January 8, 2015

GULFO: “Right to Try” just another bandage on a chronic wound – Washington Times, July 11, 2014

## The Proper Role of the FDA for the 21st Century

Joseph V. Gulfo, Jason Briggeman, and Ethan C. Roberts



*Joseph V. Gulfo, Jason Briggeman, and Ethan C. Roberts. "The Proper Role of the FDA for the 21st Century." Mercatus Research, Mercatus Center at George Mason University, Arlington, VA, February 2016.*

## ABSTRACT

The FDA's mission is to permit safe and effective new drugs, biologics, and devices onto the market in an efficient and timely manner. But fear of being blamed for the failings of approved products has caused the FDA to become too restrictive. The FDA has strayed from the safety and effectiveness standards that are set out in the law, instead applying standards for approval that are based on predicting the benefits and risks—clinical utility, disease outcomes, survival—that an “average patient” will experience. But these outcomes are better evaluated in real-world, post-market settings—that is, in the medical marketplace, where knowledge about the value of a drug or device for different types of patients can grow over time. The FDA must return to its role as gatekeeper of safe and effective drugs and devices, and refrain from attempting to anticipate the future judgments of physicians and patients regarding benefits and risks.

*JEL* code: H11

Keywords: Food and Drug Administration, FDA, medical marketplace, medical ecosystem, FDA regulations, safety and effectiveness, surrogate endpoints, clinical outcomes, benefit risk, public health decisions, private health decisions, personalized medicine

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**T**he mission of the Food and Drug Administration (FDA), as stated in the Food, Drug and Cosmetic (FD&C) Act, is “to *promote* health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely fashion.” This includes “ensuring that . . . (B) human and veterinary drugs are *safe and effective*; (C) there is reasonable assurance of the safety and effectiveness of devices intended for human use.”<sup>1</sup>

Ultimately, the FDA’s mission is to provide doctors in the medical marketplace with access to safe and effective new drugs, biologics, and devices in a prompt, efficient, and timely manner. The medical marketplace, which involves patients, payers,<sup>2</sup> and physicians, functions to identify the best products for individual patients. The starting point should be the criteria that doctors, particularly early adopters with the most need for new products in their medical armamentarium, minimally demand to see from new products before they have the confidence to start using them. But the FDA is not asking the doctors what they need; instead, it is trying to encroach on the role of physicians. Why?

In a word, *fear*. This fear stems from unreasonable expectations of perfection from certain segments of society. Fear of being blamed for the failings of approved products has caused the FDA to be too cautious in its reviews and approvals.<sup>3</sup> In a sense, the FDA has restated its mission from *promoting* health to *protecting* health, from permitting new products that can advance health to demanding certainty that products will not cause any harm. However, as drugs are small molecules designed to have an effect by binding to targets in

1. See 21 U.S.C. § 393—Food and Drug Administration (2010) (our emphases).

2. Payers are health insurance companies, accountable care organizations, closed provider networks (e.g., Kaiser Permanente), Medicare, and so on.

3. See Vahid Montazerhodjat and Andrew W. Lo, “Is the FDA Too Conservative or Too Aggressive? A Bayesian Decision Analysis of Clinical Trial Design,” August 19, 2015, [http://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=2641547](http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2641547); Alex Tabarok, “Is the FDA Too Conservative or Too Aggressive?,” *Marginal Revolution*, August 26, 2015, <http://marginalrevolution.com/marginalrevolution/2015/08/is-the-fda-too-conservative-or-too-aggressive.html>.

“When we consider that conflicting studies continue to emerge about health outcomes related to coffee and red wine, which have been in use for thousands of years, we can see the absurdity of expecting the FDA to somehow anticipate, unerringly, all possible health outcomes from the use of new drugs.”

the body, it is impossible to give assurance that no harm will ever occur.

But the expectation from certain areas of society is that the FDA completely vets all potential side effects of new drugs for all people in all situations, even effects resulting from uses that are not intended and are not in conformity with approved labeling. Such an expectation is not just impossible to satisfy—it is entirely unreasonable. When we consider that conflicting studies continue to emerge about health outcomes related to coffee and red wine, which have been in use for thousands of years, we can see the absurdity of expecting the FDA to somehow anticipate, unerringly, all possible health outcomes from the use of new drugs.<sup>4</sup>

Due to fear and pressure from the media, members of Congress, and others, the FDA does not take as its starting point the view of doctors who are on the front lines of patient care. Instead, over the last 20 years the FDA has become markedly more restrictive concerning new drugs, in particular through a focus on its efforts to anticipate clinical outcomes of drug treatment (as opposed to surrogate or intermediate endpoints, amelioration or reduction of signs and symptoms of disease, biomarkers, etc.). The effect of the increased restrictiveness verges on telling doctors how to treat patients, as though the regulators are to prescribe drugs remotely from Silver Spring, Maryland. The FDA is applauded by many, particularly those who have misinterpreted the rise of an academic movement known as evidence-based medicine, when it purports to debunk medical practice on the basis of the humongous clinical trials that it requires drug companies to perform as a condition for approval.<sup>5</sup> And so the trend has been for the FDA to become more and more restrictive, protracting its

4. Simple searches of the National Institutes of Health's PubMed research database for “coffee consumption” (<http://www.ncbi.nlm.nih.gov/pubmed/?Db=pubmed&term=coffee%20consumption>) and “red wine consumption” (<http://www.ncbi.nlm.nih.gov/pubmed/?term=red+wine+consumption>) turn up hundreds of studies.

5. Matthew Herper, “Robert Califf Could Transform the FDA—the Right Way,” *Forbes*, September 16, 2015, <http://www.forbes.com/sites/matthewherper/2015/09/16/robert-califf-could-transform-the-fda-the-right-way/>.

pre-approval processes and now frequently requiring that additional controlled trials be done after approval.<sup>6</sup>

As we will show, the FDA is straying, not only from the statutes passed by Congress, but also from its own rules, in guidance documents that are being promulgated; this is how the safety and effectiveness standards have been eroded and changed over time. Despite incessant pleas from doctors and patients for more products that might help when used appropriately, the FDA continues to raise the evidentiary threshold for permitting a new product—recasting premarket approval as a venue for the practice of evidence-based medicine. This move is aimed at satisfying FDA critics, but it consumes precious time and resources, and it dissuades drug developers (and would-be developers) from pursuing projects.<sup>7</sup>

The FDA has acknowledged the changes in its standards for product approval. In a March 10, 2015, opinion piece, two high-ranking FDA officials had this to say about the review process: “It is important to remember, however, that innovative therapies only save lives if they work properly. U.S. citizens rely on the FDA to ensure that the drugs they take are effective and that their benefits outweigh their risks. *Improving a patient’s life or lifespan must be central* to the concept of drug innovation.”<sup>8</sup> But the FDA is supposed to assure *safety and effectiveness of drugs, not life outcomes for patients*. A drug’s label indicates what the drug will have an effect on; safety and effectiveness are to be determined in the context of that labeling. The physician and the patient, acting in the medical marketplace, are to determine whether and when taking the drug will be conducive to improving a patient’s life. That we authorize physicians to prescribe drugs off-label is indicative of this division of labor.<sup>9</sup> Certainly, studies of life outcomes can be invaluable to informed decision-making by physicians and payers in situations where pointed questions have been developed about a drug’s benefits and risks for patients. But because of the multifactorial nature of disease (the many

6. Michael Dickson and Jean Paul Gagnon, “Key Factors in the Rising Cost of New Drug Discovery and Development,” *Nature Reviews Drug Discovery* 3, no. 5 (May 2004): 417–29.

7. The FDA has noted in one guidance document that “the demonstration of effectiveness represents a major component of drug development time and cost; the amount and nature of the evidence needed can therefore be an important determinant of when and whether new therapies become available to the public.” FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, May 1998, Clinical 6, 1–2.

8. Janet Woodcock and Karen Midthun, “US Can Continue to Lead in Drug Innovation,” *The Hill*, March 10, 2015, <http://thehill.com/opinion/op-ed/235278-us-can-continue-to-lead-in-drug-innovation> (our emphasis).

9. Kelli Miller, “Off-Label Drug Use: What You Need to Know,” WebMD Feature, accessed January 19, 2016, <http://www.webmd.com/a-to-z-guides/features/off-label-drug-use-what-you-need-to-know>.

and varied factors that contribute to disease development, progression, and response to therapy), it is far harder to produce good knowledge about life outcomes for patients than it is to produce good knowledge about a drug's safety and effectiveness with respect to specific disease-related parameters.

The fact that improved life outcomes for the “average patient” are frequently not proven in trials of drugs that show activity on specific disease parameters and are safe may often have more to do with the multifactorial nature of disease than with the drug. Since studies cannot control for all important disease-modulating factors, proof of disease activity and safety should be sufficient for approval; it should not be necessary to show improved life outcomes. For example, it can be shown in a trial that a drug causes dilation of the bronchial tubes, but it would be extremely difficult or impossible to prove that the drug will improve the lives of a specific cohort of asthma patients. Indeed, it is very often the case that even large, lengthy, and expensive *outcomes* trials produce inconclusive results, so to impose a blanket requirement for such trials—encompassing even those drugs whose safety and effectiveness can be proven and where there is an absence of any definite controversy—will lead to many instances in which useful drugs are needlessly suppressed, causing costs and harms to patients.

The FDA is thus imposing new standards before approval rather than allowing the medical marketplace to determine whether and for whom a new product is a real innovation. This is directly contradictory to the desires of some current legislators, as expressed in the most recent draft of the 21st Century Cures bill, that the FDA consider the individual preferences and experiences of patients.<sup>10</sup> Different patients experience conditions differently, and are willing to accept different levels of risk. An *ex ante* standard of improving the life or lifespan of an “average patient” cannot take this into account.

The shift in regulatory philosophy from promoting health to protecting health has not only increased the cost and time of drug development, it has also moved the FDA from its proper role in making public health decisions to become an improper force driving private health decisions (see table 1). We must change this philosophy in order for medical innovation to deliver on the potential that 21st century science and medicine has to offer. We need to bring the FDA into the 21st century by bringing it back to its roots: assuring drug safety and effectiveness, not outcomes.

10. H.R.6-21st Century Cures Act, 114th Congress (2015–2016), <https://www.congress.gov/bills/114/congressional-legislation/2015-2016/house-bills/6>.

TABLE 1. PUBLIC HEALTH VS. PRIVATE HEALTH DECISION-MAKING

Health decision	Public	Private
Primary considerations	safety and effectiveness	benefit/risk
Main question	whether the drug under review can be labeled for safe use under conditions proposed by the drug sponsor	whether the likely benefits outweigh the likely risks of using the drug in the patient presenting to the physician
Responsibility	FDA	physicians in the medical marketplace
Inputs into decision	clinical trial results in regulatory filings	the personal profile of the patient, under treatment, drug labeling, personal experience, literature, peer consultation
Contribution of drug intervention to the decision	determination of drug activity (pharmacologic, clinical, patient-reported, biomarker, surrogate endpoints-related) in modulating disease in the "average patient"	clinical outcomes of individual patients treated with the drug, improvements in survival, patient-reported outcomes, reduced morbidity, improved tolerability
Extenuating circumstances	conditions for which no other therapies exist	patient preferences

### MEDICAL KNOWLEDGE IS GROWING AND BEING SHARED AS NEVER BEFORE

We are firmly entrenched in the information economy. Consumers can go online, engage in social media, and ask as many friends and followers as possible about cars, appliances, schools, child care, vacations, lawn mowers, kitchen gadgets, and electronics before buying these products and services. Doctors can also access unprecedented amounts of data, and they can do so faster than ever before. They don't have to wait for the next conference or the next edition of a professional journal - they can share observations and outcomes instantaneously. Patients benefit because the doctor can combine specific knowledge about the individual patient with data on how similar patients responded to treatment. The medical marketplace will never be the same.

Owing to such trends, the future of medicine is at least as exciting as its present. Simple software and hardware can turn a smartphone into a device that can, among other things, diagnose ear infections, distinguish a heart attack from digestive distress, and identify sleep apnea. Data from Internet searches can help the medical community identify previously unknown side effects of medications. These kinds of technological advances make it easier to self-diagnose symptoms and to improve monitoring and communication of vital data, which brings down medical costs to consumers and leads to safer, more rapid, and more effective treatment.

Furthermore, at no other time in history have we been better equipped to perform real-world, large-scale outcomes and survival studies with regard to medical interventions, such as the use of drugs and devices. There is no way

that pre-approval studies of drugs and devices, in tightly defined patient populations under scripted medical management protocols, can produce the kind of evidence that is available through real-world data acquisition and the Internet of Things. What's more, in the post-approval, real-world setting, data that will enhance the selection of therapy for an individual patient can be made available in an unprecedented manner, which can truly drive personalized medicine.

#### BUT THE FDA, PERHAPS SURPRISINGLY, HAS BECOME MORE RESTRICTIVE

Given the president's 2015 State of the Union address,<sup>11</sup> which unveiled the Precision Medicine Initiative designed to give doctors a wider range of tools, knowledge, and therapies to select from when treating patients, one would think that the FDA would embrace the great opportunity represented by the information economy. Regrettably, it hasn't. The FDA has in fact moved away from personalized medicine, increasing its emphasis on trial results for an "average patient" as the standard for permitting new drugs and devices. And even though patients, doctors, hospitals, and payers now have ready access to knowledge about medical products, the FDA has become more restrictive with regard to permitting new drugs and devices.

In large part, it has done so by moving away from what is written in the FD&C Act regarding new applications. This law lists permissible reasons to refuse an application. Specifying reasons for refusal implies that approval is the default position. The safety and effectiveness criteria found in chapter 1 of the law are the most important:

(3) The results of the tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions. . . .

(5) There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.<sup>12</sup>

11. White House, "Fact Sheet: President Obama's Precision Medicine Initiative," press release, January 30, 2015, <https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative>.

12. C.F.R. Title 21, Chapter 1, Subchapter D, Part 314, Subpart D, § 314.125.

Notably absent in the law is any description of refusing an application on the basis of the FDA's predictions about how benefit-risk assessments will be made by an "average patient" and the patient's physician. The agency has also departed from the statutory language by considering possible uses outside of the labeled uses. The law states that the FDA is to judge a drug's safety, on the basis of "tests" and "investigations," in the context of the "conditions of use prescribed, recommended, or suggested in its proposed labeling." This expressly does not include possible off-label uses.<sup>13</sup> Yet the FDA now asserts that it "must also consider how people will actually use newly approved drugs once they are marketed," using "methods from social and behavioral science" to anticipate "cognitive and behavioral factors affecting human judgment and decision making in the context of health care delivery."<sup>14</sup> It is now commonplace for FDA guidance documents to stray, not only from the statutes passed by Congress, but also from the FDA's own rules. This is how the safety and effectiveness standards have been progressively eroded and changed over time.

The agency has also become more restrictive by requiring that pre-approval clinical trials be far larger than in the past<sup>15</sup>—often enrolling participants in numbers comparable to those seen in epidemiological studies of post-approval use in the population. The goal of such massive pre-approval trials is to obtain data on *outcomes* (that is, whether a patient recovers or lives longer, etc.), in order to guess at the clinical utility that a product will have once it is in real-world use—even though a predicted lack of clinical utility is arguably not a permissible reason to refuse an application.<sup>16</sup>

Such outcomes-focused trials, which must be lengthy as well as broad, are far more uncertain in their conclusions than are trials that aim to show that a drug has biological activity related to a disease and is safe to use in that setting.<sup>17</sup>

13. C.F.R. Title 21, Chapter 1, Subchapter D, Part 314, Subpart D, § 314.125(b)(2) (5).

14. FDA, *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making: Draft PDUFA V Implementation Plan*, February 2013, 2.

15. Dickson and Gagnon, "Key Factors in the Rising Cost." The authors note that data from a variety of sources indicate that the length of the process, from synthesis of a compound to approval of a new drug application, has increased, and that this increase is largely due to increases in regulatory requirements, the length of trials, and the complexity of trials.

16. Surrogate endpoints, as opposed to clinical outcomes or scales, were used in fewer than half of the pivotal premarket trials for those novel therapeutic agents that were eventually *approved* during the period 2005–2012. See Nicholas S. Downing et al., "Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005–2012," *Journal of the American Medical Association* 311, no. 4 (2014): 368–77. Generally speaking, comparably systematic data are not or cannot be assembled regarding drugs that remain unapproved.

17. Clifton Leaf, "Do Clinical Trials Work?," *New York Times*, July 13, 2013, <http://www.nytimes.com/2013/07/14/opinion/sunday/do-clinical-trials-work.html>.

For example, a cholesterol drug may safely improve cholesterol levels for a given patient, but a trial may not show the drug to have positive effects on outcomes such as the patient's lifespan. This does not mean, however, that the drug should be denied to all patients it could help. Safety and effectiveness are the measures that the FDA needs to use, as per law, in public health decision-making. And it isn't just safety and effectiveness—the question is whether the drug *can be* labeled for safe use according to the claim submitted. That is, the law in fact instructs the FDA to consider new drugs for approval on the basis of the uses submitted by sponsors (who are responding to the medical marketplace). The FDA should not be telling sponsors that their drugs must show improvement in clinical outcomes; rather, the FDA's role is to label drugs for safe administration in accordance with uses for which they determine the drugs are indeed active. It is then the job of doctors in the medical marketplace to determine the benefits and risks of using new drugs in individual patients, informed by the drug label, their experience with the drug, post-approval studies, and patient factors.

Much of the uncertainty in outcomes-focused trials comes from the many assumptions that are made about how real-world settings will differ from the controlled trial setting. The FDA's use of such assumptions flattens the real world down to the experience of an imagined "average patient." This can mean, of course, that if the "average patient" doesn't surpass certain benchmarks in a trial, the FDA will not permit the drug for use by *any* patient.<sup>18</sup> Yet it is well known that patients often vary dramatically in responsiveness to a given drug, and even though the reasons for such variation are often unknown, the responsiveness itself is often readily observable.<sup>19</sup> Therefore, in the real world a doctor and patient often have the opportunity to try a treatment, observe that it is not working, and switch the patient to another treatment. The availability of additional safe and effective treatment options will often improve the results that doctors and patients obtain by using that routine trial-and-error process.<sup>20</sup>

18. One useful discussion of the FDA's "average patient" standard is provided in Anup Malani, Oliver Bombom, and Mark van der Laan, "Accounting for Heterogeneous Treatment Effects in the FDA Approval Process," *Food and Drug Law Journal* 67, no. 1 (2012): 23–50.

19. See, e.g., Anthony Y. H. Lu, "Drug-Metabolism Research Challenges in the New Millennium: Individual Variability in Drug Therapy and Drug Safety," *Drug Metabolism & Disposition* 26, no. 12 (1998): 1217–22.

20. Such a process—observation of patient response to treatment, followed by a decision either to switch or not to switch therapies—is commonly incorporated in formal modeling of therapy selection. For one example, see Daniel Carpenter, Justin Grimmer, and Eric Lomazoff, "Approval Regulation and Endogenous Consumer Confidence: Theory and Analogies to Licensing, Safety, and Financial Regulation," *Regulation & Governance* 4, no. 4 (2010): 383–407.

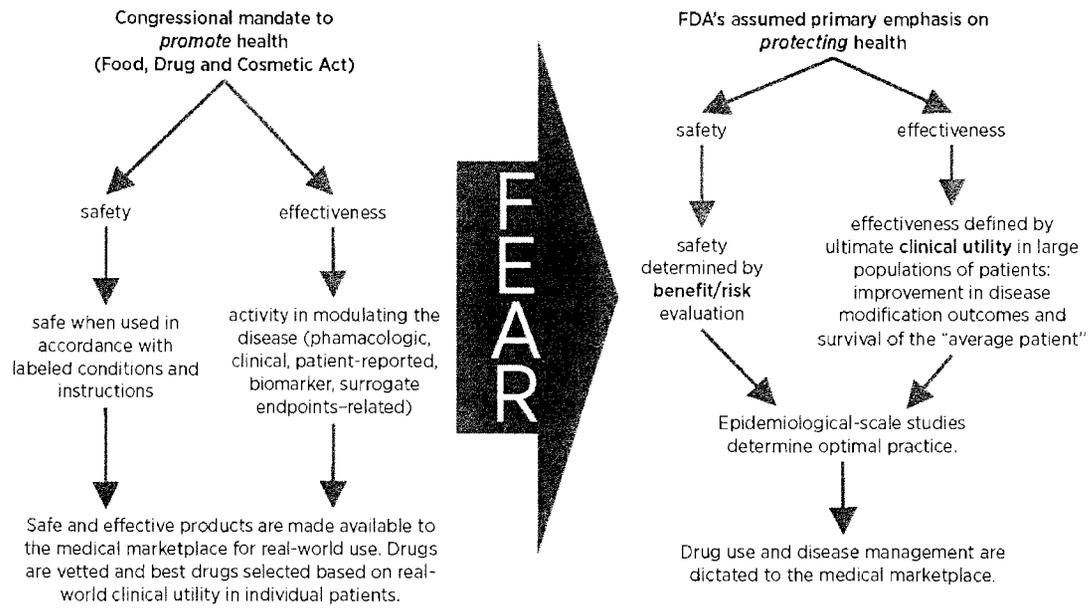
The FDA sometimes imposes another restrictive standard that impedes routine learning processes as well as medical innovation in general: the standard requiring that a new drug demonstrate *superiority* over previously approved drugs in order to be approved. (Imagine if every popular song could only be played on the radio if a panel of judges declared it “better than the Beatles!”<sup>21</sup>) An unintended consequence of the imposition of this standard has been a relative dearth of novel drugs for major diseases that some previously approved products also treat. This scenario is an embodiment of the FDA’s “protect health” mentality, where continuation of the status quo—when there are already, say, one or two drugs available to combat a given disease—is considered better than a changed situation, even when the change in question is *giving patients and physicians access to a drug that is different from existing drugs and comparable in quality*. It hardly needs to be said that such a drug, when tried, would surely be found by some patients to be *more* tolerable or useful than the previously approved alternatives. A given drug will not cause the same side effects in the same intensity for all patients, and so keeping a drug off the market because it is not deemed “superior” in fact *does* deny many individuals access to better drugs—the safe and effective options that would cause fewer or less intense side effects for them. If there were only one birth control pill available, a woman would not be able to find the pill that works best for her. So here is an obvious and frustrating instance of a missed opportunity for the FDA to promote health.

Figure 1 shows the transformation of the FDA approval process because of regulators’ fear. Safety in accordance with labeling becomes safety for an imagined “average patient” with an arbitrarily assigned risk threshold. Effectiveness as identified by activity in modulating

“Imagine if every popular song could only be played on the radio if a panel of judges declared it ‘better than the Beatles!’ ”

21. Credit for the phrase, though applied to consumer decisions as opposed to regulatory decisions, goes to Jack Scannell; see “Four Reasons Drugs Are Expensive, of Which Two Are False,” *Forbes*, October 13, 2015, <http://www.forbes.com/sites/matthewherper/2015/10/13/four-reasons-drugs-are-expensive-of-which-two-are-false/>.

FIGURE 1. FDA REGULATION FOLLOWS PHILOSOPHY



the diseases becomes statistically significant improvements in disease outcomes, requiring very large trials that are all but necessarily longer.

Finally, FDA talk of benefits and risks also creates pressure for comparative effectiveness studies to be brought into the premarket drug approval process. Although “benefit and risk” sounds like a fine construct upon which to make determinations about the usefulness of new drugs, it is not (at least for the FDA). Rather, it ushers in consideration of a new drug’s utility in clinical settings, which leads to a demand for data on hypothetical patient outcomes.<sup>22</sup> While clinical trials can show whether a drug is active in modulating disease parameters, however, even the largest trials cannot control for the myriad factors that affect ultimate outcomes. In other words, choosing to base FDA decisions on benefits and risks implies that the FDA will take on the decision roles of physicians and patients, attempting to anticipate or predict their future choices. Requiring comparative effectiveness trials is a logical but unfortunate consequence of such an attempt because someone must choose *among* drugs. Requiring comparative effectiveness trials further adds to the cost and time it takes to develop new drugs. Benefits and risks, and comparative effectiveness, can and should be analyzed post-approval, in the medical marketplace. If certain payers demand comparative effectiveness trials, it need not be an FDA function to oversee such trials.

Increased FDA restrictiveness is also manifest in required post-approval studies. In years past, required post-approval studies were strictly observational, performed to determine whether a safety signal occurred when populations of patients different from those enrolled in the pre-approval clinical trials received newly approved products. Now, the FDA is demanding very large and costly *clinical trials* after approval for some drugs, and if a drug does not meet the endpoints of these additional trials, it may be taken off the market or its labeling may be significantly altered. This amounts to a sort of pharmaceutical double jeopardy, with an attendant chilling effect on investment. Further, reasserting the “average patient” standard after some doctors and patients have found the drug useful to them and incorporated it into their routines seems particularly counterproductive.

One way to measure the effects of FDA requirements is to look at drug development costs. Estimates of total pre-approval costs show that out-of-

22. The word *benefit* naturally leads to the question “to whom?” By contrast, the word *effective* naturally leads one to ask “for what?” Couching the matter in terms of *effectiveness* thus tends to promote a focus on what it is that the drug under study can or cannot do, while couching it in terms of *benefits* tends toward speculative imaginings about patient circumstances (e.g., constructs such as “the average patient”) and other unbounded consideration of matters beyond the regulator’s expertise and awareness.

pocket expenses have increased at a rate well beyond inflation.<sup>23</sup> This is in part due to an increase in the regulatory burden and the greater length and complexity of required trials.<sup>24</sup> Even minor changes in FDA requirements, such as narrowing the window for meeting a trial endpoint, can lead to important changes in the pharmaceutical and medical technology sectors.<sup>25</sup>

Observable changes in R&D spending and drug development time may hint at the problem, but it is likely much larger than this kind of data—or any data—can show. A quote by Sergey Brin, cofounder of Google, illustrates the impossibility of empirically demonstrating the full extent of the problem:

Generally, health is just so heavily regulated. It's just a painful business to be in. It's just not necessarily how I want to spend my time. Even though we do have some health projects, and we'll be doing that to a certain extent. But I think the regulatory burden in the U.S. is so high that I think it would dissuade a lot of entrepreneurs.<sup>26</sup>

Brin has a record of success, vast resources at his disposal, and a network of connections, which makes it especially concerning that even he voices such a view. If the cofounder of Google perceives the healthcare sector this way, it is probable that there is a significant amount of unseen loss.

The price that priority review vouchers command is further evidence that burdensome regulation has caused harm. Priority review vouchers are regulatory incentives awarded to companies that develop drugs for rare pediatric and tropical diseases; upon approval of these orphan drugs, companies are awarded a voucher that can be redeemed for priority review of any future new drug application, even for drugs that are not intended to treat pediatric or tropical diseases. Priority review vouchers are transferrable—they can be

23. Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (2003): 151–85. Christopher P. Adams and Van V. Brantner attempted to replicate this study. They verified the findings and added that their own estimates varied from \$500 million to \$2 billion. "Estimating the Cost of New Drug Development: Is It Really \$802 Million?," *Health Affairs* 25, no. 2 (March 2006): 420–28.

24. Dickson and Gagnon, "Key Factors in the Rising Costs."

25. Bruce Booth and Rodney Zemmel, "Prospects for Productivity," *Nature Reviews Drug Discovery* 3, no. 5 (May 2004): 451–56. The authors note that narrowing the window for meeting an endpoint led many major firms to shift away from developing antibiotics.

26. Sergey Brin, interview by Vinod Khosla, "Fireside Chat with Google Co-founders, Larry Page and Sergey Brin," Khosla Ventures, July 3, 2014, <http://www.khoslaventures.com/fireside-chat-with-google-co-founders-larry-page-and-sergey-brin>.

sold to other companies, and frequently they are.<sup>27</sup> On August 19, 2015, United Therapeutics announced that it had agreed to sell a priority review voucher to AbbVie for \$350 million.<sup>28</sup> Presumably AbbVie believes that a priority review will lead to cost reductions that exceed the purchase price of the voucher. The expected costs to an entrepreneur of developing a drug or device are clearly quite large. Any possible venture that does not involve even larger expected benefits will not be pursued—and there is, of course, no systematic data on projects that never started.<sup>29</sup>

#### WHY HAS THE FDA BECOME MORE RESTRICTIVE?

Fear of making a mistake is the major driving force of the FDA's mission creep and increasingly onerous pre-approval requirements. In 1974, FDA Commissioner Alexander M. Schmidt said, "In all of FDA's history, I am unable to find a single instance where a congressional committee investigated the failure of FDA to approve a new drug. But the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them. The message to FDA staff could not be clearer."<sup>30</sup> In subsequent years the FDA was sometimes criticized for slow approvals or for reducing innovation, but still today the strong perception is that congressional criticism has created within the FDA an "underlying motto": "never do what's best, when you can do what's safe."<sup>31</sup> Reviewers, burned from the recalls of Vioxx, Meridia, Rezulin, and others, have made life easier for themselves by requiring larger studies focused on outcomes and event rates, and even on proving negatives (that a drug doesn't cause a particular effect). They seemingly have decided that the best way to avoid

27. Alexander Gaffney and Michael Mezher, "Regulatory Explainer: Everything You Need to Know about FDA's Priority Review Vouchers," Regulatory Affairs Professionals Society, July 2, 2015, <http://www.raps.org/Regulatory-Focus/News/2015/07/02/21722/Regulatory-Explainer-Everything-You-Need-to-Know-About-FDA%E2%80%99s-Priority-Review-Vouchers/>.

28. United Therapeutics, "United Therapeutics Corporation Agrees to Sell Priority Review Voucher to AbbVie for \$350 Million," press release, August 19, 2015.

29. The market price for a priority review voucher has risen rapidly. In May 2015, Sanofi paid \$245 million to Retrophin, and in November 2014, Gilead Sciences bought a voucher from Knight Therapeutics for \$125 million.

30. While Schmidt's oft-quoted characterization was a slight exaggeration, at the time of his statement it was essentially accurate. See Daniel Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* (Princeton, NJ: Princeton University Press, 2010), 337–40, especially table 5.6 up to 1974.

31. Tom Coburn, quoted in Hanna Krueger, "Ex-Sen. Coburn: Congress 'Beats the Crap' Out of FDA," *The Hill*, July 14, 2015, <http://thehill.com/policy/healthcare/247911-ex-sen-coburn-congress-unfairly-beats-the-crap-out-of-fda>.

criticism is to require near certainty before approval.<sup>32</sup> There has been much less pressure on them to avoid a different type of error—the error of over-caution, which leads to more victims of diseases who might have been helped by drugs that have been suppressed.<sup>33</sup> Such victims are often faceless and voiceless because the public generally cannot know what has been lost due to over-caution.

A second cause of the FDA's move away from the statute is the increasing influence, starting around 1990, of certain strands of an academic movement called "evidence-based medicine" (EBM). Evidence in various forms was of course already central in most medical decision-making, and appropriate systematic attention to improved application of evidence is to be cheered.<sup>34</sup> A sophisticated understanding of EBM allows that both researchers' production of guidelines and physicians' individual decision-making are inevitable and necessary, that the two must work in tandem, and that evidence has relevance to both.<sup>35</sup> For example, *evidence* in the context of physician decision-making can refer to evidence about guidelines themselves—for example, evidence on which guidelines to trust, on when to use them, on how to interpret them, and so forth.<sup>36</sup> But some have misinterpreted the advent of evidence-based medicine as representing an abrupt paradigm shift.<sup>37</sup> This misinterpretation sometimes manifests itself in disparagement of pre-EBM practices in the medical marketplace as being representative of an unscientific "art of medicine." In the extreme, the term evidence-based medicine has been used pejoratively to insinuate that—in the current EBM era—physicians and other caregivers can, and should, have little role in decision making. In light of the strength of the EBM movement, it seems reasonable to interpret, say, FDA insistence on outcomes studies as an EBM-inspired vote of mild to little confidence in physicians and the medical marketplace.

32. Joseph V. Gelfo, *Innovation Breakdown: How the FDA and Wall Street Cripple Medical Advances* (Franklin, TN: Post Hill Press, 2014), 239–44.

33. The distinction between cautiousness and safety is similar to the distinction between protecting health and promoting health, discussed above. On such distinctions see Aaron Wildavsky, *Searching for Safety* (New Brunswick, NJ: Transaction Publishers, 1988).

34. Jeffrey A. Claridge and Timothy C. Fabian, "History and Development of Evidence-Based Medicine," *World Journal of Surgery* 29 (2005): 547–53.

35. David M. Eddy, "Evidence-Based Medicine: A Unified Approach," *Health Affairs* 24, no. 1 (January 2005): 9–17.

36. "So many parties have jumped on the EBM bandwagon and so many clinical practice guidelines are churned out by individuals, professional organizations, insurers, and others that the benefits of uniformity may disappear in the cacophony of overlapping, conflicting, and poorly constructed guidelines. With more than 1,000 guidelines created annually, calls for 'guidelines for clinical guidelines' have been issued." Stefan Timmermans and Aaron Mauck, "The Promises and Pitfalls of Evidence-Based Medicine," *Health Affairs* 24, no. 1 (January 2005): 18–28.

37. Earl P. Steinberg and Bryan R. Luce, "Evidence Based? Caveat Emptor!," *Health Affairs* 24, no. 1 (January 2005): 81, 91n1.

It is true that certain lines of the EBM literature, such as the evidence on geographic variations in medical practice, have pointed strongly to a conclusion that the medical marketplace can err, in the sense of falling short of a standard or ideal. However, there is also little to no evidence that using the FDA premarket approval process to anticipate adoption decisions is a relatively superior approach.<sup>38</sup> Health economists Anup Malani and Tomas Philipson have put this point very bluntly:

Economists have conducted relatively little theoretical or empirical research on the efficiency of FDA policies. Ironically, if a product application were presented to the FDA with the scant amount of evidence that currently exists on the efficiency of the policies of the agency itself, such an application would likely be rejected on the basis of insufficient evidence.<sup>39</sup>

Their point is only strengthened when one notes that Malani and Philipson are speaking about premarket approval per se, and not necessarily with regard to a particularly restrictive variant.

#### THE GATEKEEPER AND THE MEDICAL MARKETPLACE

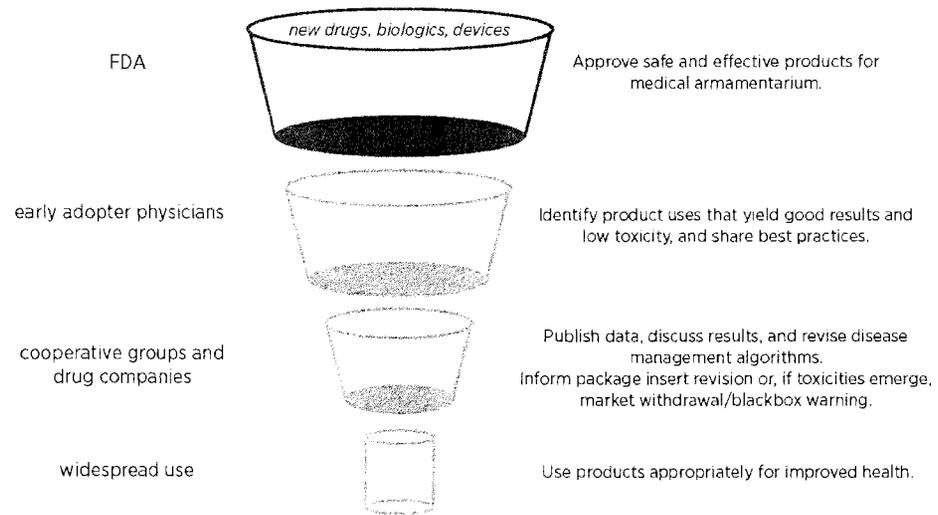
Figure 2 shows the FDA's appropriate role as gatekeeper to the medical marketplace, which is how it functioned in the 1980s and early 1990s. Regulators helped the medical community by approving safe and effective products. Then, as described above, physicians, patients, and payers in the medical marketplace identified the best products for individual patients through a process not unlike natural selection: the drugs that offered the best clinical results for appropriate patients were used preferentially.

In the 1980s and early 1990s—that is, before the current period of increased restrictiveness—the standard used by the FDA in determining whether a drug was sufficiently effective was more about observing the drug's pharmacologic activity on a disease, and less about attempting to anticipate the drug's clinical utility. Rather than endpoints such as survival or fewer bad medical outcomes (e.g., heart attacks, strokes, amputations, or

38. Jason Briggeman, *Searching for Justification of the Policy of Pre-market Approval of Pharmaceuticals*, Ph.D. diss., George Mason University, 2015.

39. Anup Malani and Tomas Philipson, "The Regulation of Medical Products," in *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*, ed. Patricia M. Danzon and Sean Nicholson (Oxford, U.K.: Oxford University Press, 2012), 101.

FIGURE 2 THE MEDICAL MARKETPLACE IN THE 1980s AND EARLY 1990s



progression of disease), trials routinely used surrogate and intermediate endpoints (e.g., fasting glucose levels, blood pressure, tumor shrinkage, and stress tests).<sup>40</sup>

How was clinical utility assured? It flowed out of the medical marketplace. The FDA of the 1980s and early 1990s knew its place in the medical ecosystem to be that of a gatekeeper of new products entering the medical armamentarium. The FDA's role was to *permit* drugs, biologics, and devices based on safety and efficacy (reasonable assurance of safety and effectiveness for medical devices), and then the medical marketplace would *adopt* the best treatments from among those permitted by the FDA, for use by individual patients. The agency was at the top of the funnel, making sure that only safe and effective products passed through. As they still are today, doctors were assigned responsibility for authorizing and guiding patient use of prescription-only drugs, and also as they are today, doctors were empowered and expected to prescribe drugs off-label when appropriate.<sup>41</sup>

How were decisions to adopt drugs made? How was personalized medicine exercised? Mostly, such decisions were based on real-world experiences of doctors treating patients and by additional clinical trials sponsored by cooperative clinical groups (e.g., National Institutes of Health), hospital networks, and the biopharmaceutical and medtech industry. This information would be shared at medical meetings and in the literature. Doctors who observed a patient experiencing an idiosyncratic adverse response would switch that patient to an alternative treatment.<sup>42</sup> In a natural selection process, doctors and patients would learn the best treatment for individual medical situations

“The FDA of the 1980s and early 1990s knew its place in the medical ecosystem to be that of a gatekeeper of new products entering the medical armamentarium.”

40. Russell Katz, “Biomarkers and Surrogate Markers: An FDA Perspective,” *Journal of the American Society for Neurotherapeutics* 1, no. 2 (April 2004): 189–95, doi: 10.1602/neurotx.1.2.189.

41. Alexander T. Tabarrok, “Assessing the FDA via the Anomaly of Off-Label Drug Prescribing,” *Independent Review* 5, no. 1 (Summer 2000): 25–53.

42. G. R. Venning, “Validity of Anecdotal Reports of Suspected Adverse Drug Reactions: The Problem of False Alarms,” *British Medical Journal* 284 (1982): 249–52.

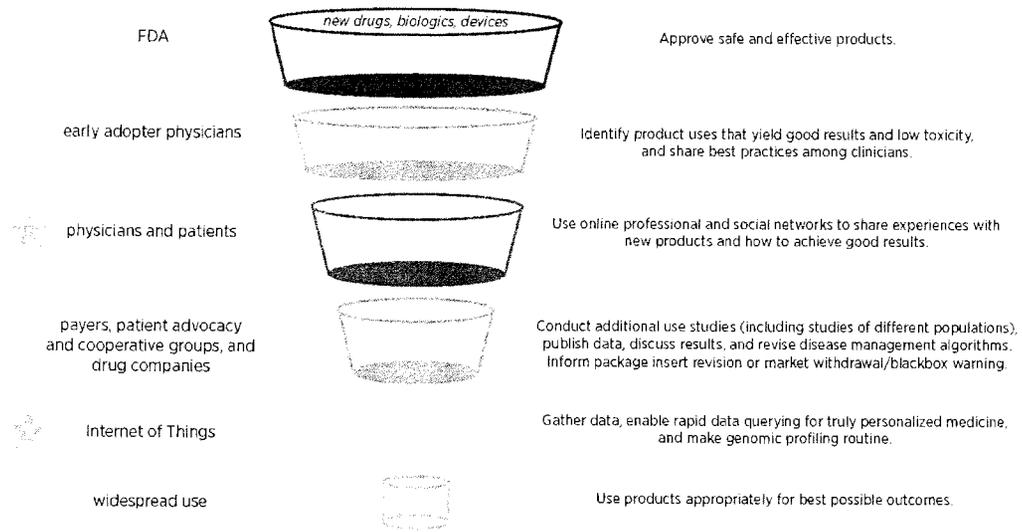
and use the appropriate drugs and devices in the medical armamentarium. This narrowed the funnel by identifying optimal uses of available safe and effective products. More often than not, these pearls of wisdom, even as they were codified in practice guidelines and medical pathways, would never make it into the package insert (that is, the labeling approved by the FDA). The ability of today's medical marketplace to vet approved products and drive the adoption of those that have the greatest clinical utility is greatly strengthened by the emergence of online patient and doctor communities for immediate sharing of knowledge and best practices. The FDA itself has acknowledged the power of the Internet by partnering with Google to use search terms and topics as a means of identifying new information about drugs.<sup>43</sup>

We believe that a reinvigorated medical marketplace system, with the FDA returned to its proper role at the top of the funnel, could help realize the promise of the information economy and personalized medicine for 2015 and beyond. FDA premarket approval is designed to deliver an initial permission decision; postmarket controls are aimed at modifying drug labels, or even withdrawing the drugs, if issues emerge in their use in the medical marketplace. *Adoption* decisions do, and should, vary over time as more is learned in clinical practice, additional trials, and epidemiological research. With knowledge so much more readily available to doctors, drugs should again be permitted on the basis of safety and effectiveness—and not rejected on the pretense that, by invoking a mythical “average patient,” the FDA can credibly wrap all future adoption decisions into its permission decision. Prescription requirements remain a viable means of restricting patients' access to drugs that are difficult to use appropriately and as directed.

Figure 3 shows the FDA at the top of the new and more dynamic medical marketplace, in its proper role of permitting safe and effective drugs onto the market. It also shows how the information economy and the ability to rapidly share and process data help doctors improve patient outcomes at a rate and scope previously not possible. The new marketplace better assures that appropriate treatments are provided to patients.

43. Michael Mezher, “FDA and Google Talk ‘Adverse Event Trending,’” Regulatory Affairs Professional Society, July 16, 2015, <http://www.raps.org/Regulatory-Focus/News/2015/07/16/22888/FDA-and-Google-Talk-Adverse-Event-Trending/#>.

FIGURE 3. THE MEDICAL MARKETPLACE AS IT SHOULD BE TODAY



REASONS TO REINVIGORATE THE ROLE OF THE  
MEDICAL MARKETPLACE

Why should we go “back to the future” in this way? Why will this system be better? We believe an important element of the answer is that doctors believe it will help patients. And, patients want their doctors to try to help them more—that is what Right to Try laws, approved now in 24 states, are all about.

Physicians and Patients Should Have More Options More Quickly

What do early adopters want to see from the FDA approval process before they start the real-world use of drugs, knowing that drug studies do not directly correlate with individual patient experiences?

1. They want products that have been evaluated in a manner that gives them confidence to prescribe drugs safely and in accordance with appropriately labeled conditions of use and instructions. In addition, they want to see data demonstrating that new compounds have activity in clinical parameters of importance to them and to their patients. Statistically significant assessments of safety, as well as data supporting the pharmacologic activity of new drugs (surrogate markers, intermediate endpoints, symptom relief, resolution or improvement of clinical signs of disease) are required prior to use by early adopters. Definitive evidence of improvement in disease outcomes and survival is not required.
2. There has been an inexorable progression toward greater and greater data demands by the FDA before approval. This greatly impedes the development of products for diseases that affect large segments of the population in favor of niche diseases, hurts patients by delaying products that can provide medical benefit, and adds to the time and cost of trials. Doctors need more drugs to treat diseases that affect millions of Americans.
3. Unfortunately, today’s FDA often requires unequivocal evidence of clinical utility to be demonstrated before approval. While the doctors are in support of having as much data as possible to inform their treatment decisions, there is no doubt that some doctors feel that post-approval studies performed by industry, as well as independent clinical investigators, are well-suited for providing evidence of clinical benefit. Moreover, they want to see clinical benefit for themselves, or they will not continue to use the drugs.
4. There are many examples of the FDA having denied approval, or having inhibited further development, of drugs that would make valuable

additions to the current medical armamentarium. Doctors want more safe and effective products that can help their patients.

Table 2 shows the minimum amount of information physicians need for several medical conditions in order to make choices with their patients, both immediately after the release of new drugs and after the drugs have been in the medical marketplace for a while. In summary, before using new drugs, doctors who are early adopters want to know that drugs can be safely administered, have pharmacologic activity, and, in some cases, have shown a hint or trend (rather than statistically significant proof derived from epidemiologic-scale studies) of improving disease outcome parameters. Definitive proof of clinical utility and outcomes or survival before approval is not necessary and unduly delays or holds back important new medicines that doctors want to use in some of their patients. The appendix contains additional discussion about the medical conditions and the development efforts of drugs to treat the diseases highlighted in the table.

#### The FDA's Expanded Role Has Created Economic Problems

Economic analysis can shed light on unintended consequences of the FDA's increasing restrictiveness and imposition of an outcomes-focused standard. Here we focus on two growing problems, both of which can be addressed by a reinvigoration of the medical marketplace model.

Increased restrictiveness has denied patients good alternatives to older drugs. There are many drugs in the current armamentarium that were approved back when there were smaller and much less rigorous trials. The FDA keeps these on the market (generally appropriately), while often refusing to approve drugs that are being developed in *today's world, with today's biomarkers and assessments, and today's brand of transparent rigorous trials*. We should, all else being equal, probably favor drugs that were developed more recently even if they demonstrate only comparable safety and effectiveness, rather than superior performance. Drugs developed in recent times have been characterized to a much greater extent (commensurate with discoveries and advances in basic biology, laboratory methods, genomics, and medicine) compared to drugs developed 15 to 30 years ago. However, by supplanting *safety* with benefit-risk and *effectiveness* with clinical utility and outcomes, the FDA has moved the goalposts, with the ironic result that older drugs have been protected from newer would-have-been competitors, even in instances when the clinical usefulness of the older drugs has faded.

TABLE 2. MINIMUM INFORMATION PHYSICIANS NEED TO MAKE DRUG CHOICES

Condition	Premarket informational needs of early adopters	Postmarket additional data welcomed to further inform therapy selection
Prostate cancer treatment	<ol style="list-style-type: none"> <li>Phase 2 data: biomarker response (drop in PSA), tumor shrinkage (radiologic evidence), patient-reported outcome improvement (bone pain), and progression-free response exceeding literature.</li> <li>Safe to use in accordance with label.</li> <li>Approval for use when standard therapies fail. <i>(The FDA often requires survival outcomes for full approval.)</i></li> </ol>	<ol style="list-style-type: none"> <li>Phase 3 &amp; 4 studies conducted by pharma companies with early adopters. When available, data on outcomes (progression-free and overall survival), as well as on broader safety experience, are to be disseminated.</li> <li>Widespread use dependent on the extent to which doctors' experiences mimic clinical trial data.</li> </ol>
Cardiovascular diseases:		
Hypercholesterolemia	<ol style="list-style-type: none"> <li>Reduction in LDL cholesterol.</li> <li>Safe to use in accordance with label. <i>(The FDA often requires cardiovascular outcomes—reduction in myocardial infarction, stroke, etc.—to be initiated as conditions of approval.)</i></li> </ol>	<ol style="list-style-type: none"> <li>Expanded safety and tolerability data.</li> <li>Head-to-head outcomes studies to decide which agents will be used preferentially.</li> <li>Additional studies in subgroups and special populations.</li> </ol>
Hypertriglyceridemia	<ol style="list-style-type: none"> <li>Reduction in triglyceride levels to within (or near) normal limits, especially in patients at high risk of bad cardiovascular outcomes.</li> <li>Safe to use in accordance with label. <i>(The FDA often requires a reduction in frequency of major cardiac events.)</i></li> </ol>	<ol style="list-style-type: none"> <li>Expanded safety and tolerability data.</li> <li>Head-to-head outcomes studies to decide which agents will be used preferentially.</li> <li>Additional studies in subgroups and special populations.</li> </ol>
Low HDL levels	<ol style="list-style-type: none"> <li>Increased HDL levels in patients at high cardiovascular risk.</li> <li>Increased HDL levels (irrespective of baseline cardiovascular risk) including a non-statistically significant trend showing improved cardiovascular outcomes.</li> <li>Safe to use in accordance with label. <i>(The FDA often requires cardiovascular outcomes—reduction in myocardial infarction, stroke, etc.—as conditions of approval.)</i></li> </ol>	<ol style="list-style-type: none"> <li>Expanded safety and tolerability data.</li> <li>Head-to-head outcomes studies to decide which agents will be used preferentially.</li> <li>Additional studies in subgroups and special populations.</li> </ol>
Metabolic Diseases:		
Hyperuricemia (elevated uric acid levels)	<ol style="list-style-type: none"> <li>Reduction in uric acid levels to within (or near) normal limits, especially a rising uric acid level.</li> <li>Safe to use in accordance with label. <i>(The FDA requires reduction in uric acid in patients with gouty arthritis as the basis for approval.)</i></li> </ol>	<ol style="list-style-type: none"> <li>Expanded safety and tolerability data.</li> <li>Data on attacks of gouty arthritis and tolerability relative to other approved agents will help decide which products are used in selected patients.</li> </ol>
Diabetes	<ol style="list-style-type: none"> <li>Reduction in serum hemoglobin A1c levels.</li> <li>Safe to use in accordance with label. <i>(The FDA often requires HgbA1c reductions and large outcomes studies to prove that the drugs do not increase risk of negative cardiovascular outcomes as conditions of approval.<sup>10)</sup></i></li> </ol>	<ol style="list-style-type: none"> <li>Expanded safety data to include effect (positive or negative) on cardiovascular outcomes, and to determine if low-lies or negative outcomes can be managed or reversed by other means, if hypoglycemic effect is substantial.</li> <li>Demonstration of improved cardiovascular outcomes, as seen with Jardiance, will increase breadth of use.<sup>10)</sup></li> <li>Additional studies in subgroups and special populations.</li> </ol>

continued on next page

Condition	Premarket informational needs of early adopters	Postmarket additional data welcomed to further inform therapy selection
Female health:		
Vaginal atrophy	<ol style="list-style-type: none"> <li>Improvement in functions/ endpoints (e.g., dryness, vaginal wall thickness, for example) and a probed basket of patient reported outcomes (prn, dyspareunia, and dysuria).</li> <li>Safe to use in accordance with label (The FDA often requires large clinical trials in each symptom, separately, pain, dyspareunia, and dysuria.)</li> </ol>	<ol style="list-style-type: none"> <li>Expanded safety and tolerability data</li> <li>Head-to-head functional and outcomes studies to decide which agents will be used preferentially.</li> </ol>
Infection	<ol style="list-style-type: none"> <li>Increased activity of vaginal secretions—brought to near premenopausal levels with reduced colonization of coliform bacteria and yeast.</li> <li>Safe to use in accordance with label (The FDA often insists on clinical utility outcomes, for example, reduction in pyelonephritis, which requires study of tens of thousands of patients.)</li> </ol>	<ol style="list-style-type: none"> <li>Expanded safety and tolerability data.</li> <li>Head-to-head functional and outcomes studies to decide which agents will be used preferentially.</li> </ol>
Sexual desire	<ol style="list-style-type: none"> <li>Increased desire, satisfaction, and sexual frequency.</li> <li>Safe to use in accordance with label (The FDA often additionally requires large outcomes studies to prove that testosterone-based drugs do not increase risk of negative cardiovascular outcomes as conditions of approval.)</li> </ol>	<ol style="list-style-type: none"> <li>Expanded safety and tolerability data.</li> <li>Head-to-head functional and outcomes studies to decide which agents will be used preferentially.</li> </ol>
Osteoporosis	<ol style="list-style-type: none"> <li>Studies showing improvement in bone mineral density in nonvertebral areas (hips and wrists) combined with reductions in vertebral fracture.</li> <li>Safe to use in accordance with label (The FDA often requires large clinical studies of reduction in nonvertebral fractures.)</li> </ol>	<ol style="list-style-type: none"> <li>Expanded safety and tolerability data.</li> <li>Head-to-head functional and outcomes studies to decide which agents will be used preferentially.</li> </ol>

(a) Boaz, Hershberg and Aris Katz, "Cardiovascular Outcome Studies with New Antidiabetic Agents: Scientific and Operational Considerations," *Diabetes Care* 36 (2013): S253–58.  
 (b) Ron Wniskw, "New Diabetes Drug Shows Sharply Reduced Risk of Heart-Related Death," *Wall Street Journal*, September 17, 2015. <http://www.wsj.com/articles/new-diabetes-drug-shows-sharply-reduced-risk-of-heart-related-death-1442528430>.

“The reason the FDA had approved no other oral drugs to treat methicillin-resistant SSSI was largely that it had been requiring *superiority* to active treatment as the criterion for approval, which is very difficult to demonstrate.”

The antibiotics crisis—a host of health problems caused by emerging bacteria that resist treatment by approved antibiotics—is a prime example.<sup>44</sup> Zyvox<sup>45</sup> (linezolid), an antibiotic granted approval by the FDA in 2000, was “the only oral drug approved for complicated SSSI (skin and skin structure infections) caused by methicillin-resistant *Staphylococcus aureus* (MRSA)” until 2014. The reason the FDA had approved no other oral drugs to treat methicillin-resistant SSSI was largely that it had been requiring *superiority* to active treatment as the criterion for approval, which is very difficult to demonstrate. (Further, it is unethical to force patients into a treatment to which they are knowingly resistant for the sake of a clinical trial—that is, a treatment that is certain to provide no benefit to them—in order to show superiority, a situation that can often complicate clinical trials.)

To address these issues, the Qualified Infectious Disease Product (QIDP) designation program, passed as part of the 2012 Prescription Drug User Fee Act (PDUFA) reauthorization (FDA Safety and Innovation Act), allowed for fast track approval of antibiotics for serious or life-threatening infections, including those caused by an antibacterial- or antifungal-resistant pathogen, which permitted the demonstration of non-inferiority—rather than superiority—to active treatment as the endpoint for clinical trials to support approval. Following this, Sivextro<sup>46</sup> (tedizolid) was approved in 2014 by demonstrating non-inferiority to linezolid. Unfortunately, outbreaks of linezolid-resistant strains of *Staphylococcus aureus* had by then been occurring for several years.<sup>47</sup> In general, over

44. See, e.g., Frances Weaver, “The Antibiotics Crisis,” *The Week*, November 16, 2013, <http://theweek.com/articles/456340/antibiotics-crisis>.

45. Pfizer, Highlights of Prescribing Information: Zyvox, last modified July 2015, <http://labeling.pfizer.com/ShowLabeling.aspx?id=649>.

46. Merck, Highlights of Prescribing Information: Sivextro, last modified July 2015, [http://www.merck.com/product/usa/pi/circulars/s/sivextro/sivextro\\_pi.pdf](http://www.merck.com/product/usa/pi/circulars/s/sivextro/sivextro_pi.pdf).

47. Philippe Prokocimer et al., “Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections,” *Journal of the American Medical Association* 309, no. 6 (2013): 559–69.

this period the problem of antibiotic resistance had continued to grow while the flow of new antibiotics diminished.

The “average patient” standard is disfavoring drugs for large-population diseases. The “average patient” standard as applied in outcomes-focused trials has caused a burgeoning of narrow, niche claims.<sup>48</sup> Once the domain, rightfully and appropriately, of rare pediatric diseases such as enzyme deficiencies, targeting narrow diseases is now a preferred development pathway for even the largest companies because of the FDA’s implicit and explicit incentives, such as priority review vouchers, Breakthrough Therapy designation, Fast Track review, and Accelerated Approval.

Could these incentives cause companies to abandon pursuit of drugs to treat diabetes, heart failure, obesity, chronic obstructive pulmonary disease, addiction, early-stage cancer, and other diseases with massive numbers of patients? For claims of effectiveness in those diseases, the FDA may require clinical trials with tens of thousands of patients, assessing not only disease outcomes but also survival.<sup>49</sup> Meanwhile, for narrow, niche claims—which are often created by simply taking refractory (disease recurrence despite prior treatment) populations or those with a specific mutation—the FDA requires comparatively very little in the way of testing. Not only are required trials smaller and thus less costly for niche drugs, there is also a lower bar for approval. Recall that—unfortunately—the FDA often considers “the benefits and risks of *other available therapies*” when making approval decisions on new drugs.<sup>50</sup> But a maker developing a niche drug, where there are no available therapies, doesn’t have to worry about the FDA attempting to estimate the drug’s value compared to existing drugs. Furthermore, the specificity of a niche drug assures its good performance in an “average patient,” and there is a limited number of patients that would be exposed should the drug turn out to be more toxic than originally thought. For all these reasons, the final decision to approve a niche drug is often a no-brainer.<sup>51</sup> The FDA loves to tout

48. Joseph V. Gultfo, “Corrupting the Common Cure,” *Economic Intelligence, U.S. News & World Report*, April 27, 2015, <http://www.usnews.com/opinion/economic-intelligence/2015/04/27/fdas-orphan-drug-designation-warps-medical-research>.

49. See, e.g., Malorye Allison, “Can Cancer Clinical Trials Be Fixed?,” *Nature Biotechnology* 29 (2011): 13–15.

50. FDA, *Structured Approach to Benefit-Risk Assessment* (our emphasis).

51. Drugmakers are also explicitly incentivized to develop niche drugs. The FDA uses rewards such as priority review vouchers and extended periods of market exclusivity to induce makers to develop drugs for rare diseases. The Breakthrough Therapy designation, made law in 2012, provides regulatory incentive for developers to pursue drugs that address significant unmet medical needs, including niche, refractory claims. And there are new incentives for niche product development in the 21st Century Cures bill.

niche-drug approvals and wants them to weigh heavily in evaluations of FDA performance (i.e., PDUFA)—and Congress has generally let the FDA get away with it.<sup>52</sup>

#### The FDA Should Pay Heed to the Spirit of the Law

We believe that the system of the 1980s and early 1990s was more in keeping with the law than is the more restrictive regime the FDA now imposes. Back then, Congress limited FDA consideration of a drug's effectiveness to the effect represented on the proposed labeling.<sup>53</sup> Congress intended drug developers to conduct clinical trials and submit applications for uses of their products that they see fit, assuming that market forces would drive the selection of meaningful and appropriate endpoints in order for their products to compete. Drugs were meant to be safe when used as labeled, and to have some activity in modulating a targeted clinical parameter. FDA approval was not to be interpreted as meaning that a drug could be supposed risk-free for an "average patient" or as meaning that a drug's efficacy had been measured relative to other drugs.<sup>54</sup> But in practice, it is the FDA that tells companies what is and is not appropriate evidence, and today's FDA has moved away from pharmacodynamics activity, surrogate markers, and intermediate endpoints to survival and major health outcomes. Companies have no choice but to listen.

The increased sophistication and efficiency of today's medical marketplace in carrying forward a natural selection process to arrive at the best products for appropriate patients should give us confidence in reasserting the spirit of the law as described above. In particular, the capability and importance of payers in assessing medical value has grown enormously. Payers have a very strong incentive to select from among the safe and effective products those that are of the greatest medical value—that is, the ones that provide health

52. If FDA review performance were meeting goals set out in the law—such as the goal of 10 months for a standard new drug application review—some niche-drug exclusivity incentives (see previous note) could be reduced or dropped. But for true orphan diseases, e.g., congenital enzyme deficiencies, exclusivity inducements will still be needed.

53. C.F.R. Title 21, Chapter I, Subchapter D, Part 314, Subpart D, § 314.125(b)(5).

54. Another important benefit from returning to more tightly defined standards for safety and effectiveness would be enhanced precision of the informational function served by an FDA approval decision. That is to say, the meaning of an approval—what a drug's approval by the FDA says (and does not say) about the drug—has been muddled by the greater uncertainty inherent in outcomes-focused trials and the application of the "average patient" concept. On the importance of public understanding of the meaning of a drug's approval by the FDA, see Lisa M. Schwartz and Steven Woloshin, "Communicating Uncertainties about Prescription Drugs to the Public: A National Randomized Trial," *Archives of Internal Medicine* 171, no. 16 (2011): 1463–68.

outcomes that are satisfactory to physicians and patients. Large payers, particularly Centers for Medicare and Medicaid Services, often demand—and sometimes sponsor—post-approval studies that provide evidence on outcomes, which give assurance to late adopters or cause early adopters to reconsider. Furthermore, a marketplace with multiple payers tends to mitigate negative impact from any idiosyncratic obstinacy on the part of the regulator. When there are multiple payers, there are multiple opportunities for innovative products to be studied and appreciated, and then later more widely adopted, perhaps even by a stubbornly closed-minded payer once others have validated the value of the intervention. A similar dynamic, of course, applies with regard to physicians: early adopters use the products first, and then late adopters may or may not follow.

#### CONCLUSION: CONGRESS SHOULD ACT TO DEFINE FDA STANDARDS FOR SAFETY AND EFFECTIVENESS

The good news is that the fix for mission creep is quite easy: Congress can guide the FDA back to the letter and spirit of the FD&C Act by more explicitly defining safety and effectiveness. Doing so can prevent the FDA from dictating to the medical marketplace how new drugs, biologics, and devices should be used to help individual patients. There are several steps Congress can take to put the FDA back in its proper role:

1. Explicitly limit the FDA to considering the safety of intended uses, according to the label. FDA reviews should not be permitted to speculate about the safety of off-label uses or of uses in populations beyond those the label indicates.
2. Define safety with regard to the likelihood of causing death, debilitation, or severe harm. This definition would focus FDA reviewers on filtering out the most dangerous drugs and allow the medical marketplace to determine appropriate uses for medicines that might be blocked under a more restrictive safety threshold. Such a definition is aligned with the fact that individuals experience conditions differently, and it places the focus on whether the drug can be labeled in such a way as to promote its safe administration, in accordance with the law.
3. Define effectiveness as having positive activity on the disease (amelioration or reduction of signs and symptoms, surrogate endpoints, biomarkers, etc.).
4. Require the FDA to expand its use of surrogate endpoints (including biomarkers) in trials and reviews. This should include specific, actionable

targets so that the FDA can be held accountable by the public if it fails to take action.

Congress should couple these reforms to the law with a strengthened norm against undue criticism of the FDA by Congress. Risk cannot be eradicated from the use of drugs, and human foresight is limited; therefore poor outcomes cannot by themselves justify the placing of blame for those outcomes upon the FDA. Whenever the FDA is assiduous in following the law and acting appropriately on the knowledge available at the time, then it is to be supported. Congressional leaders should vocally affirm such a norm in order to reduce the fear that has led the FDA to a stance of excessive cautiousness and protraction.

The FDA has an integral role in the medical marketplace as arbiter of appropriately defined safety and effectiveness, but the FDA's judgment with respect to safety and effectiveness clearly has gone awry. Congress must act to address this so that the other constituents of the ecosystem can perform their roles in order to ensure that the best products for each individual patient are used in a manner that will enhance the health of all Americans in a prompt, efficient, and timely fashion.

## APPENDIX:

## EXAMPLES OF THE IMPROPER ROLE OF THE FDA IN DRUG DEVELOPMENT AND REVIEWS OF NEW DRUG APPLICATIONS

The FDA's efforts to dictate to the practice of medicine and to supplant the medical marketplace in determining the most appropriate use of drugs for individual patients are very apparent in the development requirements it imposes on drug companies and the labeling restrictions it places on new products. This section highlights recent examples in which safety and effectiveness were not the primary focus of the FDA. In these examples, the FDA assumed the role of the medical marketplace by demanding data on clinical utility, clinical benefit, and disease outcomes as conditions of approval.

## Hypercholesterolemia

Hypercholesterolemia is a particularly interesting example because it demonstrates the FDA's approach to surrogate markers, the use of which it does not support as the basis of product approvals in other than narrow or niche disease populations.

The finding that LDL cholesterol reduction leads to improved survival has been shown in numerous landmark studies of several different drugs (e.g. pravastatin, atorvastatin, rosuvastatin) over the last 20 years. Why must new drugs to reduce cholesterol be made to show improved survival? With all of the studies that have been performed on multiple different compounds, if LDL lowering is not a good surrogate for cardiovascular outcome, the concept of surrogate endpoints is hollow.

At the June 2015 FDA Advisory Committee meetings for evolocumab (Repatha by Amgen) and alirocumab (Praluent by Sanofi and Regeneron), both monoclonal antibodies directed against a new target in cholesterol synthesis, impressive data demonstrating dramatic LDL reductions were reviewed. The FDA approved the products on the basis of LDL lowering for very high-risk patients, but is withholding approval for broader patient populations until the studies on survival and cardiovascular outcomes (major cardiovascular events, abbreviated MACE) are completed and positive. Many in the medical community are not in support of withholding that approval:

“I was really focused on the very large unmet medical need in patients who are high risk,” said panel member Dr Philip Sager (Stanford University School of Medicine, San Francisco, CA) in explaining his “yes” vote. “It's more likely than not this drug

will actually be able to reduce cardiovascular outcomes. I do acknowledge the uncertainty in not knowing what the cardiovascular outcomes will actually show, but I was unwilling to wait until 2017 or 2018 to get those results.”<sup>55</sup>

Michael H. Davidson, MD, FACC, FNLA, professor and director of the lipid clinic at the University of Chicago Pritzker School of Medicine, said more populations should have been recommended for immediate indication. “I was disappointed that the panel did not recommend approval for statin intolerance, which is difficult to define, but from a patient perspective is clearly a real issue,” he said. “The FDA panel vote is a sober reminder that there are many skeptics who want outcome trials before utilizing these very effective and well-tolerated agents.”<sup>56</sup>

The European Commission approved Amgen’s Repatha (evolocumab) to treat patients with uncontrolled cholesterol who need intensive low-density lipoprotein cholesterol reduction, which includes statin-intolerant patients.<sup>57</sup> The FDA approved Praluent and Repatha only for patients with cardiovascular disease who need more help getting their cholesterol under control, including sufferers of a rare genetic disorder called familial hypercholesterolemia, but didn’t indicate Praluent and Repatha for statin-intolerant patients.<sup>58</sup>

Heart disease is the leading cause of death in the United States. One would think that the FDA would want to get as many safe and effective drugs on the market as possible in order to reduce the number of deaths due to heart disease. However, rather than accepting proof that a drug reduces LDL, the FDA withholds approval for the general population until drug makers have conducted longer and more expensive studies. As any student of Economics

55. Michael O’Riordan, “Approve PCSK9 Inhibitor Evolocumab, FDA Panel Recommends,” *Medscape.com*, June 10, 2015, <http://www.medscape.com/viewarticle/846236>.

56. Erik Swain and Adam Taliercio, “FDA Advisory Panel Backs Approval of PCSK9 Inhibitors,” *Cardiology Today*, July 2015, <http://www.healio.com/cardiology/ehd-prevention/news/print/cardiology-today/%7B48c08e5-0d4d-4cb2-8706-010ee8a95886%7D/fda-advisory-panel-backs-approval-of-pcsk9-inhibitors>.

57. Joe Barber, “Amgen’s First-in-Class Cholesterol-Lowering Therapy Repatha Approved in EU,” *FirstWord Pharma*, July 21, 2015, <http://www.firstwordpharma.com/node/1300683>.

58. FDA, “FDA Approves Praluent to Treat Certain Patients with High Cholesterol: First in a New Class of Injectable Cholesterol-Lowering Drugs,” news release, July 24, 2015, <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455883.htm>; FDA, “FDA Approves Repatha to Treat Certain Patients with High Cholesterol,” news release, August 27, 2015, <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm460082.htm>.

101 knows, increasing costs leads to less of a given action. Increase the costs to drug makers of marketing cholesterol drugs, and they will make fewer cholesterol drugs.

#### Correction of Metabolic Derangements

Metabolic derangements are medical conditions manifested in abnormal laboratory tests, initially, which if untreated can lead to clinical manifestations, such as cardiovascular disease or diabetes. While doctors are often appropriately loath to “treat lab tests,” intervening to normalize grossly abnormal laboratory parameters is good medicine in most circumstances. It seems clear, however, that the FDA will not approve drugs based on their effects on these laboratory endpoints alone. Metabolic derangements include correction of serum uric acid, triglyceride, HDL cholesterol, and glucose abnormalities.<sup>59</sup> Most diseases are quite complex, so it is extraordinarily difficult to conduct trials that, amid the multiple factors that simply cannot be controlled, can ferret out clinical benefits resulting from the correction of derangements. So when clinical benefit is made the standard for approval, doctors and patients are denied access to compounds that both correct derangements and are safe when used as labeled. Following are two examples of these conditions and drugs that treat them.

#### Hypertriglyceridemia

When Amarin Pharmaceuticals sought to obtain approval for use of Vascepa in patients with elevated triglyceride levels (above 200 mg/dL), the FDA required the company to perform a study demonstrating significant triglyceride lowering and to recruit at least half the patients in a cardiovascular outcomes study (reduction in MACE, including myocardial infarction, stroke, and death).<sup>60</sup> The company filed a new drug application in compliance with the directive from the FDA, but the FDA then expanded the requirements, stating that it now wanted to see the results of the outcomes study as a condition of

59. Joel Schiffenbauer, “Gout: Clinical Review and Trial Design Issues” (presented at the FDA Arthritis Advisory Committee, June 3, 2004), [http://webeache.googleusercontent.com/search?q=cache:T36lOV0hWYAJ:www.fda.gov/ohrms/dockets/ac/04/slides/2004-4044S2\\_01.Schiffenbauer.ppt+&cd=2&hl=en&ct=clnk&gl=us](http://webeache.googleusercontent.com/search?q=cache:T36lOV0hWYAJ:www.fda.gov/ohrms/dockets/ac/04/slides/2004-4044S2_01.Schiffenbauer.ppt+&cd=2&hl=en&ct=clnk&gl=us).

60. Triglycerides are a type of fat, and excessive levels are associated with a risk of heart disease. Approximately one-fourth of Americans have elevated triglycerides. See Margaret D. Carroll, Brian K. Kit, and David A. Lacher, “Trends in Elevated Triglyceride in Adults: United States, 2001–2012” (NCHS Data Brief No. 198, Centers for Disease Control, May 2015).

approval. Medical experts made the case to the FDA that the drug should be approved at this time for lowering triglycerides (even if not for reducing risk of cardiovascular outcomes in patients with triglyceride levels above 200 mg/dL) for a very practical reason: patients with triglyceride levels above 200 mg/dL are often taking fish oil supplements on their own. However, the supplements are not of definite composition and quality, and they often have impurities that are deleterious to patients' health. This common-sense argument did not sway the FDA.

But on August 7, 2015, in their ruling on Amarin's lawsuit against the FDA, the federal courts stated that the company "may engage in truthful and non-misleading speech promoting the off-label use of Vascepa." Now, Amarin is permitted to market Vascepa for use in patients with triglyceride levels above 200 mg/dL under its First Amendment rights to free speech.<sup>61</sup> The FDA has not amended its policies in light of the Amarin decision.

#### Low HDL Cholesterol

Low HDL cholesterol is a known risk factor for patients with cardiovascular disease, but the FDA has not approved drugs that raise HDL cholesterol despite the fact that several agents have been shown to be effective at doing so. Niacin, for example, increases HDL; however, it was not shown to decrease MACE outcomes. Many doctors believe this was due to confounding issues in the trial, and—since niacin is available—such doctors use niacin to increase HDL.

Drugs of a new class called CETP (cholesteryl ester transfer protein) inhibitors have shown significant effectiveness in raising HDL. On October 12, 2015, Eli Lilly announced that the development of its CETP inhibitor, evacetrapib, was stopped even though there were no safety issues because the trial was unlikely to show a reduction in cardiovascular events, as determined by the independent data-monitoring committee. This is unfortunate because there is no telling how this drug may have been shown to be beneficial when used in the real world. The FDA's insistence on cardiovascular outcomes data obscures the medical imperative of raising HDL and the potential benefits that could be assessed in actual use and in post-approval studies in subpopulations of patients with low HDL levels.<sup>62</sup> Nevertheless, if HDL cholesterol can be increased safely

61. Thomas M. Burton, "Amarin Wins Off-Label Case against FDA," *Wall Street Journal*, August 7, 2015, <http://www.wsj.com/articles/amarin-wins-off-label-case-against-fda-1438961747>.

62. The studies of CETP inhibitors are flawed in the sense that the CETP inhibitors are administered on top of optimum statin therapy; it is likely that the effect of raising HDL is partly masked in the studies by the benefits conferred by lowering LDL.

and reliably, why shouldn't agents be approved so that doctors in the medical marketplace can determine clinical utility in their patients, especially upon review of subgroup analyses and trend identification from pre-approval studies and large post-approval studies?

#### Prostate Cancer

The circumstances surrounding the use of Taxotere (docetaxel) in prostate cancer also shed light on the medical marketplace in action and on what doctors need to see before early adopters use new drugs. This particular drug was originally approved in 1996 for breast cancer.<sup>63</sup> A Phase I/II trial in prostate cancer in 34 patients, published in 1999, demonstrated a 50 percent decline in PSA (prostate specific antigen) and five partial responses (significant reduction in the size of tumor lesions); 8 of 15 patients were able to discontinue narcotic analgesics use for bone pain.<sup>64</sup>

Unfortunately, it was not until two phase III studies of Taxotere *versus* mitoxantrone in hormone refractory patients were conducted that Taxotere was approved for use treating prostate cancer patients on May 19, 2004. A statistically significant survival advantage (18.9 months versus 16.5 months) was demonstrated.<sup>65</sup>

The six-year delay in Taxotere's approval for use on prostate cancer so that improved *survival* could be demonstrated made no sense, given that the drug was approved for use on breast cancer in 1996 and there was strong evidence of its activity on prostate cancer in 1998.<sup>66</sup> Luckily, Taxotere was given a compendium listing by Medicare, so there was a tremendous amount of off-label use of the drug occurring in the medical marketplace before the accumulation of survival outcomes data:

A study on the diffusion of use of Taxotere in medical practice demonstrated that broader use of Docetaxel [Taxotere] preceded

63. Taxotere (Docetaxel), CenterWatch, accessed January 21, 2016, <https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/110/taxotere-docetaxel>.

64. Daniel P. Petrylak et al., "Phase I Trial of Docetaxel with Estramustine in Androgen-Independent Prostate Cancer," *Journal of Clinical Oncology* 17, no. 3 (March 1999): 958–67.

65. "FDA Approval for Docetaxel," NIH National Cancer Institute, last modified March 28, 2014, <http://www.cancer.gov/about-cancer/treatment/drugs/fda-docetaxel>.

66. The American Cancer Society estimates that there will be over 200,000 new cases of prostate cancer in the United States in 2015 alone. See "How Many Men Get Prostate Cancer?," American Cancer Society, January 30, 2015, <http://www.cancer.org/cancer/prostatecancer/overviewguide/prostate-cancer-overview-key-statistics>.

phase III evidence for its efficacy, indicating extensive off-label use.<sup>67</sup>

The off-label use of Taxotere in the medical marketplace was a very good thing, but how many more patients could have benefitted had the FDA approved Taxotere for use when ample evidence of its potential had been accumulated years in advance?

#### Female Health

The FDA's extreme caution is evident even after drugs are approved and have been on the market for years. Take, for example, combination hormonal contraceptives (birth control pills, rings, and patches). These products are so safe that California and Oregon have announced that they will be made available over the counter despite their current FDA prescription drug labeling. That labeling contains very frightening language (called "class labeling") conveying safety concerns, particularly for women who smoke and who are over 35 years of age. However, the condition that contraceptives prevent—that is, pregnancy—also poses risks, often much greater ones. The FDA's labeling does not include fair balance because it fails to report on the risk of similar adverse outcomes from pregnancy. In short, the FDA doesn't conduct proper risk-risk analysis.

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67. Joseph M. Unger et al., "The Diffusion of Docetaxel in Patients with Metastatic Prostate Cancer," *Journal of the National Cancer Institute* 107 (2015): djv412.

## ABOUT THE AUTHORS

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ABOUT THE MERCATUS CENTER AT GEORGE MASON UNIVERSITY

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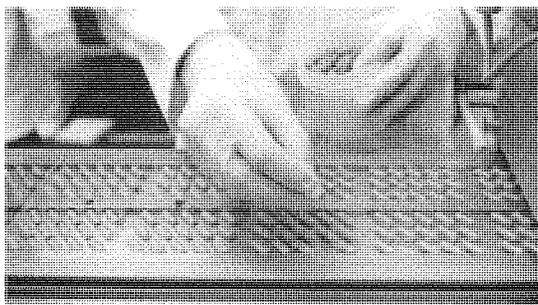
Founded in 1980, the Mercatus Center is located on George Mason University's Arlington and Fairfax campuses.



February 19, 2016, 07:00 am

## FDA must focus on drug safety and effectiveness, not patients' life outcomes

By Joseph Gufo, contributor



As the Senate Committee on Homeland Security and Governmental Affairs meets next week for a hearing on "Connecting Patients to New and Potential Life Saving Treatments," it is important to remember the appropriate role of the Food and Drug Administration (FDA) in promoting the health of Americans. (Full disclosure: I have been called as a witness to testify at this hearing.)

The FDA's mission is to provide doctors in the medical ecosystem with access to *safe and effective* new drugs, biologics, and devices in a prompt, efficient, and timely manner. The medical marketplace, which involves patients, payers and physicians, functions to then identify, and preferentially use, the most appropriate products in individual patients. This is how the law was designed.

Despite incessant pleas from doctors and patients for more safe and effective products that might help when used appropriately, the FDA continues to raise the evidentiary threshold for permitting a new product — recasting pre-market approval as a venue for the practice of evidence-based medicine to determine clinical utility, benefit, and health outcomes, pre-approval. This move is aimed at satisfying FDA critics, but it consumes precious time and resources, and it dissuades drug developers (and would-be developers) from pursuing projects.

The FDA has acknowledged the changes in its standards for product approval. In a March 10, 2015, opinion piece, two high-ranking FDA officials had this to say about the review process: "It is important to remember, however, that innovative therapies only save lives if they work properly. U.S. citizens rely on the FDA to ensure that the drugs they take are effective and that their benefits outweigh their risks. Improving a patient's life or lifespan must be central to the concept of drug innovation."

But the FDA is supposed to assure *safety and effectiveness of drugs, not life outcomes for patients*. A drug's proposed label indicates the effect it is purported to have; safety and effectiveness are to be determined in the context of that labeling. The physician and the patient, acting in the medical marketplace, are to determine whether and when taking the drug will be conducive to improving a patient's life. That we authorize physicians to prescribe drugs off-label is indicative of this division of labor.

Certainly, studies of life outcomes can be invaluable to informed decision-making by physicians and payers. But there are many and varied factors that contribute to disease development, progression and response to therapy. It is far harder to produce good knowledge about life outcomes for patients than it is to produce good knowledge about a drug's safety and effectiveness with respect to specific disease-related parameters.

Moreover, the appropriate place to evaluate life outcomes is in the post-approval setting, by the medical marketplace. Trying to do so pre-approval, before a new drug has settled into practice, is not scientifically prudent. The myriad of real-world factors that may modulate ultimate clinical benefit cannot be known or controlled in pre-approval studies, no matter the size, without informed data that become available only after a safe and effective drug has been in use for a period of time. Thus, the way that FDA currently approaches drug approval can actually mask clinical benefit. If clinical utility is used as the criteria for approval, many drugs that are safe and effective and could help patients will

2/19/2016

FDA must focus on drug safety and effectiveness, not patients' life outcomes | TheHill

never see the light of day.

The other problem with the FDA's current approach is that it is directly contrary to the precision medicine movement. The FDA makes its determinations based on the responses of the average patient in clinical trials. While immediate- and near-term measures of effectiveness (reducing pain and tumor size, and increasing air movement in the lungs, for example) are appropriately evaluated by calculating average patient responses, clinical benefit is not appropriately assessed in this manner. Many patients may truly benefit from a drug; however, the benefit may not be seen in enough patients to pass the average patient hurdle. As long as the drug is safe and effective as per its labeled conditions of use, clinical benefit should be the domain of patients and doctors, not the FDA.

In essence, the FDA, which should be the gatekeeper of safe and effective products that enter the medical armamentarium, has put itself in the position of judging which drugs are most beneficial. The funnel diagram available [here](#), in a piece I co-authored for the Mercatus Center, depicts the roles and responsibilities of medical marketplace constituents in the diffusion of new drugs and devices into practice. The law provides for the FDA to be at the top of the funnel and for the medical marketplace to decide from among the FDA-approved safe and effective products which are the most beneficial; therefore, which are used the most (bottom of the funnel). However, the FDA, in demanding data from drug developers, pre-approval, to determine which drugs are most beneficial, is putting itself at the bottom of the funnel as well.

At no other time in history have we been better equipped to perform real-world, large-scale outcomes and survival studies with regard to medical interventions, such as the use of safe and effective drugs and devices. There is no way that pre-approval studies of drugs and devices, in tightly defined patient populations under scripted medical management protocols, can produce the kind of evidence that is available through real-world data acquisition and the Internet of Things. What's more, in the post-approval, real-world setting, data that will enhance the selection of therapy for an individual patient can be made available in an unprecedented manner, which can truly drive personalized medicine.

The law instructs the FDA to consider new drugs for approval on the basis of the uses submitted by sponsors. Sponsors are responding to needs identified in the medical marketplace. The FDA should not be telling sponsors that their drugs must show improvement in clinical outcomes; rather, the FDA's role is to label drugs as "safe" for uses that the agency finds substantial evidence has been presented. It is then the job of doctors in the medical marketplace to determine the benefits and risks of using new drugs in individual patients, informed by the drug label, their experience with the drug, post-approval studies, and individual patient factors.

As discussed in my recent paper noted above, "[The Proper Role of the FDA in the 21st Century](#)," it is imperative that the FDA get back to focusing on safety and effectiveness as the pre-approval standards. The flow of new innovative therapies that can advance health is dependent upon all players in the medical marketplace performing their roles, starting with the FDA making safe and effective products available. We the public and Congress need to acknowledge that the FDA has a daunting enough responsibility to ensure that new medical products are safe and effective, and avoid the pitfall of also demanding perfect public and private health outcomes from the FDA, which is simply impossible. It is fear on the part of the FDA that has driven it to demand proof of clinical utility and benefit in lieu of safety and effectiveness. The first step is acknowledging that medicine is an art, not a science, and that the FDA is not the lone participant in the medical ecosystem that is responsible for advancing the health of Americans.

*Gufo is the executive director of the Rothman Institute of Innovation and Entrepreneurship at Fairleigh Dickinson University and author of "Innovation Breakdown: How the FDA and Wall Street Cripple Medical Advances" (Post Hill Press). He has more than 25 years of experience in the biopharmaceutical and medical-device industries and is the former CEO of Mela Sciences. Follow him on Twitter @josephgufo.*

**TAGS: Food and Drug Administration, FDA, Drug, pharmaceutical, approval**

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From the Boston Business Journal:

<http://www.bizjournals.com/boston/blog/bioflash/2016/02/meet-fda-critic-joseph-gulfo-the-antonin-scalia-of.html>

## Meet FDA critic Joseph Gulfo, the Antonin Scalia of the life sciences

Feb 17, 2016, 2:28pm EST

If scientists still can't determine whether coffee, red wine and aspirin are ultimately good for us, how can the U.S. Food and Drug Administration say whether any of the drugs it reviews will help patients in the long run?



Joseph Gulfo, MD, is author of the book, "Innovation Breakdown," and an outspoken critic of the FDA.

That's one argument made by Joseph Gulfo, the main author of a paper questioning the federal agency in charge of approving new drugs. His point of contention: There's been a kind of mission creep at the FDA over the past two decades beyond its original role of making sure drugs are safe and effective.

Gulfo, the former CEO of **MELA Sciences**, argues the FDA too often interprets the meaning of "effective" as beneficial for the average patient over the long run, as opposed to simply doing what the drugmaker claims. He argues that evidence of long-term benefit only

comes after widespread use, not from clinical trials. It's a distinction, he says, that keeps too many potentially beneficial drugs off the market.

There's a long list of drugs that have been rejected — despite patient objections — because the FDA said they didn't prove effectiveness. For example, Lemtrada, the multiple sclerosis drug by **Sanofi** Genzyme (NYSE: SNY), was denied approval in late 2013, only to be approved about 10 months later with no new trial information. And a kidney cancer drug by Aveo Oncology (Nasdaq: AVEO) was rejected in 2013 despite showing more efficacy than existing drugs in slowing the disease's growth. And **Sarepta Therapeutics** (Nasdaq: SRPT) is now facing a harsh review from the agency over its potential drug for Duchenne muscular dystrophy despite hundreds of patients willing to take the risk that the drug may not work as well as it has in a 12-patient trial.

Gulfo co-authored his FDA critique with Jason Briggeman and Ethan Roberts. All three are affiliated with the **Mercatus Center at George Mason University**.

In an interview last week, I asked Gulfo whether the FDA should lower its standards for proven effectiveness. His response: "I'll never say I want lower standards. I want effective drugs."

"A lot of times I tell people, 'Don't blow up the FDA. We need them to do what they do,'" he continued. "But they have to do what they were put into business to do — not more. ... they've now ordained themselves as the arbiters of clinical utility. And that's not in the law."

Gulfo also said the FDA's study mandates often "mask benefit," saying, "I really believe benefit can only be determined when (a drug)

is on the market.”

Another problem with the current system, Gulfo says, is a focus on the “average” patient. Plenty of people get a benefit from drugs that don’t prove they help the average patient, he said. Gulfo argues that the FDA is usurping the job of patients and doctors in saying what drugs a patient should try.

You could describe Gulfo as an “originalist” of the law that created the FDA in the same way Justice Antonin Scalia was an originalist in interpreting the Constitution. The fact that the FDA requires increasingly large trials for drugs for diseases that affect millions of patients — like diabetes, Alzheimer’s or obesity — means fewer companies want to attempt to develop those drugs. Instead, drugs for smaller and smaller subsections of cancer patients (oncology drugs make up more than a third of all drugs being developed in the Boston area) are becoming more and more popular.

“The beauty of today’s medical marketplace is, now you have the payers saying, why do we pay more for this drug? Because they’ve proved survival versus just raising the HDL,” he said. “So now the companies, post-approval, would be competing that way. But (the FDA) wouldn’t be the gatekeeper to getting it on the market based on safety and effectiveness.”

**Don Seiffert**  
BioFlash Editor  
*Boston Business Journal*



## COMMENTARY: Return FDA to its proper role

JOSEPH V. GULFO 12:06 a.m. EST February 7, 2016



(Photo: Getty Images/Stockphoto)

When I received my driver's license my father said to me, "Congratulations, son — now you really learn how to drive." Driver education courses only ensured that I knew how to operate the vehicle safely and appropriately to get from point A to point B. I had eight fender-benders in my first decade behind the wheel, and I haven't had one accident for the last decade. My father was right. I learned how to operate a car very well — after I had my license for a while.

If the Department of Motor Vehicles approved driver's licenses like the Food and Drug Administration approved new drugs and devices, driving tests would go on for months and cost a tremendous amount of money. I would have been tested on driving to points B to Z and countless other scenarios. If the DMV started doing this, Americans would surely say the DMV had lost its way.

Well, the FDA has lost its way and as President Barack Obama's nominee for commissioner of the FDA — Dr. Robert Califf — moves through the nomination process, the agency's proper role in the medical ecosystem should be scrutinized.

Congress intended the FDA to license drugs for approval, and then let the medical ecosystem prescribe the drugs in real world circumstances — guided by FDA's licensing instructions, of course — to arrive at the most appropriate uses for individual patients.

The FDA's role is clearly defined in the Federal Food Drug and Cosmetic Act: "to promote health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely fashion." This includes "ensuring that ...drugs are safe and effective ... (and) there is reasonable assurance of the safety and effectiveness of devices."

The two most important parts of the FDA's mission are to judge new products on the basis of safety and effectiveness, and to do so quickly. The median time of approval of novel drugs is 304 days. Considering that 10 months is the target review period for all new drug applications, the FDA is late half the time.

The reason that the FDA is incorrigibly late, and the reason that many companies don't even try to develop drugs for many diseases that affect millions of Americans, is because the FDA has lost sight of its proper role. The FDA is supposed to be the gatekeeper of medicines that become available to the medical marketplace of physicians, patients, hospitals, payers, and medical community. Congress intended for the FDA to approve only those drugs that could be labeled for safe use and demonstrated the clinical effects claimed by drug developers.

Instead, the FDA is imposing its own standard for what constitutes a good drug. Rather than licensing products for use by doctors, the FDA is trying to dictate the practice of medicine. Rather than entering products that are safe and effective into the medical marketplace for the physicians to use and determine which are best for individual patients, the FDA is endeavoring to tell doctors and patients, upon approval, which drugs are best and how they are to be used. This is not how the system was set-up, nor is it possible.

In my recent research paper for the Mercatus Center on "On the Proper Role of the FDA," we make the case for the FDA to return to its proper role: arbiters of safety and effectiveness, period. The FDA must be stopped from insisting on long-term outcomes that require humongous clinical trials, which are exceedingly difficult, time consuming, and costly to demonstrate, especially before approval. If the FDA were returned to its proper role, new drugs would be approved quickly, true personalized medicine would be facilitated, and both drug development costs and prices would be reduced.

You and your doctor need to decide which therapies are best for you and which are most beneficial, not the FDA. The only way that can happen is if the agency assumes its proper role in the medical ecosystem.

*Joseph V. Gulfo is a visiting scholar with the Mercatus Center at George Mason University and executive director of the Rothman Institute of Innovation and Entrepreneurship at Fairleigh Dickinson University. He wrote this for InsideSources.com*

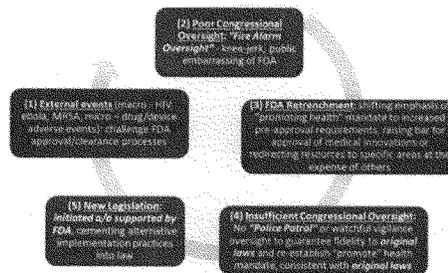
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December 22, 2015, 07:00 am

## Appropriate oversight is needed to change FDA behaviors, not more laws

By Joseph Gulfo, contributor



Joseph Gulfo

Oversight of the executive branch is a main duty of Congress that flows from the many and varied express powers of Congress in the Constitution, including appropriating funds, enacting laws, and impeaching and removing civil officers. However, as former House Speaker Tip O'Neill (D-Mass.) once exclaimed, "Members like to create and legislate, but we have shied from both word and deed of oversight."

Not only has Congress shied away from oversight, it has been used more as a "fire alarm" than as "police patrol," in the words of Mathew McCubbins and Thomas Schwartz. Congress has been deficient in "police patrol" oversight — that is, constant watchful vigilance to ensure that Food and Drug Administration (FDA) laws are enacted dutifully. But it has been quite aggressive in exercising "fire alarm" oversight that comes from hearings in response to events, for example, adverse reactions with medical products.

There have been many high-profile hearings on drugs including antidepressants Vioxx, Rezulin and Avandia. In all of these, the FDA is basically accused of inappropriately approving products that are unsafe. Of course, the issues are not so cut and dry. This kind of knee-jerk oversight, which provide great theater and incentives of their own, greatly damages the cause of medical innovation: As former FDA Commissioner Alexander Schmidt said in 1974: "In all of FDA's history, I am unable to find a single instance where a congressional committee investigated the failure of FDA to approve a new drug. But the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them. The message to FDA staff could not be clearer."

The case of Avandia is particularly disconcerting. Even when the FDA does the right thing — for example, approving an excellent drug that helps millions of patients — it is castigated and publicly humiliated. A New England Journal of Medicine publication of a meta-analysis of 42 small clinical trials revealed an increased likelihood of significant cardiovascular toxicity in patients taking the drug, so the FDA restricted the drug's use in response to pointed criticism at a congressional hearing. Here is what the FDA had to endure at a Senate hearing on the matter: "This report poses several troubling questions for this subcommittee. Most obviously, if Avandia is unsafe, how did it ever get on the market in the first place? For that matter, why is it still on the market, right now? And what does the case of Avandia tell us about the FDA's current ability to conduct its drug safety responsibilities?"

Subsequently, the FDA removed the restrictions from the label when the drug was shown not to cause increased cardiovascular problems, following a re-analysis of a very large prospective study, rendering the meta-analysis flawed. But the damage was done: The FDA changed the regulations to require larger and larger clinical trials and disease outcome endpoints for products that are intended for large chronic diseases, like diabetes. Knee-jerk oversight triggered by a flawed analysis had severe unintended consequence.

Sadly, Dr. Robert Califf, nominated to be the new FDA commissioner, was in full support of erroneously demanding larger and larger trials in the midst of the Avandia saga. As Matt Herper writes, "In 2008, after Steven Nissen from the Cleveland Clinic had openly criticized Avandia, the GlaxoSmithKline diabetes drug, he proposed a new standard for studying diabetes medicines that would insist they be tested in clinical

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trials involving thousands of patients to see if they had any effect on heart attack rates. When Nissen mentioned the idea at an open public meeting, Califf was fast to back it." And, these sorts of unnecessarily large, expensive and time-consuming studies have remained as the new standard; they were not walked back when the case of Avandia was shown to be a false alarm. Just last week, the FDA noted the following: "continued monitoring" of Avandia, Avandamet and Avandaryl had turned up "no new pertinent safety information" about the drug. So, the agency lifted the final layer of safety measures that it erroneously imposed. But sales of the drug were crushed; as reported by FiercePharma, "The safety questions drove Avandia revenues down from a peak of \$3 billion before the controversy to \$183 million in 2011, just before generics hit the market."

At the Senate HELP (Health, Education, Labor and Pensions) committee's confirmation hearing for Califf on Nov. 15, 2015, he doubled down:

**Sen. Elizabeth Warren (D-Mass.):** Do you agree with arguments to lower standards for FDA approval of drugs and devices?

**Califf:** I have never been a proponent of lowering standards for anything. ... I have been in favor of raising standards. In no case would I argue to lower the standard. I think I have been staunch in that regard.

It is understandable that the FDA would retrench when it is attacked. The agency then protects itself from future attack by: (1) raising the bar for product approvals by moving away from the statutory criteria of safety and effectiveness and demanding proof of clinical utility, clinical outcomes and survival; (2) demanding larger and larger trials that cost tremendous amounts of time and money; (3) shifting its emphasis to pre-approval requirements versus a balance of pre-approval data and post-market controls and surveillance; and (4) preferentially approving products for niche diseases rather than those that affect millions of Americans.

After the FDA retrenches in response to criticism and then issues new rules and guidance documents with alternative interpretations and implementations of the laws, Congress does not perform the appropriate police patrol oversight to re-direct the FDA back to its mandate, forcing the FDA to honor the letter and spirit of the laws that are passed. No, it does something worse: It actually passes more laws, for example, as part of each PDUFA (Prescription Drug User Fee Act) and MDUFA (Medical Device User Fee Act) reauthorization that takes place every five years, and in other legislation, like 21st Century Cures. This legislation, drafted in consultation with the FDA, then codifies the FDA's new positions taken in response to inappropriate fire alarm oversight.

The vicious cycle starts over again the next time an unfortunate adverse events occur with drugs and devices that are on the market, which will invariably come to be. And this is how regulation kills medical innovation and hurts patients.

In our latest **M3 Alert**, we examine the effects of this vicious cycle and offer solutions to reducing regulatory burden so that medical innovations that can truly promote the health of tens of millions of Americans can flourish, keeping pace with the amazing scientific advances that are being made. Unfortunately, better oversight, alone, cannot accomplish this — we need some laws to undo the damage that many turns of the vicious cycle has wreaked. For example, the FDA must be made to return to safety and effectiveness (as measured by activity in modulating disease signs and symptoms, surrogate endpoints and biomarkers) and allow doctors and patients to determine clinical benefit. Of course, better oversight will require yearly reports of FDA performance with respect to product reviews and approvals in comprehensible terms, like calendar days and averages, as well as reports from the FDA ombudsman regarding issues that arise between the FDA and drug developers. And Congress should resist the temptation to publicly flog the FDA at fire-alarm hearings when unwanted unfortunate toxicities arise, which they invariably will, this is the nature of medical and scientific progress.

As Speaker Newt Gingrich said, "This is the city [Washington] which spends almost all of its energy trying to make the right decisions and almost none of its energy focusing on how to improve implementing the right decisions. And without implementation, the best ideas in the world simply don't occur."

We have excellent ideas that are not reaching patients. We need congress to start performing oversight appropriately to make the FDA's first priority is promoting health, not protecting itself from attack.

*Gulfo is the executive director of the Rothman Institute of Innovation and Entrepreneurship at Fairleigh Dickinson University and author of "Innovation Breakdown: How the FDA and Wall Street Cripple Medical Advances" (Post Hill Press). He has more than 25 years of experience in the biopharmaceutical and medical-device industries and is the former CEO of Mela Sciences. Follow him on Twitter @josephgulfo.*

**TAGS:** **Vioxx, Rezulin, Avandia, Food and Drug Administration, FDA, Robert Califf, Drug, pharmaceuticals**

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# MI<sup>3</sup> Alert



## Medical Innovation Impact Index

11/30/15 - Report #7

### General Description of Issue

Oversight of the Executive Branch is a main duty of Congress that is an implied, rather than an enumerated power - it was seen in the Federalist Papers (48, 49, and 51) as an inherent power of representative assemblies, which enacted public law. Oversight also derives from the many, varied express powers of the Congress in the Constitution - it is implied in the legislature's authority, among other powers and duties, to appropriate funds, enact laws, and impeach and remove from office the President, Vice President, and other civil officers. Congress could not reasonably or responsibly exercise these powers without knowing what the executive was doing; how programs were being administered, by whom, and at what cost; and whether officials were obeying the law and complying with legislative intent. However, as former House Speaker Tip O'Neill once exclaimed, "Members like to create and legislate, but we have shied from both word and deed of oversight." As former Speaker Newt Gingrich said, "This is the city [Washington, DC] which spends almost all of its energy trying to make the right decisions and almost none of its energy focusing on how to improve implementing the right decisions. And without implementation, the best ideas in the world simply don't occur." Congress certainly expends great effort passing laws that have the goal of enhancing medical innovation, for example PDUFA (Prescription Drug User Fee Act) and MDUFA (Medical Device User Fee Act) reauthorization. The question is whether better Congressional oversight would result in a greater number of more profound medical innovations reaching patients more quickly.

### Purports To Do

Congressional oversight of the FDA could be a very powerful force to ensure that the letters and spirits of FDA laws are enacted in a manner that truly enhances medical innovation. Congress has at its disposal many opportunities to conduct this oversight, including: (continued on pg. 2)...

Success in Achieving Objective: +3

### Unintended Consequences

#### Inaccurate Performance Reports:

As mentioned above, the FDA is required to make reports to Congress on review time performance under PDUFA [Federal Food, Drug, & Cosmetic Act (FD&C)] (continued on pg. 3)...

Emergence of Unintended Consequences: -3

### Potential Positive Impact on Innovation

The potential positive impact on medical innovation that would follow effective Congressional oversight is enormous. Oversight on just a handful of policies could have a huge impact: (continued on pg. 2)...

Positive Impact on Innovation: +3

### Potential Negative Impact on Innovation

Congress has been deficient in "police patrol" oversight, that is, constant watchful vigilance to ensure that FDA laws are enacted dutifully. But, it has been quite aggressive in exercising "fire alarm" oversight that comes from hearings in response to events, for example adverse (continued on pg. 6)...

Negative Impact on Innovation: -4



If poor oversight were eliminated and proper oversight were implemented, a substantial positive impact on medical innovation is likely

### Recommendations

As Walter Oleszek of the Congressional Research Service states in Congressional Oversight: An Overview:

*Congressional oversight ideally involves the continuous review by the House and Senate, especially through their committee structures, of how effectively and efficiently the executive branch is carrying out legislative mandates. The "continuous watchfulness" precept—an obligation statutorily assigned to the standing committees by the Legislative Reorganization Act of 1946—implied that Congress would henceforth participate actively in administrative decision-making, in line (continued on pg. 10)...*

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## Purports To Do (continued from pg. 1)

1. **Hearings and investigations** - hearings, in particular, focus generally on the efficiency and effectiveness of federal agencies and programs. They are also conducted in response to issues that arise as a perceived consequence of agency action or inaction.
2. **Authorizing process** - the regular reauthorization process of laws focuses great attention to spending and whether the spending authorized by Congress results in the desired effects. For example, PDUFA and MDUFA require reauthorization every 5 years.
3. **Appropriations** - as James Madison stated, "The power over the purse may, in fact, be regarded as the most complete and effectual weapon with which any constitution can arm the immediate representatives of the people, for obtaining a redress of every grievance, and for carrying into effect every just and salutary measure."
4. **Inspectors General** - conduct investigations and audits of agencies to improve efficiency, end waste and fraud, discourage mismanagement, and strengthen the effectiveness and economy of agency operations.
5. **Government Accountability Office** - the office submits reports to Congress annually, describing ways to root out waste and mismanagement in executive branch programs and to promote program performance.
6. **Reporting Requirements** - numerous laws require executive agencies to submit reports periodically, and as required by specific events or certain conditions. For example, the FDA is required to provide Congress with yearly reports of review performance under PDUFA and MDUFA.
7. **Senate Confirmation Process** - through public questioning and review of credentials of individuals nominated by the President to lead agencies, Congress can bring to light issues in the implementation of the law by the agencies.
8. **Casework** - activities by members pursuant to issues raised by individual constituents.
9. **Informal** - member and staff contacts with agency personnel.

To the extent that many portions of FDA laws are designed to promote health through medical innovation, Congress has the mandate and multiple means at its disposal to conduct appropriate and effective oversight to ensure that the provisions and programs are being enacted as intended and achieving the desired goals.

## Potential Positive Impact on Innovation (continued from pg. 1)

1. If **PDUFA and MDUFA review time goals were enforced**, drug approval times would be cut in half and new devices would reach patients much more quickly:
  - a. In 2013, the FDA's **median** approval time for drugs was 304 days – this means that review times exceeds the PDUFA goal of 10 months for 50% of applications.
  - b. In the first half of 2015, the average review time for a Pre-Market Approval Application (PMA) was 17.1 months (MDUFA goal 180 days) and Humanitarian Device Exemption (HDE) took 16.7 months (MDUFA goal 75 days). In 2014, the average review time for a 510(k) was 6 months (MDUFA goal 90 days), and a company submitting a 510(k) had just a 22% chance of getting it cleared within the 3 month target, and a 61% chance of getting it cleared within 6 months.
  - c. Moreover, many programs that were implemented to expedite the review and approval of certain classes of novel products (rare and diseases for which there are no other therapies or significant unmet medical needs) would not be needed if the FDA met the target review times in PDUFA and MDUFA.
2. If Congress conducted proper oversight of the FDA, the **safety and effectiveness standards** for drug and device approval, as well as the reasonable assurance of safety and effectiveness standard and least burdensome approach for medical devices would be appropriately followed. The FDA has moved away from approving drugs and biologics that are - as stated in the regulations - "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling" on the basis of clinical trials that demonstrate activity in important disease parameters (clinical activity in ameliorating disease signs and symptoms, surrogate endpoints, and biomarker responses) in favor of endpoints like Major Adverse Cardiac Events (MACE) and survival. Moreover, in practice, the FDA has replaced the safety and effectiveness standard with "clinical benefit," going so far as to tell sponsors which indications for use the FDA deems appropriate as opposed to reviewing clinical studies and data for the claims that sponsors endeavor to develop. This is not how the laws are written or intended. The standards for FDA approval have become more onerous resulting in longer and larger clinical trials, which prevent and delay important medicines and devices from reaching patients. (continued on pg. 3)...

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## Potential Positive Impact on Innovation (continued from pg. 2)

The law is very clear regarding the evidentiary standard for drug approval – “the term “substantial evidence” means “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof” (FD&C 505 – 21USC 355(d)).” Substantial evidence does not refer to clinical benefit or survival or other disease outcomes, rather to conducting adequate studies from which to conclude that the purported effects are real and reliable.

- a. Indeed, if Congress exercised proper oversight to enforce review times and standards of safety and effectiveness, it would not have been necessary for them to pass more laws ushering-in the rapidly-expanding series of regulatory incentives for niche carve-out areas of “high unmet medical need” with such programs as Fast Track, Priority Review, Breakthrough Therapy Designation (BTD), and Qualified Infectious Disease Products (QIDP), pediatric exclusivity, and Rare Pediatric and Tropical Diseases Priority Review vouchers.
3. If Congress conducted proper oversight, issues that arise in the review of new products would be properly adjudicated. Sponsors have the ability to challenge FDA reviewers through the **FDA Ombudsman**. However, the Ombudsman does not report to the commissioner, rather, the Center for Drugs Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH) each possess a separate ombudsman who reports to the center directors. If the ombudsmen reported to the commissioner and made regular reports to Congress as part of oversight, the FDA would be less likely to change approval standards, ignore prior agreements with companies on the clinical studies required to demonstrate safety and effectiveness, and would be less likely to request information during reviews that extends the review time limit, all of which would increase the certainty, consistency, and timeliness of new product reviews, which are the intended effects of the laws.
4. If Congress conducted proper oversight of the **Advisory Committee process** for new drugs, biologics, and devices, experts in the medical fields of study would be required to review new products. However, often, the FDA does not include several or any physicians who treat the disease under review. “For the purpose of providing expert scientific advice and recommendations to the Secretary (secretary of HHS – Health and Human Services) regarding a clinical investigation of a drug or the approval for marketing of a drug under section FD&C 505 or section 351 of the Public Health Service Act, the Secretary shall establish panels of experts or use panels of experts...” The statute goes on to say, “...members who are qualified by training and experience to evaluate the safety and effectiveness of the drugs to be referred to the panel and who, to the extent feasible, possess skill and experience in the development, manufacture, or utilization of such drugs,” and “...two or more members who are specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated.” If experts were included on panels routinely, the importance of findings from clinical studies would be better appreciated, labeling recommendations would be more clinically relevant, and more drugs and devices would reach patients sooner.

## Unintended Consequences (continued from pg. 1)

Section 736B. – 21 USC 379h-2) and MDUFA (FD&C Section 738A. – 21 USC 379j-1). However, the reports are very difficult to interpret and have little grounding in the real world metrics that Congress requested. As former FDA reviewer Henry Miller pointed out:

*I was struck by the dissonance between a statement by (FDA Commissioner) Dr. Hamburg several years ago and the FDA's performance where it counts—getting new medicines to patients. She bragged that “[p]reliminary results of reviews completed during FY 2010 indicate that FDA has the potential to meet or exceed almost all (11 of 12) FY 2010 review performance goals.” But 2010 was the worst year for drug approvals in a quarter century. This kind of disconnect is typical of not only FDA but of other federal agencies: They create easily-met performance milestones that may have little relationship to the agency's actual mission. Invoking the old medical cliché, the operation was a success but the patient died.*

Take for example the way review time is counted. The regulations call for non-priority NDA's (New Drug Approvals) to be conducted within 10 months. However, in reports to Congress, the FDA counts review time in “review days” not calendar days, whereby the FDA stops and starts the review clock at its discretion, typically requesting that sponsors answer questions that emerge in the review of new products by submitting PMA, NDA, and BLA amendments, which then extend the review period. This has the effect of increasing the percent of applications reviewed within target dates defined in PDUFA and (continued on pg. 4)...

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## Unintended Consequences (continued from pg. 3)

MDUFA and reported by the FDA to Congress, making performance appear to be within (or close to) review period goals, even when, on a calendar basis, review times far exceed the statutory targets. Also note that the FDA reports performance in median review times; average review times are calculated by outside analysts.

The laws that Congress passed do not say that reviews should be conducted within a certain number of review days, rather they state periods of time (months for drugs and biologics and days - not "review days" - for devices). Moreover, the FDA reports its performance in median review days, not average review days. Apparently, Congress did request that the FDA report the average number of days, but the average review time has not been adopted by the FDA as the primary measure. And, the FDA does not report average review time performance on a rolling ongoing basis:

*As stated in the 2014 MDUFA Performance Report: FDA committed to report the average total time to final decision once decisions were made for 99 percent of the PMA cohort and 95 percent of the 510(k) cohort. FDA has made decisions on 98 percent of the FY 2013 510(k) cohort and the average total time to decision is 126 total days. Currently, FDA has made decisions on 73 percent of the FY 2013 PMA cohort, 16 percent of the FY 2014 PMA cohort, and 58 percent of the FY 2014 510(k) cohort and cannot yet report average review times. Once the required percentage of each cohort has received a decision, FDA will report the average time to final decision in future reports.*

Even when Congress performs some degree of oversight - demanding performance reports, for example - it does not insist on receiving a clear accounting of performance based on discrete measures that it desires to review. This has significant unintended consequences - poor oversight gives the appearance that the FDA is performing well in its mission to promote health, when it is not. Absence of transparent information is one thing; accepting misleading information is quite another. And, Americans are not served well by either. As Walter J. Oleszek of the Congressional Research Service explains:

*Woodrow Wilson, in his 1885 classic titled Congressional Government, declared that Congress informing function "should be preferred even to its legislative [lawmaking] function." He explained: Unless Congress have and use every means of acquainting itself with the acts and dispositions of the administrative agents of government, the country must be helpless to learn how it is being served; and unless Congress both scrutinize these things and sift them by every form of discussion, the country must remain in embarrassing, crippling ignorance of the very affairs which it is most important it should understand and direct.*

### Redundant and Conflicting Laws:

Because the first inclination of lawmakers is to pass laws rather than to perform oversight, many new laws are redundant with laws that have been passed previously, and conflict with prior laws:

1. Consider FDASIA (Food and Drug Administration Safety and Innovation Act) that reauthorized PDUFA in 2012. One of the key provisions of this law was Breakthrough Therapy Designation (BTD), a program to expedite the review and approval of a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness. Looking at the Guidance Document on Expedited Programs for Serious Conditions - Drugs and Biologics, one is hard pressed to see how BTD added to the other programs that were already in the law to accomplish this, including Fast Track [included in the 1997 PDUFA reauthorization called the Food and Drug Administration Modernization Act (FDAMA) of 1997], Priority Review (included in the 1992 Prescription Drug User Fee Act), and Accelerated Approval (FDASIA 2012). Moreover, many products have been given several of these designations, and Orphan Drug Designation, as well (see Esbriet - perfenidone, Opdivo - nivolumab, and Xalkori - ceritinib); in fact, 56% of novel products approved in 2012 qualified for multiple expedited programs, thereby demonstrating the redundancy and lack of need of BTD. These programs are very redundant, both in substance and spirit. If Congress knew the contents of the law by performing proper oversight, these laws would not have been passed. Deficiencies in the implementation of Priority Review, for example, could easily have been addressed in oversight, rather than in two major laws that ushered-in Fast Track and Accelerated Approval. And, if the law needed to be tweaked subsequent to the acknowledgement of deficiencies in the original statute that came to light during actual implementation, subtle amendments to Priority Review could have sufficed. (continued on pg. 5)...

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Unintended Consequences (continued from pg. 4)

Comparison of FDA's Expedited Programs for Serious Conditions

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review
Nature of program	Designation	Designation	Approval Pathway	Designation
Reference	<ul style="list-style-type: none"> <li>Section 506(b) of the FD&amp;C Act, as added by section 112 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and amended by section 901 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)</li> </ul>	<ul style="list-style-type: none"> <li>Section 506(a) of the FD&amp;C Act, as added by section 902 of FDASIA</li> </ul>	<ul style="list-style-type: none"> <li>21 CFR part 314, subpart H</li> <li>21 CFR part 601, subpart E</li> <li>Section 506(c) of the FD&amp;C Act, as amended by section 901 of FDASIA</li> </ul>	<ul style="list-style-type: none"> <li>Prescription Drug User Fee Act of 1992</li> </ul>
Qualifying criteria	<ul style="list-style-type: none"> <li>A drug that is intended to treat a <u>serious condition</u> AND nonclinical or clinical data demonstrate the <u>potential to address unmet medical need</u> OR</li> <li>A drug that has been designated as a qualified infectious disease product<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>A drug that is intended to treat a <u>serious condition</u> AND preliminary clinical evidence indicates that the drug <u>may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies</u></li> </ul>	<ul style="list-style-type: none"> <li>A drug that treats a <u>serious condition</u> AND generally provides a <u>meaningful</u> advantage over available therapies AND demonstrates an effect on a <u>surrogate endpoint</u> that is reasonably likely to predict clinical benefit or on a <u>clinical endpoint</u> that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)</li> </ul>	<ul style="list-style-type: none"> <li>An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness OR</li> <li>Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A<sup>3</sup> OR</li> <li>An application for a drug that has been designated as a qualified infectious disease product<sup>3</sup> OR</li> <li>Any application or supplement for a drug submitted with a priority review voucher<sup>3</sup></li> </ul>

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## Potential Negative Impact on Innovation (continued from pg. 1)

reactions with medical products. Recently, calls for Congressional hearings on surgical meshes, intrauterine devices for birth control, and endoscopic equipment that spread antibiotic resistant infection have been made. There have been many high profile hearings on drugs, including antidepressants, Vioxx, Rezulin, and Avandia. In all of these, the FDA is basically accused of inappropriately approving products that are unsafe. Of course, the issues are not so cut and dry. However, this kind of oversight greatly damages the cause of medical innovation:

*As early as 1974, FDA Commissioner Alexander M. Schmidt said: "In all of FDA's history, I am unable to find a single instance where a congressional committee investigated the failure of FDA to approve a new drug. But the number of times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them. The message to FDA staff could not be clearer." In other words, no problem as long as the victims are invisible.*

Faced with Congressional oversight that seeks to blame the FDA when toxicities emerge from the use of new products that have been approved, the FDA does three things: (1) it retrenches and shifts its emphasis to a significantly disproportionate reliance on pre-approval requirements, as opposed to postmarket controls, thereby adopting a "protect health" posture at the expense of its "promote health" mandate, as defined in the law; (2) it re-states statutorily-defined approval standards for safety and effectiveness (based on substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling submitted for review by sponsors) to unequivocal clinical utility and clinical benefit (as defined by the FDA, not sponsors), as well as to survival and disease outcomes; and (3) it seeks to limit the populations for which new drugs are approved to treat, hence, the unprecedented rise in orphan drug designations - two hundred ninety-one in 2014 - and approvals for niche specialty claims in recent times. These three actions reduce the likelihood that the FDA will be ridiculed in the future for toxicities that may occur with the use of approved drugs. But, they severely hinder the development of new products that may be of great help to patients.

The case of Avandia, a diabetes medication, is particularly illustrative: (1) a New England Journal of Medicine publication of a pooled study meta-analysis revealed an increased likelihood of significant cardiovascular toxicity in patients taking the drug; (2) the FDA restricted the drug's use in response to pointed criticism at a Congressional hearing; and (3) the FDA removed the restrictions from the label when the drug was later shown not to cause increased cardiovascular problems, following a re-analysis of a very large study. But the damage was done - the FDA changed the regulations to require larger and larger clinical trials and disease outcome endpoints for products that are intended for large chronic diseases, like diabetes. Knee-jerk oversight triggered by a flawed analysis had severe unintended consequences.

*A study led by Dr. Steven Nissen of the Cleveland Clinic linked Avandia to a 43% increased risk of having a heart attack and a 64% increased risk of death due to heart disease. The findings, based on data pooled from 42 small clinical trials, were published in the prestigious New England Journal of Medicine.*

*Those results prompted some experts to question how well the FDA was monitoring the safety of prescription drugs. Just a few years earlier, the federal agency withdrew its approval of the painkiller Vioxx after evidence emerged that it doubled the risk of heart attacks and strokes. When the critique of Avandia emerged, three major congressional committees announced their intention to investigate.*

*The FDA responded by adding warning labels to Avandia.*

*A new analysis this year by an FDA advisory panel suggested the initial concerns about Avandia were overblown. Members of the panel pointed to design flaws in Nissen's study and said their evaluation found no evidence that the drug made patients more vulnerable to heart attacks or other heart problems.*

*The initial "signal of increased risk of heart attacks" reported by Nissen in 2007 has not been confirmed, the FDA said in the statement.*

*As a result, the FDA will no longer require doctors to limit Avandia prescriptions to certain patients. Its new label will likely state that anyone with Type 2 diabetes can use the drug in combination with diet and exercise to control their blood sugar, the agency said.*

Attacks on the FDA at Congressional hearings due to the Avandia meta-analysis data, that were shown to be erroneous later, were vicious:

*The report, by Sens Max Baucus (D-MT) and Charles Grassley (R-IA), concluded that there are "serious health risks associated with Avandia." It also criticized the structure of the FDA, particularly the fact that those who make decisions about drug approvals are the same experts who must later oversee drug safety. (continued on pg. 7)...*

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## Potential Negative Impact on Innovation (continued from pg. 6)

*Introducing the Congressional hearing, subcommittee chair Rep Rosa DeLauro (D-CT) said: "This report poses several troubling questions for this subcommittee. Most obviously, if Avandia is unsafe, how did it ever get on the market in the first place? For that matter, why is it still on the market, right now? And what does the case of Avandia tell us about the FDA's current ability to conduct its drug safety responsibilities?"*

What does the FDA do when it is attacked in this way – as stated above, it runs for cover and ratchets-up the pre-approval requirements for drugs that are used chronically in large numbers of patients and preferentially approves drugs for niche diseases and conditions. Of great concern is that the President's nominee for FDA Commissioner, Dr. Robert Califf, is a fervent supporter of onerous approval requirements, which stifle medical innovation:

*Califf's industry ties run deep. He worked closely with drug companies in the best possible way: convincing them to do large, expensive, and, for Duke, profitable clinical trials that helped prove the effectiveness of major medicines like Sanofi's Plavix, Merck's Vytorin, and Johnson & Johnson JNJ Xarelto. But he has not been a pushover, ever, and his goal has always seemed to be to make sure that doctors and patients have the best evidence possible for deciding what drugs to give to patients. He has not always been easy on industry.*

*In 2008, after Steven Nissen from the Cleveland Clinic had openly criticized Avandia, the GlaxoSmithKline diabetes drug, he proposed a new standard for studying diabetes medicines that would insist they be tested in clinical trials involving thousands of patients to see if they had any effect on heart attack rates. When Nissen mentioned the idea at an open public meeting, Califf was fast to back it.*

*"I can't imagine a situation, given what we know now, other than a screening mechanism followed by some sort of trial for the net risk and benefit versus risk," Califf said at the time.*

*Industry has hated these trials, arguing that they are preventing new diabetes drugs from being developed.*

It can be fully expected that the FDA will continue to move away from the safety and effectiveness standard and demand outcomes and survival data routinely with the new leadership and in response to other unfortunate medical issues that will invariably happen with new marketed drugs as more and more experience is obtained with their use. Dr. Califf was asked this direct question at the Senate HELP (Health Education Labor and Pensions) Committee hearings on his nomination as new FDA Commissioner on November 19, 2015:

*In one pointed exchange, Warren asked Califf about the propriety of clearing therapies at such a rapid rate, once again referencing Califf's ties to the industry. "Your relationships also raise concerns about your motivations," said Warren. "Do you agree with arguments to lower standards for FDA approval of drugs and devices?"*

*"I have never been a proponent of lowering standards for anything," Califf shot back. "I have been in favor of raising standards. In no case would I argue to lower the standard. I think I have been staunch in that regard."*

When the FDA, understandably does retrench and tries to protect itself by making the drug approval hurdles higher in response to public ridicule and accusations of poor job performance hurled at them at Congressional hearings, Congress does not do its job. It does not perform the proper oversight to re-instruct the FDA that its mission is to promote health as defined in the statute ("to promote health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely fashion"). Through oversight, Congress doesn't re-direct the FDA to uphold safety and effectiveness as the standards for approval, and reinforce least burdensome approach (for devices). And, Congress actually aids the FDA in preferring to approve drugs for niche diseases at the expense of diseases that affect large populations of patients by passing laws like FDASIA (Breakthrough Therapy Designation) and 21st Century Cures (Priority Review for Breakthrough Devices and many other provisions), which largely focus on orphan conditions, those affecting less than 200,000 patients per year.

And so, the vicious cycle: (1) external events, such as the emergence of public health crises (ebola, HIV, methicillin-resistant staphylococcal infections) and adverse events of approved products call into question the adequacy of FDA's approval policies; (2) poor Congressional oversight (publicly humiliating the FDA when products are associated with undesired events); (3) FDA retrenchment in the form of disproportionate focus on pre-approval requirements as opposed to post-approval vigilance, and redirecting efforts to specific areas at the expense of others; (4) lack of Congressional oversight to force the FDA to comport itself in accordance with original laws when the FDA understandably shies away from its directives to promote health, and (5) passing of unnecessary and contradictory laws (initiated a/o supported by the FDA) that cement the alternative approach the FDA has taken, which conflicts with Congress' original intent, and stymie medical innovation. (continued on pg. 8)...

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## Potential Negative Impact on Innovation (continued from pg. 7)

The law provides for a balance between pre-approval hurdles and post-approval vigilance and makes clear that approval should not be denied in cases where questions about a drug or device could be answered in the post-approval setting via postmarket studies and controls. The law also permits the FDA to demand post-approval studies as conditions of approval, and after products have been on the market. Moreover, the FDA has broad powers after drugs are approved to exercise enforcement by imposing restrictions, revising labeling, and executing injunctions and drug seizures; it can also charge companies that do not comply with its directives with misdemeanors (where intent need not be established) and felonies. Therefore, shifting emphasis to pre-approval requirements is not needed:

- a. **513(a)(3)(C)** - In making a determination of a reasonable assurance of the effectiveness of a device for which an application under section 515 has been submitted, the Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls;
- b. **505(k)(3)(C)**- ESTABLISHMENT OF THE POSTMARKET RISK IDENTIFICATION AND ANALYSIS SYSTEM- The Secretary shall, not later than 2 years after the date of the enactment of the Food and Drug Administration Amendments Act of 2007, in collaboration with public, academic, and private entities— (i) develop methods to obtain access to disparate data sources including the data sources specified in subparagraph (C); (ii) develop validated methods for the establishment of a postmarket risk identification and analysis system to link and analyze safety data from multiple sources, with the goals of including, in aggregate— (I) at least 25,000,000 patients by July 1, 2010; and (II) at least 100,000,000 patients by July 1, 2012; and (iii) convene a committee of experts, including individuals who are recognized in the field of protecting data privacy and security, to make recommendations to the Secretary on the development of tools and methods for the ethical and scientific uses for, and communication of, postmarketing data specified under subparagraph (C), including recommendations on the development of effective research methods for the study of drug safety questions.
- c. **505(o)** - POSTMARKET STUDIES AND CLINICAL TRIALS; LABELING; (3) STUDIES AND CLINICAL TRIALS.— (A) IN GENERAL.—For any or all of the purposes specified in subparagraph (B), the Secretary may, subject to subparagraph (D), require a responsible person for a drug to conduct a post-approval study or studies of the drug, or a post-approval clinical trial or trials of the drug, on the basis of scientific data deemed appropriate by the Secretary, including information regarding chemically-related or pharmacologically-related drugs. (B) PURPOSES OF STUDY OR CLINICAL TRIAL.—The purposes referred to in this subparagraph with respect to a post-approval study or post-approval clinical trial are the following: (i) To assess a known serious risk related to the use of the drug involved. (ii) To assess signals of serious risk related to the use of the drug. (iii) To identify an unexpected serious risk when available data indicates the potential for a serious risk. (C) ESTABLISHMENT OF REQUIREMENT AFTER APPROVAL OF COVERED APPLICATION.—The Secretary may require a post-approval study or studies or post-approval clinical trial or trials for a drug for which an approved covered application is in effect as of the date on which the Secretary seeks to establish such requirement only if the Secretary becomes aware of new safety information.
- d. **505 (p)** - RISK EVALUATION AND MITIGATION STRATEGY: (1) IN GENERAL.—A person may not introduce or deliver for introduction into interstate commerce a new drug if—(A)(i) the application for such drug is approved under subsection (b) or (j) and is subject to section 503(b); or (ii) the application for such drug is approved under section 351 of the Public Health Service Act; and (B) a risk evaluation and mitigation strategy is required under section 505-1 with respect to the drug and the person fails to maintain compliance with the requirements of the approved strategy or with other requirements under section 505-1, including requirements regarding assessments of approved strategies. (2) CERTAIN POSTMARKET STUDIES.—The failure to conduct a postmarket study under section 506, subpart H of part 314, or subpart E of part 601 of title 21, Code of Federal Regulations (or any successor regulations), is deemed to be a violation of paragraph (1).

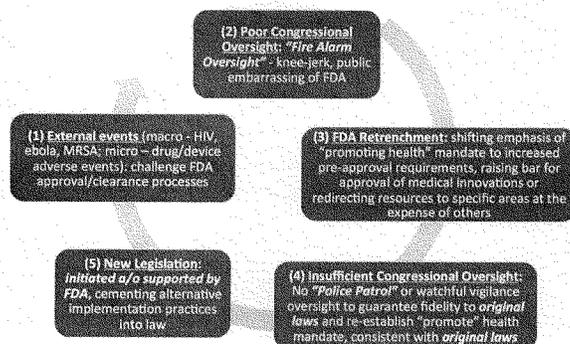
Proper Congressional oversight is essential to demand that the FDA use post-approval controls in lieu of more onerous pre-approval requirements. The vicious cycle of improper Congressional oversight is responsible for the progressive deterioration of the safety and effectiveness standard in deference to more onerous clinical utility and disease outcomes and survival endpoints. (continued on pg. 9)...

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## Potential Negative Impact on Innovation (continued from pg. 7)



A direct sequelae of this vicious cycle is the rise of specialty pharmaceutical products, those intended for small populations of patients. The FDA, following public ridicule in oversight hearings of drugs for diabetes and arthritis, has imposed new standards for approval - not only must drugs for diseases that affect millions of Americans (diabetes, cardiovascular disease, COPD, obesity, etc.) prove clinical utility (as opposed to disease activity as embodied in the effectiveness standard), they must be studied in huge trials and either show an improvement in - or no deleterious impact on - survival and major adverse cardiac events. And, even at that, the FDA requires large and expensive post-approval studies to confirm the findings.

The FDA has imposed a de facto "better than the Beatles" standard, as well, basically, if the drugs are not shown to be more effective or safer than drugs already on the market (in large trials using the "average patient standard") the FDA denies their approval. [This is very unfortunate because often, many patients experience benefit of a drug on an individual basis and the effect is lost when patient responses are averaged over the entire study population.] So, companies have increasingly foregone the development of drugs for these diseases and focused on rare diseases and conditions for which no other therapies exist. These qualify for Orphan Drug, Fast Track, BT, Expedited Review, and Accelerated Approval, which provide substantial regulatory incentives (reduced review times, smaller trials, etc.).

...Add to that the benefit of lower R&D costs. Derek Fetzter, director, global strategic analytics/global strategic marketing & market access, at Janssen Pharmaceutical Services, says that this made it worthwhile for a big firm like J&J to make a move into the specialty arena: "Improving on the many good drugs on the market is a significant, technical challenge," he observes. "This is because demonstrating smaller, incremental benefits actually requires more patients in a clinical study, from a statistical point of view, and thus is more costly."

Compared to PCP-focused candidates, specialty medicine clinical development can be not only less expensive but offer a nearer-term opportunity for cashing-in on an investment. Specialty medicine candidates typically are vetted by big pharma along the dimensions of demonstrating substantial innovation, where R&D efforts can require fewer patients and significant differences can be demonstrated over a shorter period of time.

There are regulatory rewards, too. The most prominent "X-factor" in new drugs—the FDA—displays more love toward products that aspire to occupy salient treatment voids as opposed to those gaining incremental yardage vs. existing therapy. Indeed, this is an essential element of FDA's charter.

"One central factor FDA takes into account in determining the speed of review of a new product application is whether it addresses an unmet medical need, hence potentially translating into shorter time to market," says Wayne Pines, former FDA associate commissioner, who is now president of regulatory services and healthcare for APCO Worldwide. "A usual review is 10 months and a fast-track or priority review is six months or less." (continued on pg. 10)...

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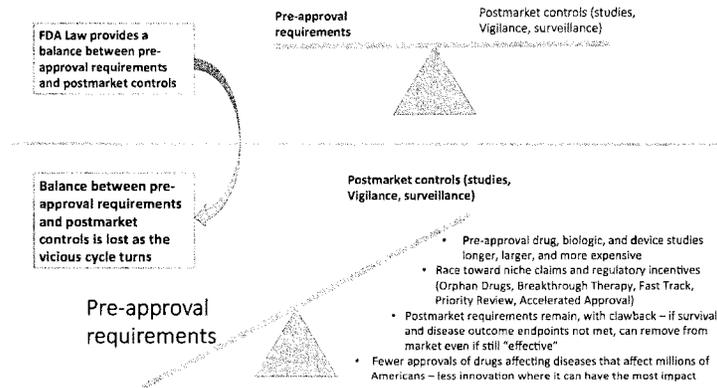
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## Potential Negative Impact on Innovation (continued from pg. 7)

Another upshot of Congress not performing appropriate oversight is the passage of an increasing number of laws, many of which are redundant. Neither the FDA nor industry can keep pace. The fact that the 21st Century Cures Act includes provisions for training FDA reviewers on least burdensome approach validates what many have observed over the last several years in dealing with FDA reviewers – due to great turnover at the agency, new reviewers are not knowledgeable of the law, especially the fundamental bedrock grounding principles of the law. Rather, they are trained, with other personnel, on the new laws that Congress passes. And, because of the new and changing laws and difficulties in dealing with the FDA, industry is spending more on regulatory affairs. A 2012 study found that:

*Top 50 pharmaceutical companies have increased their regulatory affairs budgets by an average 27% since 2010. Small drug manufacturers, as well as medical device companies, also increased their regulatory affairs budgets during the same timeframe.*



## Recommendations (continued from pg. 1)

*with the observation that “administration of a statute is, properly speaking, an extension of the legislative process.” Oversight, in brief, is crucial to the lawmaking process. Only by investigating how a law is being administered can Congress discover deficiencies in the original statute and make necessary adjustments and refinements. As a Senator stated, “We must do more than write laws and decide policies. It is also our responsibility to perform the oversight necessary to insure that the administration enforces those laws as Congress intended.”*

But, Congress had not been exercising “continuous watchfulness” with respect to FDA in its mission to promote health through the review and approval of new medical products.

Notwithstanding James Madison’s words regarding the power of the purse in Congressional oversight, Congress does not effectively wield this power principally because only 55% of the FDA is funded by taxpayer dollars. Approximately 45% of FDA’s 2016 budget of \$4.74 billion is paid for through user fees; for fiscal year 2016, the user fees include \$2,374,200 for an NDA (New Drug Application), \$261,388 for a PMA (Pre-Market Approval Application) and BLA (Biologics License Application), and \$5,228 per 510k. It appears that Congress has relinquished oversight to the biopharma and medical device industries. (continued on pg. 11)...

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## Recommendations (continued from pg. 10)

however, fear of the FDA and of repercussions from publicly criticizing the FDA render this form of oversight ineffective. But, PDUFA and MDUFA have definite performance targets for FDA. The problem has been that Congress has allowed the FDA to produce its own scorecard and set its own objectives with respect to PDUFA/MDUFA goals, which do not accurately portray FDA performance. Therefore, with respect to user fee re-authorization, we recommend the following:

1. A Government Accountability Office (GAO) investigation of FDA performance with respect to review times under PDUFA/MDUFA, accounting in calendar days. This would include anonymous industry surveys that would ferret-out the appropriateness of FDA review day determinations (based on major deficiency letters and amendments to new product applications and other mechanisms that extend the review clock). The GAO would also be asked to prepare a standard report template for FDA performance parameters that is comprehensible and grounded in real-world metrics, for example, calendar days.
2. 2017 User Fee Reauthorization provisions:
  - a. As a condition of the legislation, Congress should withhold FDA PDUFA and MDUFA funds until NDA, BLA, PMA, and 510k performance targets are achieved. Alternatively, companies could be refunded for applications that are not reviewed within target time frames (1% reduction in user fees per day exceeding review period limit. For small companies, a transferrable tax credit of \$10,000 per day of delay.)
  - b. The FDA should be required to make yearly reports to Congress on review time performance in calendar days; and, Congress should conduct yearly hearings on FDA performance.
  - c. Quarterly reports to Congress by the FDA ombudsman's office (which should report to the Commissioner, not to the FDA center directors) regarding grievances that have been raised by companies in the FDA review of their products. Perhaps, if, as a matter of law, Congress were made aware of problems as they occurred, proper oversight would follow. Also, this would protect industry from FDA repercussions.

Unfortunately, proper oversight, alone cannot make-up for the problems that have been caused because of the lack of effective Congressional oversight for many years. Therefore, other provisions must be included in the user fee reauthorization to essentially re-set the FDA on the foundations that were established prior to the user fee era:

1. Restatement of **promoting health** as the FDA's principal function with respect to new products. The law states the following as the FDA's mission - "to promote health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely fashion." Of course, protecting health is part of promoting health, however, the FDA has elevated "protecting" health as its main mission. Promoting and protecting health are two different postures - the latter looks to preserve that which currently exists while the former engenders optimism and belief in the advancement of scientific discoveries as a means of improving the health of Americans. Implicit in promoting health is an understanding that occasionally new products may not be found to be as desirable as we would like them to be, however, the only way to have genuine progress is to accept and deal with "bleeding edge" issues as we try to bring cutting edge treatments and diagnostics to patients as soon as possible. The law is actually biased toward embracing medical innovation by assuming that new drugs that undergo the drug development gauntlet would be approved, **unless** the drugs (or applications) had certain deficiencies [see 21 USC 355(d) Grounds for refusing application; approval of application; "substantial evidence" defined]. This attitude and inclination is not embodied in many FDA regulations and guidance documents, as well as in new sections of the law that have been passed as part of reauthorization legislation. The law also provides for a balance between pre-approval hurdles and post-approval controls and makes clear that approval should not be denied in cases where questions about a drug or device could be answered in the post-approval setting via postmarket controls (studies, vigilance, and surveillance).
2. Restatement of **safety and effectiveness** as the only requisite standards for approval of new products. (For devices, reaffirmation of reasonable assurance of safety and effectiveness, and least burdensome approach is needed.) Legislation needs to explicitly state that effectiveness is to be evaluated by the FDA in accordance with the labeling proposed by the sponsor and that the FDA is not to impose standards requiring demonstration of clinical utility for approval. The FDA can and should limit the claims based on the data - if there are no clinical benefit data in the application, then clinical benefit should not be claimed. Likewise, legislation that explicitly lists acceptable measures of effectiveness that can support approval - pharmacodynamics effects on disease parameters, clinical signs and symptoms, biomarkers, surrogate endpoints, patient-reported data, comparative effectiveness, clinical outcomes, and survival. A strong caveat that comparative effectiveness, survival, and disease outcomes are not needed to demonstrate effectiveness, but are needed to obtain claims that include these parameters is needed. The legislation should also state the approved label will contain the (continued on pg. 12)...

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## Recommendations (continued from pg. 11)

measures used to determine effectiveness and claims will be limited to the specific findings. The FDA can be permitted to establish categories of approval according to the nature of the evidence used to support effectiveness, and if sponsors so desire to obtain additional, "higher order," categories (for example, survival and disease outcomes), supplemental approval applications can be submitted.

3. Provisions for Breakthrough Therapy Designation, Accelerated Approval, Fast Track, Priority Review and Accelerated Approval should be rescinded -with enforcement of the effectiveness standard defined in #2 above and with the FDA meeting its review time frames these programs will no longer be needed. [Orphan Drug designation and QIDP should remain.]
4. Post-approval studies should be limited to amassing greater safety databases to inform labeling. Studies performed to generate evidence for higher order effectiveness claims shall not result in market withdrawal if higher order effectiveness objectives are not met. This is in contrast to the current regulations, which allow for rescinding product approval if drugs approved on the basis of surrogate endpoints are not shown to have improved disease outcomes and survival in post-approval studies.
5. Personalized medicine in the real-world should be fostered, as well. Legislation should make clear which decisions are the domain of the FDA (public health) and those that are the domain of physicians, patients, and other members of the medical marketplace ecosystem. The FDA is responsible for safety and effectiveness. Clinical utility and clinical benefit often cannot be easily measured or analyzed in "average patient studies" because these can vary greatly from patient to patient. If sponsors seek claims that communicate clinical utility and clinical benefit, then, the sponsor must present data to the FDA that supports these claims in a meaningful percentage of patients, even if the exact profile of responding patients cannot be defined for labeling purposes, either demographically or genetically. To further foster personalized medicine, the data from clinical trials should be made available to practicing physicians who would then be able to query the databases to obtain knowledge of the effects of the drugs on patients given certain demographic and genetic profiles; this will aid physicians in their private health decisions, that is, whether to use the drugs in real-world patients.

Another recommendation is for Congress to refrain from using hearings as a venue to publicly embarrass and humiliate the FDA when products that have been approved are shown to have undesirable effects and toxicities when used in the real world in larger numbers of patients. This starts a vicious cycle that stifles medical innovation: poor oversight > lack of oversight > regulatory drift > redundant and contradictory laws > poor oversight... It also sets an expectation in the eyes of the public for the FDA to be perfect when it comes to the review and approval of new products. We should not be conditioned to expect perfection, rather, we should be assured that proper mechanisms are in place to appropriately judge the safety and effectiveness of new products and to track them and rapidly report any issues that might emerge after approval. The FDA should then act, appropriately, either with revised labeling or other actions, including removal from the market in extreme settings. Congress would do well to reinforce to the public that the FDA is just one member of the medical ecosystem marketplace - physicians, medical societies, hospitals, cooperative research groups, drug companies, and clinical researchers have an important responsibility to disseminate information quickly and to educate medical professionals and the public. Placing blame at the door of the FDA is neither accurate nor conducive to fostering medical innovation.

According to Mr. Oleszek:

*The rise of the administrative state (the plethora of federal departments, agencies, commissions, and boards) has produced a policymaking rival to Congress. Administrators do more than simply "faithfully execute" the laws according to congressional intent (which may be vague). Federal agencies are filled with knowledgeable career and non-career specialists who, among other things, write rules and regulations that have the force of law, enforce the rules via investigations and inquiries; formulate policy initiatives for Congress and the White House; interpret statutes in ways that may expand their discretionary authority or undermine legislative intent; and shape policy development by "selling" their ideas to lawmakers and committees via the hearings process, the issuance of agency reports, and in other ways. The large role of the executive branch, whose activities affect nearly every citizen's life, underscores the critical role of oversight in protecting the policymaking prerogatives of Congress and holding administrative entities accountable for their actions and decisions.*

No government regulatory agency wields more power than the FDA, which regulates 25% of the US economy. It has amassed more and more power largely through the expanding body of FDA law passed by Congress and regulations and guidance documents that it issues. As we have seen with each PDUFA and MDUFA reauthorization legislation, passing more laws does not change the behavior of the FDA - only Congressional oversight can ensure that the FDA comports itself with the letter (continued on pg. 13)...

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## Recommendations (continued from pg. 11)

and intent of the original laws.

Congress must do a better job of FDA oversight if the scientific discoveries that are being made at an accelerated pace are to be quickly developed into products that can affect the lives of patients today.

*Address Inquiries to Joseph Gulfo, MD, MBA, Executive Director - Rothman Institute of Innovation & Entrepreneurship*

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January 08, 2015, 10:00 am

## FDA 2014 approvals – the message behind the numbers

By Joseph V. Guffo, MD, MBA

The FDA provided an update on new drug approvals in 2014, stating that as of December 15, thirty-five new drugs were approved, compared to 27 in 2013.

Here is the high level summary:

1. Fifteen of the 35 drugs were Orphan Drugs, the highest number since the Orphan Drug law was passed in 1983.
2. Fifty-seven percent of the approved drugs had Priority Review tags.
3. Thirty-seven percent of novel drugs were on the Fast Track review route.
4. The agency noted it clocked a shorter median approval time for expedited drugs, at 6.5 months in 2014 compared to 7.9 months in 2013.

By the end of the year, the FDA website stated 41 new drugs were approved, in 2014, 14 more than in 2013. Here's the rub - 40 percent are for rare diseases, underscoring the industry's focus on specialized products, where competition is limited, development is easier (thanks to the FDA programs, like Breakthrough Therapy Designation), and annual prices often exceed \$100,000.

The message to drug developers and patients could not be clearer – the FDA will preferentially look at and approve the “no brainer” applications, those that are intended for small populations, and for which no other therapies exist, no matter how few patients qualify.

This performance reiterates the FDA's continued fear-based approach to product review and approvals, despite its statements to the contrary and various programs, like the redundant and superfluous Breakthrough Therapy Designation pathway that it continues to tout.

The Agency is very proud of this performance, and because of that, they will not change their point of view or their policies. Problem recognition is the first step to change and reform. No one at the FDA seems to see the problem. Rather, they are celebrating this performance.

With respect to pricing of these niche therapies, drug makers and investors see an irresistible confluence of forces – the FDA making it very easy to develop niche products, Orphan Drug Designations validating that these indications are indeed rare, and the combination of the “Breakthrough” and “rare” labels commanding high prices. Thus, achieving profitability is made much easier.

Interestingly, 316.10(8)(ii) of the Orphan Drug Act states:

“For drugs intended for diseases or conditions affecting 200,000 or more people in the United States, or for a vaccine, diagnostic drug, or preventive drug that would be given to 200,000 or more persons per year, a summary of the sponsor's basis for believing that the disease or condition described in paragraph (b)(6) of this section occurs so infrequently that there is no reasonable expectation that the costs of drug development and marketing will be recovered in future sales of the drug in the United States.”

The intent of the Act is to promote the development of therapies for rare diseases by offering 2 additional years of market exclusivity. The rationale, of course, is because the rarity of the disease would render profitable commercialization impossible. That's not what is happening with the new drugs that the FDA is approving for rare diseases - very high prices are making many products for these conditions achieve near blockbuster, if not multi-blockbuster, status.

Take, for example, cystic fibrosis, a condition that affects 30,000 patients in the US and about 1,000 new patients per year - clearly, this is an Orphan indication. Yet, Vertex Pharmaceuticals is a \$28.7B company, charging \$300,000 per year for Kalydeco, a therapy for just a small subset of CF patients.

There is an UN-Holy Trinity of FDA fear, which promotes the development of niche products, Orphan Drug designations, which command high reimbursement rates, and investor demands for predictable and steady growth that is turning our drug development companies into niche product developers.

The Senate is about to add more incentives onto this triad - The Dormant Therapies Designation, which would confer 15 years of exclusivity on new drugs and biologics for which there is “one or more unmet medical need.” This is the same language used in Breakthrough Therapy Designation, Fast Track Accelerated Approval, Priority Review, and Orphan Drug. This program would only provide further incentives for the development of niche products at the expense of products that could help many patients. And, it is perfectly consistent with the type of drugs that FDA is preferentially approving, based on

1/10/2015

FDA 2014 approvals – the message behind the numbers | TheHill

fear.

A healthy dose of common sense and perspective is needed to understand the perverse effects of these combined forces.

The first place to start is the FDA, which needs to get back to promoting health and stop putting labels, like "breakthrough therapy," on products. The FDA needs to do what it is paid to do - review and approve new drugs in a timely fashion.

Instead of the science and medicine driving the development of new products, FDA policies are doing so.

And, patients continue to suffer.

*Giffa is the author **INNOVATION BREAKDOWN: How the FDA and Wall Street Cripple Medical Advances** (Post Hill Press) and CEO of Breakthrough Medical Innovations. He has more than 25 years of experience in the biopharmaceutical and medical device industries and is former CEO of MELA Sciences.*

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## GULFO: 'Right to try' just another bandage on a chronic wound

New initiatives can't mask need for closer look at FDA

By Joseph V. Gallo M.D. -- Friday, July 11, 2014

"Right to try" laws aim to broaden access to experimental drugs for people who are terminally ill. Colorado's law was enacted in May, and in Louisiana and Mississippi, the laws are waiting on the governors' signatures. In Arizona, right-to-try will be put to referendum this fall.

Right-to-try gives hope to patients who have none. The public wants right-to-try laws, but the FDA does not like them. In a recent editorial in USA Today, FDA Commissioner Margaret Hamburg wrote, "The column 'Right to try experimental drugs: Column' misleads the public on the Food and Drug Administration's approach to allowing access to experimental drugs. The agency is an important part of the process, helping to ensure that patients are protected from potentially harmful drugs or one that doesn't work ..."

The FDA response is at the heart of the problem. Notice the commissioner's use of the word "protected." When a patient is dying, who or what are they trying to protect? The benefit-to-risk ratio is overwhelmingly favorable in this setting with virtually any experimental product. According to Section 1003, Subpart 1 of the Federal Food, Drug, and Cosmetic Act, "The Administration shall promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner."

Oddly, this is not what the FDA says about itself. Instead, the FDA website states: "What We Do. [The] FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices."

"Promoting" and "protecting" are not synonyms that can be freely interchanged; they represent completely different ideologies. Protecting serves to further preserve the antiquated medical status quo. It assumes current medicine is always safe, when that is often not the case.

What about misleading the public? In a May piece in FDA Voice, the commissioner touted the fact that in 2013, the approval times for drugs was faster in the United States than in Europe and Asia. From 2003 to 2014, the median approval time in the United States was 304 days. The article omitted the fact that these are "review days," as opposed to "calendar days," that the FDA starts and stops the review clock at its discretion and that the statutory requirement is 10 months for every drug, not a median performance metric for all drugs. This is the reason for incessant calls for FDA reform.

The commissioner went on to laud new legislation that was passed in July 2102 called FDASIA (FDA Safety and Innovation Act), which included the new Breakthrough Therapy Designation. Since the enactment of this piece of legislation, 44 products (of the 178 that applied) were granted the designation and six products were approved. The piece highlights the approval of "a late-stage lung-cancer drug" four months ahead of its goal date (as defined by PDUFA — Prescription Drug User Fee Act).

The details about this product (Zykadia) were not mentioned. The drug is approved to treat patients with lung cancer that possess the ALK mutation, which make up 5 percent to 7 percent of all non-small-cell lung cancer, and who have failed or are intolerant to Xalkori. This is a very small number of patients — so small that the drug received Orphan Drug Designation. Not only that, the drug also received Priority Review and Accelerated Approval, rendering Breakthrough Therapy quite moot.

As Janet Woodcock, director of FDA's Center for Drug Evaluation and Research, stated in May at a Friends of Cancer Research meeting, Breakthrough Therapy is intended for products that show "spectacular results" and would be "game changers." The circumstances in which this would most likely occur are in niche settings where there are no alternative treatments so that the benefit-to-risk ratio would be overwhelmingly positive.

Sure enough, 34 percent of drugs receiving this redundant and superfluous designation have been targeted cancer drugs. The travesty is that this program and the others encourage drug makers to develop products for small niche claims.

9/13/2014

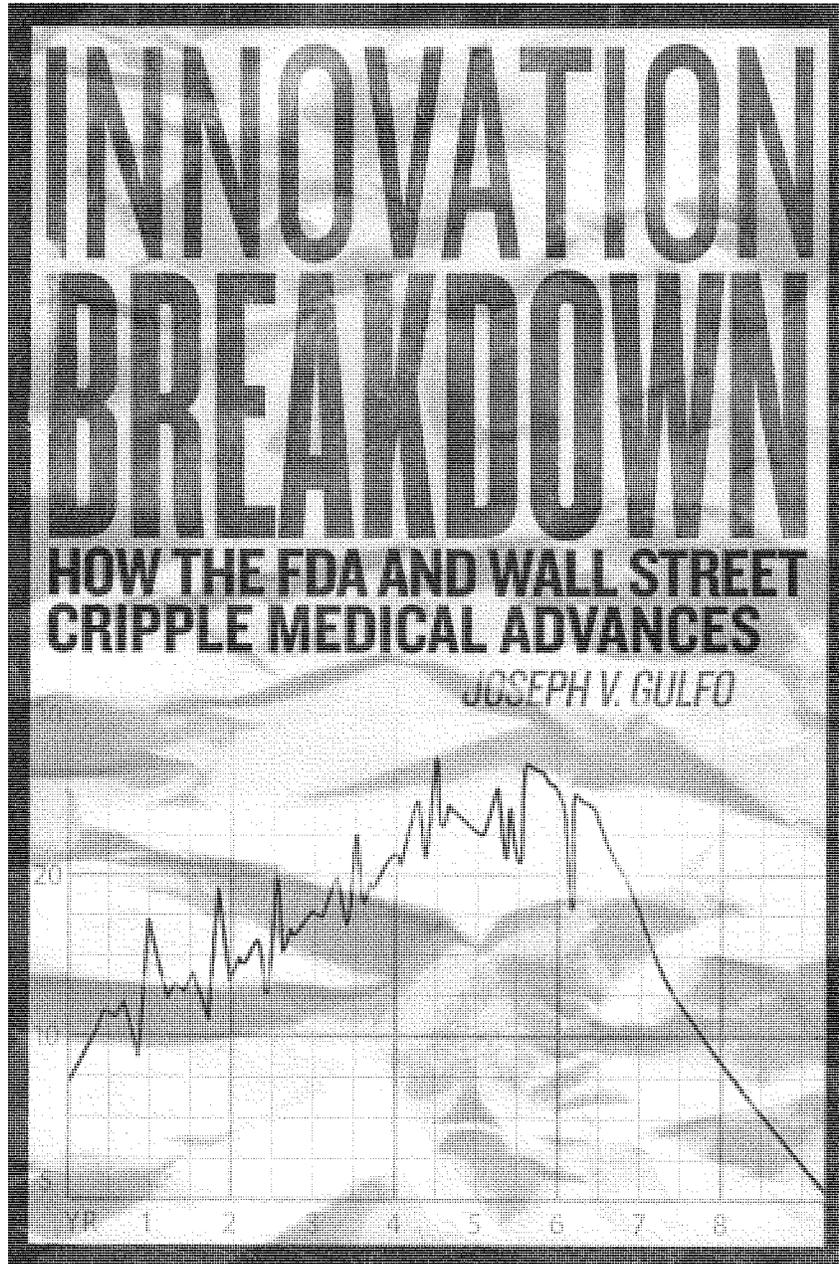
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Americans want drugs for all conditions approved faster — that's what right-to-try is all about. They want the FDA to promote health, not to protect the medical status quo; to review all drugs quickly, not just those that could provide "spectacular results" in the estimation of the FDA.

Right-to-try is the latest Band-Aid on the chronic wound of FDA performance. Bandages before it that have failed include PDUFA, MDUFA, Breakthrough Therapy and the Transparency Initiative. The reason for failure is because none of them address the fundamental problem causing the wound; that is, FDA's ideology.

As with chronic wounds, when the fundamental medical condition is not addressed, amputation is the unfortunate next step to save the patient.

*Joseph V. Gulfo, M.D., is the author of "Innovation Breakdown: How the FDA and Wall Street Cripple Medical Advances" (Post Hill Press) and CEO of Breakthrough Medical Innovations.*



**PRAISE FOR *INNOVATION BREAKDOWN***

“Finally, a behind-the-scenes look at the mysterious and often poorly executed approvals process of the FDA. An important book for consumers, physicians, investors, and scientists—anyone who is interested in medical advances that can save lives.”

—JOSEPH PIERONI, retired CEO and President, Daiichi Sankyo Inc.

“By focusing on the fate of one small company, Joseph Gulfo has written a riveting tale of how the FDA slows down crucial medical innovations, just when we need them the most. Policymakers on both sides of the aisle should absorb his prescriptions for fixing the system.”

—MICHAEL MANDEL, PhD, Progressive Policy Institute

“Dr. Gulfo has written an important book that deserves to be read by everyone interested in having access to new medical treatments. The enormous and all too often insurmountable challenges in bringing breakthrough medical products to doctors are not unique to small biotech and medtech companies, rather, even the industry-leading firms struggle against these forces. And, in the end, it's the patients who suffer.”

—BRIAN LEYLAND-JONES, MD  
Vice President, Molecular and Experimental Medicine  
Avera Cancer Institute, Sioux Falls, SD

“Finally, an incisive look at the path that medical innovation takes through the FDA, the courts and the public advocacy groups and the crippling effect it has on advancing new treatments to treat and diagnose disease. Today's regulatory/legal/public advocacy complex is stifling progress and killing medical breakthroughs. Joseph Gulfo lays out why this has happened, how to fix it and how to make all our voices heard.”

—NANCY LURKER, CEO, PDI Inc.

“A fascinating read of the relentless challenges a passionate entrepreneur faced and overcame to bring a medical breakthrough to patients.”

—SUSAN SCHERREIK,  
Founding Director, Seton Hall University Center  
for Entrepreneurial Studies

# INNOVATION

**HOW THE FDA AND WALL STREET  
CRIPPLE MEDICAL ADVANCES**

*JOSEPH V. GULFO, MD, MBA*

MD, MBA Biopharma/Medical Technology  
Entrepreneur and Investor

A POST HILL PRESS BOOK

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How the FDA and Wall Street Cripple Medical Advances  
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*To Adele*

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# INNOVATION

HOW THE FDA AND WALL STREET  
CRIPPLE MEDICAL ADVANCES

## Introduction

**Y**ou've heard of stand-up guys. Well, I'm a start-up guy. I've spent my entire twenty-five year career working for small company start-ups and "turnarounds" in the biopharmaceutical and medical technology communities. I've overseen the development and regulatory approval of three breakthrough medical products. I've also raised \$160 million in the public markets. My passions are cancer and medical innovation.

*Innovation Breakdown—How the FDA & Wall Street Cripple Medical Advances* highlights lessons that I have learned over my 25+ years, focusing particularly on the incredible and unprecedented behavior by the U.S. Food and Drug Administration (FDA) as well as the utterly destructive influence of Wall Street's fast money hedge funds on a promising little company. The victim of that treachery and destruction? MELA Sciences, a small medical device manufacturer that has spent 17 years endeavoring to mitigate the debilitating effects of melanoma, the most aggressive form of skin cancer known to man. Over 150,000 Americans are diagnosed with melanoma *every single year*, and one American dies *every single hour* of the disease. That's a tragic statistic, and for two reasons. The first: it's always a tragedy

when anyone dies. The second: *no one* should die of melanoma. Why? Because it's the only cancer you can see coming, and it can therefore be eradicated if it's caught in time. And that's what MelaFind, a revolutionary product made by MELA Sciences, can help us do. But only about a hundred and fifty of the machines are in use today, as opposed to the much greater number that ought to be. As a result, more people are dying from melanoma than should be. The real victims of the FDA and Wall Street, in other words, are the patients.

The book includes a collection of first-hand, personal, and tell-all stories about the long and arduous journey MELA took to get MelaFind to market and the innumerable moments along the way when it was nearly derailed. First, the FDA tried to destroy it. When they couldn't, Wall Street tried. Neither succeeded, but they left the company so wounded that it might not actually survive, alone, in the end. The stories are alternately tragic and humorous, fascinating and frustrating. But they all highlight the unnecessary challenges of bringing true medical innovation to the people who need it—the patients. Here's the bad news: the system is horribly broken and needs to be fixed. But here's the good news: I know how to fix it.

*Innovation Breakdown* is much bigger than one product or one person. The story of MelaFind, in other words, is simply the prism through which I hope to advance some broader truths and reveal the pervasive dysfunctions of a system that is supposed to help advance the cause of our collective health but is actually hindering it.

I wrote this book for several reasons, the most important of which was to sound the alarm about an emergency situation that matters to everyone. And it is this: if a revolutionary device such as MelaFind has to endure what it did in getting to market, there's almost no hope for those things that are equally revolutionary but also a little more complicated—a list that includes pretty much *everything* under development. Why is that? Because MelaFind isn't some futuristic biotechnology technology that does something like analyzing your DNA in real-time in the hopes of telling you about your medical future. It doesn't require a visit to an operating room, nor, in fact, does it require that you endure even the slightest bit of pain. It simply takes a picture of a questionable mole and gives

your dermatologist greater certainty in deciding whether that mole should be removed or not. That's it. And that's what makes this story so flabbergasting—if something that is both non-invasive *and* potentially life-saving had so much difficulty first getting through the FDA and then through the gauntlet that is small-company public market financing, what does that portend for other true scientific breakthroughs that have the potential to help tens of millions of Americans live happier, better, and longer lives? MelaFind is based on technology that's been deemed good enough to be used in the U.S. Star Wars missile defense program that protects us from enemies outside our borders. And yet a bunch of Washington bureaucrats and Wall Street shysters tried to stop us from using it to protect us from enemies inside our own bodies.

I hope this book can educate the public about the innovation, regulatory approval, and marketing challenges that every medical technology company faces at one time or another. I hope that it will inspire people with its tales of persistence and leadership and also entertain with real-life drama and humor, often in the face of pending doom and certain failure. I hope it will encourage others who have experienced similar treatment at the hands of regulatory agencies and other parts of this broken system to speak out in support of its reform, for that is the only way it can be fixed. But most importantly, I hope it will inform the collective consciousness of both the importance and opportunity of breakthrough medical innovation as well as the alarming threats that it faces. The implications are nothing short of profound: a failure to better foster innovation in this country will have disastrous effects not only on our health but on our economy too.

Part One lays out, quite clearly, the devastation caused by skin cancer, and makes clear the need for something that can better help us detect it when it is curable. It also describes how medical innovation occurs in small companies and details the challenges in moving those start-ups along a course that is anything but straightforward. It addresses issues such as the psychology of inventors and founders *versus* investors, the challenges of attracting and retaining talent, and the vagaries of early phase product development.

Part Two takes a deep dive into the unlawful actions and cover-ups by the U.S. FDA that had to be overcome in our effort to bring MelaFind to market. That is, to obtain approval of a non-invasive product that saves lives. It is a brutal blow-by-blow account of a public slugfest that forever damaged the company. While the right side won in the end, it was nevertheless a bitter—and important—enough fight that it ended up being chronicled by the country's major media—the *Wall Street Journal*, Bloomberg TV, and *Fortune* magazine.

Part Three explains how the unnecessary and very public battle with the FDA left an indelible mark on the company, a taint that was exploited by nefarious Wall Street actors who then preyed on the company for their own benefit. It details how with a Scarlet Letter on its back and an albatross around its neck, Wall Street's short sellers and dark pool traders made it impossible for the company to advance the product along the normal, yet time consuming and expensive, course toward widespread use and adoption. That's a path that *every* medical innovation must take en route to becoming a medical staple, but it's also a path along which Wall Street's bad actors lie in ambush.

Here's the silver lining, though: until this system *is* fixed, it does offer long-term investors extremely attractive opportunities to invest in oversold stocks like MELA. I was unable to secure such investment as CEO of the company, but had I been on the other side of the table, I surely would have invested myself. The opportunities are numerous.

Part Four offers a cure for the broken system that nearly ruined the company, and in doing so has arguably killed countless patients by delaying, if not ultimately preventing, widespread adoption of this product. Simply put, the FDA has stopped pursuing its mandate to promote the public's health. Instead, it has put up every roadblock imaginable to stop true breakthrough medical innovation. If we don't cure what ails the system, it's going to succeed in stopping it entirely. The book concludes with a prescription for change, a Medical Innovation Manifesto.

I hope you enjoy reading it more than I did living it.

JOSEPH GULFO  
*June, 2014*

STATEMENT OF  
NANCY GOODMAN  
EXECUTIVE DIRECTOR  
KIDS V CANCER  
BEFORE THE  
COMMITTEE ON HOMELAND SECURITY  
AND  
GOVERNMENTAL AFFAIRS  
U.S. SENATE  
FEBRUARY 25, 2016

Connecting Patients to New and  
Potential Life Saving Treatments

Thank you Chairman Johnson, Ranking Member Carper, and Members of the Committee for inviting me here today. I am honored to testify before you about how to connect patients to new and potential life saving treatments.

I am the Executive Director of Kids v Cancer. But more importantly, I am the mother of Jacob, a very sweet, beautiful boy who died when he was 10 of a pediatric brain cancer. Despite the remarkable developments in cancer research, the drugs and protocols used to treat Jacob were 40 years old. The day after Jacob died, I launched Kids v Cancer to focus on changing the landscape of pediatric cancer research and to make it possible for children to get access to cutting edge new treatments.

When Jacob was in end stage cancer, I contacted eight different companies, requesting access to their unapproved drugs for Jacob. Finding the right person to contact was very difficult. The companies did not have point of contacts on their webpages, SEC filings or other public outlets. For some companies, I contacted the CEO, others the CMO, other the head of business development. For one company, it was my cousin's friend. It was all very *ad hoc*. The process was confusing and took me away from my son. Of the eight companies, six never got back to me. Two formally considered my request and declined.

The purpose of the Right To Try laws is to help patients get access to drugs they would not otherwise get access to. That is a serious problem, and that is a goal I share, but I think we need to take a broader approach to this problem and that has been the focus of Kids v Cancer.

Kids v Cancer's first step was to incentivize companies to develop drugs specifically for pediatric cancers and other pediatric rare diseases. In 2012, Congress passed the Creating Hope Act as part of PDUFA. That has created nearly \$800 million in market incentives – at no cost to the taxpayer – for companies that get a new drug for pediatric cancer approved by the FDA. The Creating Hope Act is up for renewal as part of the 21<sup>st</sup> Century Cures bill passed by the House. I urge the Senate to renew it as well.

Our second step was to make new drugs being developed for adult cancers available for kids as well. In 2003, Congress passed Pediatric Research Equity Act (PREA), which requires companies developing drugs for adults to conduct pediatric trials on such drugs where it could benefit children. The problem is that PREA has not kept up with the science. PREA only requires clinical trials if the children have the same "indication" – that is, if children have the same type of cancer. But now we know that even though children don't get breast cancer or

lung cancer, the mechanism of action in these cancers might also be evident in pediatric cancers such as neuroblastoma or medulloblastoma, the type of brain cancer Jacob suffered from.

We have proposed the Kids Innovative Drugs Initiative, a modest change to PREA that would update it to take into account these new scientific developments and ensure that drugs being developed for adults that could have relevance to pediatric cancers are tested on children as well. I urge Congress to pass the KIDS initiative as soon as possible, either as part of the 21<sup>st</sup> Century Cures bill or as part of PDUFA.

And that brings me back to Right to Try laws. Yes, when it comes to seeking compassionate use access to unapproved drugs, the paperwork is onerous and the process time-consuming. In response, Kids v Cancer is launching a Compassionate Use Navigator. We are working to better inform physicians on how to apply for compassionate use applications for their pediatric cancer patients with drug companies, the FDA and their hospitals. We hope to provide point of contacts for drug companies, we will post the new FDA expanded access form, and we will work with the institutional review boards of the hospitals where the patients will be treated. We will offer to counsel physicians personally on specific applications. In addition, we will collect information about the efforts and outcomes of pediatric cancer compassionate use applications.

The Compassionate Use Navigator is not the whole solution to the challenge of access to new treatments. However, it will give parents of dying children more time with their kids. It will lessen the burden of their physicians as they apply for compassionate use applications. We hope it will encourage more physicians of kids with cancer to apply for compassionate use. And, we hope this program will eventually lead to more children gaining access to compassionate use drugs.

In addition, Kids v Cancer supports the Andrea Sloan CURE Act to have drug companies make available to the public their policies on requests for compassionate use access, including the minimum criteria for approving requests and the time needed to make a decision. I urge Congress to pass the Andrea Sloan CURE Act as part of the 21<sup>st</sup> Century Cures bill.

But from my personal experience and from working with dozens of other families, my sense is that the fundamental problem is not the FDA, but the incentives faced by the companies. Even though the FDA approves virtually all compassionate use applications it receives, and even though it has indicated that an adverse reaction to a drug provided for compassionate use will not adversely affect a company's application for that drug's approval, companies remain risk averse and would rather not provide such drugs.

But even if one could change that, the results would be one-off anecdotes. We cannot afford to take an *ad hoc* approach to addressing pediatric cancer, the number one disease killer of children in America. We need to address the lack of access seriously ill children have to novel, unapproved drugs not only by one-off compassionate use applications, but even in clinical trials. That's why initiatives such as the Creating Hope Act and the KIDS Initiative are so important.

Any bill that makes it easier for children to get access to drugs they need to survive and live happier, healthier lives is, of course, welcomed, but we need to do more than address anecdotes. We need to change the landscape of pediatric cancer research. We need to ensure that children with cancer and other life threatening illnesses, like my son, Jacob, have access to new and potentially life saving treatments.

Thank you very much.

Meet Jordan McLinn...my 6 year old son from Indianapolis, IN.

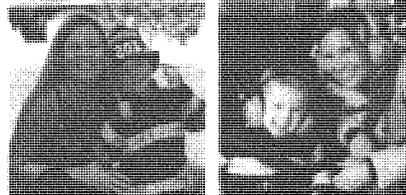
Diagnosed with Duchenne Muscular Dystrophy at age 3. Life expectancy 20ish. Unacceptable.

Treatments **exist** that can slow the progression of this muscle wasting disease!

Please help Jordan and other boys like him access safe treatments that can add time and quality to their lives. He is already starting to decline physically. He is in a race with the clock for his life.



**Please consider sharing your voice** at the upcoming advisory committee meeting for eteplirsen to remind the FDA to use the tools you gave them in 2012 with the passage of FDASIA. The FDA has the power to say **YES** for the first time in history to a drug that slows the progression of Duchenne Muscular Dystrophy. It's a drug that is safe... and working! After four years, 10 out of the 12 boys receiving eteplirsen were still walking. This is **unprecedented**. Only one of the 13 boys in the external control group was still walking after four years.



Jordan does not have time to wait for the standard approval process for these treatments but you gave the FDA the tools and support they need to grant **accelerated approval**...just like they've done with HIV/AIDS, several types of cancers and other diseases. We need your help encouraging them to use these tools more often with rare diseases like Duchenne so that boys like Jordan can live longer, walk longer, feed themselves longer and hug their mommies longer.

Sincerely,

Laura McLinn, Jordan's Mommy

(317) 753-1661

[LauraMcLinn@yahoo.com](mailto:LauraMcLinn@yahoo.com)

[www.TeamJordan.org](http://www.TeamJordan.org)

\*A decision on the accelerated approval of eteplirsen is expected to be made by the end of May. We are currently waiting for the new advisory committee date to be posted. It was postponed in January due to the blizzard. They will post the new date on the federal registry, hopefully any day now.

## Jordan Joseph Nelson McLinn, Age 5

Date of Birth 5/15/09

6131 S. Meridian St. Indianapolis, IN 46217

Mommy's contact info: [mslauraflores@yahoo.com](mailto:mslauraflores@yahoo.com) (317) 753-1661

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**Objective:** To obtain a job at the fire station helping the firefighters.

**Qualifications:** I am strong. I love God. I love helping people. I am super smart.

**Challenges:** I have Duchenne Muscular Dystrophy. Science says within 3 to 7 years I will be in a wheelchair and within 15 years I will most likely be living in heaven because all my muscles will be deteriorated. We don't really believe that though.

**Skills:** Taking Care of Dogs, Cleaning, Building Things, Playing with Cars & Trucks, Dancing, Cooking, Making People Smile

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*Jordan says he wants to be a firefighter when he grows up. He was given a fatal diagnosis of DMD last year. It would be awesome if there is anything he can do maybe once a week for a short time to help out at the fire station. We are pretty flexible with days/times. He is an awesome little boy, happy and full of life! Please let me know if I can bring him in for an, "interview". Thank you for your consideration.*

- Laura McLinn ☺

Celebrating  
40 Years  
of Hope

February 19, 2016

Sen. Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs  
328 Hart Senate Office Building  
Washington, DC 20510



**MACC  
FUND**

Hope for Kids

Dear Chairman,

On behalf of the children and their families, thank you for your continued interest in the fight against childhood cancer. You have shown a great personal interest through your willingness to meet in Milwaukee with some of our great doctors in the MACC Fund Center at Children's Hospital of Wisconsin as well as meeting with other childhood cancer advocates in Washington, DC. Your willingness to Chair this Hearing to better understand the issues will be most hopeful as well.

Eddie Doucette and I started the MACC Fund 40 years ago to help provide funding in large part at the time to help Eddie's son, Brett, who was a toddler battling leukemia. I saw firsthand the impact of cancer in a child and the effect it has on the families. When we started the MACC Fund in 1976, the overall cure rate for childhood cancer was 20%. Four decades later, that overall cure rate has risen to 80%. The MACC Fund support totaling over \$55,000,000 has played an important role in this along with federal support. Even children in the 80% category can have "late effect" issues and can relapse requiring more research. Cancer is still the leading disease-related cause of death in children with cancer, just like it was 40 years ago.

The look in the eyes of a parent dealing with cancer in 2016 is the same as it was in 1976. It is a look of fear. The most common theme from the hundreds of parents I have met over the years is that of Hope. They view the MACC Fund's mission of "Hope Through Research" and increased cure rates as tangible signs. That fear is punctuated by the financial toll on a family which is overwhelming as concerns over "making ends meet" is a constant concern.

The MACC Fund is proud to be part of the solution in the proverbial private / public partnership of support. The \$55 million which the MACC Fund has contributed in Wisconsin to provide cutting edge research at the Medical College of Wisconsin in the *MACC Fund Research Center*, at Children's Hospital of Wisconsin in the *MACC Fund Center* and at the University of Wisconsin's Carbone Cancer Center in the *MACC Fund Childhood Cancer Research Wing* has led to exciting results which impacts the treatment of children throughout the state, the nation and the world. The evolution of gene therapy holds great promise. All of us hope for a cure in our lifetimes. If not us, our granddaughters will celebrate that day.

While an ultimate cure is our goal, steps taken along the way by Congress to help eliminate red tape, provide incentives for innovation, remove the existing barriers which stand in the way while stream lining the processes for families which are already facing far too much would be most helpful. We just had our annual meeting including a presentation from Dr. David Margolis, whom you met and who is one of the nation's brightest stars in cancer. He told a story of a drug which could have helped one of his patients, but regulations did not allow it to be used for a child – even though it could have saved the child's life. The sadness in his voice told it all. Thus, your efforts in streamlining "Right to Try" initiatives are most welcome. As a father and grandfather like me, I know you and your associates will do all you can to help the children.

Thank you once again for your ongoing interest, support and leadership.

Sincerely,

MIDWEST ATHLETES AGAINST CHILDHOOD CANCER, INC.

  
Jon McGlocklin  
President, Co-Founder

CC: Sen. Tom Carper

Celebrating 40 Years of Hope • 1976-2016

MIDWEST ATHLETES AGAINST CHILDHOOD CANCER, INC.  
10000 W. Innovation Drive, Suite 135 • Milwaukee, Wisconsin 53226  
Phone: 414.988.5830 • Fax: 414.988.6170 • www.maccfund.org



REBECCA KLEEFISCH  
Lieutenant Governor  
STATE OF WISCONSIN

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February 26, 2016

U.S. Senator Ron Johnson  
Chairman  
Committee on Homeland Security and Governmental Affairs  
328 Hart Senate Office Building  
Washington, DC 20510

Dear Chairman Johnson:

I understand that you are holding a hearing this week on opportunities to reform the Food & Drug Administration's processes in order to provide greater flexibility for terminal patients to explore additional treatment options. As you consider these policy issues, permit me to share my family's story as one example of the impact of these legislative choices.

Long before my own cancer diagnosis, there was my father's. At age 52, 36 years into his romance with my mom, the strongest man I knew was given months to live with pancreatic cancer. Everyone knows that's a killer. That's what I found out when I looked it up. I was a journalist at the time, and, accustomed to digging for answers, I sought advice from a more senior reporter...who also happened to have cancer.

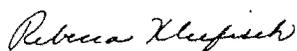
Duane Gay was a Milwaukee TV legend whose status was elevated even further when he welcomed viewers into his very personal, ferocious battle with a rare soft-tissue cancer. When I reached Duane, he was trying another experimental drug. His will to live was enormous. He was a newlywed, building his dream house with his new bride, and hopeful to return to a career he was born to do. I asked for advice for Dad. Duane had seen all the cancers; they all pass you in the oncology ward or the radiation floor. He knew my dad had a bad one and so he fast-forwarded.

"Just try anything," he advised, referring to the experimental drugs he was known for taking. "Anything to keep you alive until the next best thing comes along. And then that will keep you alive until the next best thing." Duane tried study drug after study drug. When one didn't constitute a total fix, but gave him a few more weeks of life, he tried the next trial drug he could get. Duane didn't need to tell me that one day, he hoped "the next best thing" was the drug that would finally cure his cancer. He didn't need to tell me. I understood.

My Dad didn't have time to get into clinical trials, though. Most he was excluded from. I called doctors in the U.K., Canada, and across America to discuss their research that I had read in medical journals online. Dad didn't qualify to use any one of their drugs or procedures. Our doctors told us that my dad would die from his pancreatic cancer. I was convinced that with enough work I could find "anything to keep him alive until the next best thing comes along. And then that would keep him alive until the next best thing." But my dad never had access to the next best things. I would read about hopeful advances, only to have my hope dashed when no human trial was available, no FDA approval yet on the horizon...at least not on Dad's time-frame. The horizon came quickly for Dad. It was only about four months and I was never able to find the same experimental drugs that kept Duane going. I wonder if Dad had had the right to try experimental treatments one of them would have been the next best thing. I will never know, but some patient might.

A patient like the lady in the red knit cap at Serb Hall I met last Friday. She came up to me after I had given a speech and she told me that, just like me, she had been diagnosed with colon cancer. But unlike me, she had not recovered. Like my dad, she was Stage 4. I told her that I hoped her oncologist would one day be a stranger to her. I promised I would pray for her. And I told her to "just try anything. Anything to keep you alive until the next best thing comes along. And then that will keep you alive until the next best thing." I told her to keep hoping, because the next best thing might be a cure for her. Cancers seem to be deeply personal. A drug that kills cancer in one patient may be like a sugar pill in another. But on the hope that just one patient, left alone after every effort by conventional medical logic, might be that miracle, shouldn't those with little hope left have a right to try?

Sincerely yours,



Rebecca Kleefisch  
Lieutenant Governor  
State of Wisconsin

February 24, 2016

Sen. Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs  
328 Hart Senate Office Building  
Washington, DC 20510

Dear Chairman,

My name is Stephen Finger. I am 39 years old and am an economics professor at the University of South Carolina. I grew up across the river from the Capital in Arlington, Virginia. I went to Yorktown High School and then to Princeton. Three years ago I was diagnosed with ALS. Between my son James's first birthday and his sister Mary Adair's third, I was told, what I thought was a minor issue with my hands, was a disease that would rob me of my ability to play catch, to play tag, to walk, to speak, to eat, to breath.

My family's lives where forever changed and if one thing was clear, it was that time was of the essence. And just as we recognized the need to live urgently; to hug today, to laugh today, to live today, to love today. We also recognized the need to act today. I applaud the Committee for looking at this issue and I urge you to direct the FDA to utilize the tools at their disposal to facilitate the search for a cure for ALS and other serious diseases with limited therapeutic options. While in an ideal world it would be nice to completely rewrite the regulations related to drug development, the first step is to simply make sure current regulations are enforced and utilized in the ways that they were intended.

The 2012 Food and Drug Administration Safety and Innovation Act, with near unanimous support in both the House and Senate, reinforced the "Agency's longstanding commitment to regulatory flexibility regarding the evidence required to support product approval for the treatment of serious or life-threatening diseases with limited therapeutic options". Every now and then, you hear about a disease like Ebola that captures the public's attention that leads to aggressive action by the FDA. Even though ALS may not have the same PR campaign behind it, to the patient who is diagnosed every 90 minutes, to the families who lose a loved one to the disease every 90 minutes, ALS is no less a nightmare. We ask that the FDA uses the flexibility, efficiency, and urgency required to fight this disease, and mandated by law.

Accelerated Approval is not a new program. It has been around for over 20 years, specifically designed for situations like this. Congress has provided the FDA with the ability to act with the urgency this situation merits. Because ALS is a complex disease and progressions vary, meeting traditional standards of efficacy will require additional large and lengthy trials. Well we don't have time for that and Accelerated Approval was specially designed to address this. That is the directive Congress has given. I have spoken with decision-makers with the FDA and they insist that they are open to examining applications for accelerated approval. However when I have talked with researchers and sponsors, they stressed they do not want anything that jeopardizes their relationship with the FDA. Therefore it is vital that the FDA publicly directs sponsors to utilize these types of programs in the many disease spaces where they are not currently used.

Now sure after Phase I and Phase II trials there are still risks, but there will still be risks after Phase III and more importantly, we all know what the risk of inaction is. Accelerated Approval does not mean

we enter the wild, wild west. Postmarketing surveillance data must still be collected and approval could still be revoked if confirmatory trials do not go well. Some patients may be angry if approval is revoked for a treatment that they believe is being beneficial. However, isn't that a PR issue that we are willing to bear in order to give dying patients access to potentially effective drugs? Given safety data, given evidence of efficacy, given the prognosis of the disease, given the urgency of the situation, isn't that a risk we are willing to take? Isn't that a risk the FDA is supposed to take?

Since 1962, by law, the FDA has required "Substantial evidence" of effectiveness. The required statistical significance level for any trial should minimize the impacts of Type I and Type II errors. To my knowledge there is nothing that states that  $p < 0.05$  for a two-tailed test is substantial, but 0.10 is not or  $p = 0.05$  for a one tailed test is not.

No one wants to risk switching to a new mouse trap if the current one is working. However, if the current one isn't working, or in the case of ALS you currently do not have one, you are more willing to take a chance on a better mousetrap. In a disease such as ALS, with few clinically significant treatment options and a stark prognosis, the cost of approving an ineffective or dangerous treatment (1 in 40 under their current statistical standard), must be weighed against the cost of delaying or rejecting an effective treatment given the alternative for patients. Delaying approval for an effective treatment means that more of my friends will die, it decreases the odds that I will see my kids grow up.

At a minimum,  $p = 0.05$  for a one tailed test is more appropriate in this setting. The purpose of a trial is to test if a treatment is effective. Therefore, the null hypothesis should be that a treatment is not effective. As with accelerated approval, as long as the FDA insists on adequate postmarketing surveillance and data collection, the impact of giving conditional approval to a treatment that is ultimately proven to be ineffective can be minimized, while we expedite the availability of effective treatments to this population.

I believe in many ways the FDA is at a crossroads. New technology, more personalized medicine, and better data analytics is changing the way that trials will be conducted in the future. In addition, patients now have better ways to coordinate and make their voices heard. They will not die quietly while a risk-averse system speaks eloquently about a one-size-fits-all status quo. I will not do that. I will fight for the system to work for me so that I can see my son's first day of kindergarten, so I can see my daughter learned to ride a bike. Congress has done its part to give the FDA the tools to move into the 21<sup>st</sup> century and act more effectively, efficiently, and urgently to help sponsors find treatments to deadly diseases. It is now up to the FDA to choose to use these tools or to force more radical steps to be taken.

I thank the Committee for working on this issue and I thank the FDA for doing everything possible to speed drug development for serious diseases with no current treatment options.

Sincerely,

Stephen R. Finger, PhD  
1319 Greenhill Rd.  
Columbia, SC 29206  
803-361-0644

February 20, 2016

Senator Ron Johnson  
Chairman Senate Committee on Homeland Security and Governmental Affairs  
328 Hart Senate Office Building  
Washington, DC 20510

Regarding the February 25 Hearing – Connecting Patients to New and Potential Life Saving Treatments

Dear Chairman Johnson,

Three years ago to the day of this hearing, the FDA conducted an all-day hearing on ALS. Dozens of people with ALS and caregivers made a difficult trip to Silver Spring to testify. Dozens of scientists and organizational representatives testified, too. It was a day when FDA officials sat face-to-face with dying people who were begging for the right to take some risks. It was a day when caregivers gave the FDA some concrete suggestions for changing the drug approval process to save their loved ones. It was a day when a mother of a young man with ALS asked that this not turn out to be a dog-and-pony show. Three years later, it is clear that it was nothing more than a dog-and-pony show.

Three years. 20,000 American funerals later. A half million global funerals later. We all deserved more than a dog-and-pony show.

I realize that the FDA has a huge responsibility to keep Americans safe. I appreciate that. They would rightly feel blood on their hands if something were approved that did more harm than good. Why don't they feel the blood on their hands today when people die from ALS, protected to death from experimental drugs? Why don't they feel the blood on their hands today when people with ALS die from the FDA-approved morphine that makes them more "comfortable" in death?

A basketball game is played differently in the last 60 seconds, especially when you're behind. The last two minutes of a football game can be a magnificent display of adapting to the situation. Yet our game-planners for drug access and approval have one playbook. Today the drug approval process for a simple therapy for a relatively healthy child is substantially the same as for a possible drug for that child's parent dying from ALS. No Hail-Marys are allowed for that child's Mom or Dad. That's just wrong.

I personally think that Right-to-Try laws are not the answer. We need a strong FDA at the center of drug development. We shouldn't be building networks of drug access that only work for people of substantial means. Yet those Right-to-Try laws have brought an important conversation to this hearing, and I am grateful for that.

The Legislative Branch has provided the FDA with a path of Accelerated Approval that is designed to let them change the game plan for terminal, unmet-need diseases. Why doesn't the FDA use it for ALS? Is it liability? Is it concern over payers (which I don't believe is the responsibility of the FDA)? What is the problem?

And please don't try to tell us that Expanded Access Programs are the answer. They simply aren't viable when the entire market for a new drug is the unmet-need disease and the science is dreadfully expensive. They don't work for ALS. We need to encourage drug developers, not discourage them.

We learned at that FDA hearing three years ago that drug developers are frustrated because they don't get to collaborate with the FDA. They submit. The submission is accepted or rejected. If it's the latter, they have to start over. Are drug developers afraid to propose new ideas for fear they will be rejected?

I'm a Boomer. I'm old enough to remember when we all had access to drugs that had just been tested for safety but not for efficacy. As an adult today blessed with good health, I appreciate the FDA changes of the 1960s that require efficacy testing of the drugs my doctor prescribes. But as the daughter of a woman lost to ALS, I also know that she should have been given a chance to try something -- something that may or may not have helped her. Something she could have accepted with eyes wide open about risk. Something that could have advanced the science more quickly for another mother.

Last year Gregg Doyel, a talented sports journalist for the *Indianapolis Star*, wrote a column about his friend, Maureen, who was dying from ALS. She was a beautiful human being. She was a mother and wife. She wanted access to try something. She wanted a chance at a Hail Mary. Gregg's article ended with some words that I hope stick with everyone in this hearing room. Actually, I hope they sting, too. - "For god's sake, you coldhearted bureaucrats, they're dying."

Sincerely,

Mary Catherine Collet  
4475 Clover Lake Drive  
Indianapolis, Indiana 46228-3044  
317-293-5013  
mcollet@comcast.net

cc: Senator Thomas Carper  
cc: Senator Dan Coats  
cc: Senator Joe Donnelly  
cc: Senator Lisa Murkowski

February 24, 2016

The Honorable Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs  
328 Hart Senate Office Building  
Washington, DC 20510

Dear Mr. Chairman,

In light of the hearing you are holding tomorrow entitled *Connecting Patients to New and Potential Life Saving Treatments*, I want to urge you to consider the importance of extending the right-to-try principal through accelerated drug approvals and expanded access to experimental drug trials. Patients diagnosed with terminal illnesses without known cures deserve every opportunity to try and fight for their lives. Ensuring expanded drug access and faster drug approval times by the Food and Drug Administration is critical for improving these patients' chances of survival and quality of life as they battle devastating diseases. Furthermore, the desire of these patients to control their own destinies is also in the public interest, as experimental treatments provide important data and evidence that help advance the body of knowledge to the benefit of all Americans.

I know firsthand the devastation of incurable disease as my mother was diagnosed with ALS last year and died September 12, 2015. Of the many terrible memories of this experience, the one that most impressed itself on me was her unwavering desire to fight her disease as best she could, and to control the outcome to the best of her ability. I wish fervently that she had had more options to try in her fight. While mine is only one example, I know that there are many other Americans who wish, along with their families, to have the right to try potential drug treatments as they battle terrible illnesses. I urge you to take the lead in changing our outdated drug approval process in order to provide this right to those who wish to take control of their own fate when faced with a terminal diagnosis.

Sincerely,

Sabrina Abu-Hamdeh

CC: Senator Thomas Carper, Ranking Member

February 24, 2016

The Honorable Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs  
328 Hart Senate Office Building  
Washington, DC 20510

Dear Mr. Chairman,

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Sincerely,

Sabrina Abu-Hamdeh

CC: Senator Thomas Carper, Ranking Member

February 23, 2016

Sen. Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs  
328 Hart Senate Office Building  
Washington, DC 20510

Christopher Engstrom  
1295 Herringbrook Rd.  
Eastham, MA 02642

Dear Chairman,

I am only 44 years young. I now live with my parents who are 72 and 78. I have had ALS for four years; I cannot walk, talk, move my arms nor my hands. I cannot swallow and have to eat through a feeding tube. My breathing is shallow and I may soon need to have a tracheostomy and a rely on a vent to survive.

Four years ago I was very healthy and athletic. I have been a long distance runner since high school and a competitive swimmer since age seven. For my entire life, I have defined myself as an artist and being passionate about immersing myself in nature. As a teacher, I taught my students that the natural world is not separate from us; it sparks curiosity, creativity, holds insights and is key to our survival. Nature is everything to me. In sum, I LOVE LIFE and I don't want to give it up!

I never thought this would or could happen to me. I didn't even know what ALS was. Now I cannot draw or paint and my running, hiking, swimming, surfing and skiing has been replaced with wheelchair accessible paths. I should not complain that I may have less than one year of life left to live because I have had opportunities and experiences that the majority of people have not. I grew up in an upper middle class neighborhood; I have always had running water, clean clothes, an abundance of nourishing food, excellent education, a home and a loving family.

So why should anyone care about me? I ask myself that daily. And my answer is that everybody is equal and we all have the right to live. It does not matter what race, gender, ethnicity, religion, social status or income level we are; anyone could find themselves in my shoes—with a terminal illness with no known cure, possibly one year to live, no hope to prolong life and no options. Shouldn't we ALL have the right to try promising medicine that is not yet approved by the FDA if we are faced with death? Wouldn't you want this for your family? Wouldn't you want the FDA to do everything in its power to fast track a promising new drug or treatment?

It is the death of hope that destroys the soul; the body follows. I am nearly out of hope. How much more does my family and I have to endure? Because my disease has advanced so quickly, I never qualified for trials. Now my only option for hope is having a tracheostomy and be on a vent. I would need around the clock care which medicare does not cover. Therefore, I have to choose between my family's home, their freedom, the quality of their future lives and my future breathing through a vent and being completely dependent.

Why don't I have more options? Me and thousands of others with terminal illnesses have the RIGHT TO TRY medicine that could help! FDA and Chairman, respectfully HEAR MY CALL!!

Sincerely,  
Christopher Engstrom

Senator Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs  
328 Hart Senate Office Building  
Washington D.C.

February 23, 2016

Dear Chairman Johnson,

I'm writing to plead your help in expediting the process for trials/treatments for those who are terminally ill. January 11<sup>th</sup>, 2015 my otherwise extremely healthy, active husband, father, son, brother, uncle and friend was diagnosed with ALS, which as you know is a death sentence. We have three amazing children who will be left broken hearted without their father, and we are willing to try anything that offers HOPE and prolonged life. Mike would love to watch each of our kids make it through high school, and at this time, without the opportunity to pursue investigational medicines, this dream will most likely not be a reality. We are urgently pleading for you to please speed along the trials/treatments and open them up to whoever is willing to take the risk and try.

There are many promising drugs/treatment on the horizon, but people fighting terminal diseases need them NOW! People with terminal diseases don't have time to lose. They don't have the luxury to wait five to ten years, while the FDA takes an inordinate amount of time to determine the "safety" and "effectiveness" of these trials. Simply put these patients have everything to lose if not granted the "Right to Try".

There is a 100% chance that people with ALS and other terminal illnesses will die; there is no cure for this disease or many others. But if there is investigational drugs/procedures that many have some chance in helping people both recover their quality and quantity of life, they should be allowed to try it, at their own discretion and of their own free will. This is what Right to Try Laws allows for and should be on the forefront of reaching out to medical companies and allowing them to practice.

For example, given the strong performance and good safety profile of neural stem therapies, virtually every person with ALS would want to participate in these procedures if they were afforded the opportunity. Why should people with ALS not be able to participate in this therapy as it has already been approved for muscle/tendon/joint repairs? The FDA needs to not stand in the way of promising medicines/therapies for those suffering with terminal diseases. The FDA, while under pressure, bent the rules in the 1980s and 1990s to allow drug access to patients with AIDS, then a fatal diagnosis. More recently, under the harsh light of international publicity, the FDA allowed for ZMapp, which had NEVER been tested on humans to be given to Westerners who contracted Ebola, thus saving their lives.

Please attend to this matter with a sense of urgency and willingness to fully consider and factor into the regulatory policy and decision making, the perspectives of all those suffering with a terminal disease that allows all the opportunity to access promising new medicines/treatments at the earliest possible point in the learning process.

Thank you,

Nicole Cimbura  
Highlands Ranch, CO 80129

February 21, 2016  
Sen. Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs  
328 Hart Senate Office Building  
Washington, DC 20510

Dear Chairman,

As a parent that received a "terminal upon diagnosis" for my perfectly healthy nine-year old I struggle with the fact that, for far too many of us, there simply are no options. My daughter, Gabriella, was diagnosed with Diffuse Intrinsic Pontine Glioma, DIPG, a terminal brain cancer, in November 2012. This is the same cancer that Neil Armstrong's daughter had 50+ years ago. No viable treatments have been developed in all of these years. The outcome for those diagnosed remains the same - DEATH within 9 - 12 months.

WHY is it that we can successfully send a man to the moon - and return him to earth - but we cannot save his daughter or the thousands of children that have been diagnosed in these 50 years? WHY are we still giving children cancer drugs that were developed 30, 40 and even 50+ years ago? Drugs that have known side effects such as organ failure, causing secondary cancers and death. Yet we have promising drugs that are currently being developed and available for clinical trials but our children cannot use them because they are for adult use only. Please explain this to me.

When my daughter's cancer began to regrow post-radiation I called every hospital in the country that had some sort of protocol that held the possibility of extending and saving her life. To no avail. The general response from the doctors was that Gabriella was too young and that perhaps in 6 - 12 months the trial would open for children. My daughter didn't have another six months. I BEGGED for my daughter's life and was basically told that her life wasn't important enough to make an exception. (Please note that every doctor that I spoke with was filled with anguish that the laws forbade them to fulfill their Hippocratic oath - to work in the best interest of their patient and to save every life that they could.) Do you know how many parents hear this exact same thing every day? Can you imagine having to beg for your child's life only to be told that even though there was a treatment that could potentially save their life it would never be available to them - because the government wouldn't allow it?

Why are there barriers that keep children from receiving potentially lifesaving therapies? Shouldn't every child have access to compassionate use? Why does the FDA have a god-like voice over who can receive treatment and who can't? Modernizing the FDA to allow the doctors and parents to make potentially life saving decisions for their terminally ill children could lead to a life saved, a new treatment or even a cure that would otherwise never been discovered.

Thank you for your advocacy on behalf of our children. We need and appreciate your help and your voice to make the changes that will save lives.

With high regard,  
**Ellyn Miller**  
Executive Director  
Smashing Walnuts Foundation  
[www.smashingwalnuts.org](http://www.smashingwalnuts.org)

February 21, 2016  
Sen. Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs  
328 Hart Senate Office Building  
Washington, DC 20510

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With high regard,  
**Ellyn Miller**  
Executive Director  
Smashing Walnuts Foundation  
[www.smashingwalnuts.org](http://www.smashingwalnuts.org)



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CC: Sen. Tom Carper

2/24/2016

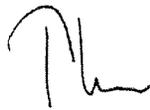
Sen. Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs  
328 Hart Senate Office Building  
Washington, DC 20510

Dear Chairman,

My wife Trickett Wendler, passed March 18, 2015 after a 2 year battle with ALS. When she was first diagnosed, we scoured the country to find the best doctors, medicine, treatments, etc and were sadly disappointed to find the lack of measurable progress made for this horrific disease. In fact, the only "treatment" drug prescribed for my wife was the exact same drug that was prescribed to her father over 20 years ago...literally no progress. Without a known cause or cure, we were resigned to accept the unforgiving certainty of a terminal diagnosis.

I will tell you that once we were out of options, our desire to transform the possibilities became the singular focus of our life. I have three small children with a hereditary gene that predisposes them to this intolerant disease. That is why it is infinitely important to provide patients with alternatives where none exist. The Right to Try provides something that doctors, drug manufacturers, legislators, etc, cannot provide: hope. Sadly, my wife did not have this option, but I write to you today to implore to you the importance of providing hope where none exists. I pray every day that progress is made to find a cure and that my children are not given the same drug that their mother and grandfather were given, but if none is made I pray that my children will have the Right to Try.

Sincerely,

A handwritten signature in black ink, appearing to be 'Tim Wendler', with a stylized 'W' and 'L'.

Tim Wendler

CC: Sen. Tom Carper



## Patient Access to Investigational Therapies

Many states across the country are considering so-called "Right to Try" legislation to provide patients with access to investigational therapies before they are approved by FDA. However, for over two decades, FDA has had processes in place to do just that. Expanded access, which is sometimes called "compassionate use," supplements the clinical trials process. FDA believes enrollment in clinical trials remains the best option for patients wishing to gain access to investigational drugs—it assures adequate protection for patients and leads to the collection of data that could eventually result in FDA approval of the investigational therapy, which provides the broadest availability to patients. Patients who are not eligible for a clinical trial because of where they live, their age, or some other disqualifying factor have the option to seek expanded access if they have serious or life-threatening conditions and no comparable or satisfactory alternative is available.

FDA acts quickly in response to expanded access requests and allows almost all of them to proceed. In fact, FDA authorized more than 99 percent of individual patient expanded access requests received in Fiscal Years 2010-14. Emergency requests are often granted immediately over the phone. For non-emergencies, the Agency strives to respond promptly and, in general, does not take longer than 30 days. Moreover, FDA continues to improve its processes. In response to feedback from physicians that the expanded access form was challenging, in February 2015, FDA announced the development of a new draft form for individual patient expanded access that is estimated to take only about 45 minutes to complete.

Expanded access to investigational treatments requires the active involvement and cooperation of parties other than FDA, including drug companies and healthcare providers. FDA can encourage drug companies to offer expanded access to their investigational therapies, but companies may choose not to do so for various reasons, including lack of available drug or a desire to focus their attention on completing the clinical trials necessary to support FDA approval.

### Facts:

- FDA has a longstanding and well-established process for individual patients to obtain access to investigational therapies—expanded access, which is sometimes called compassionate use.
- FDA allows almost all expanded access requests to proceed: more than 99 percent of individual patient expanded access requests made from 2010-14 were granted.
- FDA responds to individual patient expanded access requests quickly; emergency requests are often granted immediately over the phone. For non-emergencies, the Agency strives to respond promptly and, in general, does not take longer than 30 days.
- FDA is improving expanded access to make it easier to apply; a new proposed form for individual patient expanded access requests is estimated to take physicians only about 45 minutes to complete.

FDA is an important part of the process and helps to ensure patients are adequately protected from unnecessary risk. The independent scientific review provided by FDA is an essential component of patient protection, particularly because one is considering treatments for which safety and efficacy have not been demonstrated.

### Contact Us

For more information, please contact FDA's Office of Legislation at 301-796-8900, or see FDA's website: <http://www.fda.gov/ExpandedAccess>.

Updated: November 2015



**Abigail Alliance for Better Access to Developmental Drugs**

*www.abigail-alliance.org*  
501 (C3) non-profit incorporated in Virginia  
8881 White Orchid Place Lorton, VA 22079 703-646-5306

*Board of Directors: Doug Baxter: David's Father, Cancer Advocate, Gene Krueger: Abigail's Step Father, Cancer Advocate, Anne Agnew: Strategy Consultant Entrepreneurial Ventures., Prince Agarwal: Cap Analysis, Deutsche Bank, Sjaak Vink: Board Member CuresWithinReach, Cofounder myTomorrows, Ron Trowbridge: Chief of Staff U.S. Supreme Court Chief Justice, Executive U.S. Information Agency, College Vice President and Professor Ret.*

**U.S. Senate Hearing  
Connecting Patients to New and Potential Life Saving Treatments  
Committee on Homeland Security and Government Affairs**

Dear Chairman and committee members,

The American people are clearly speaking to the nation about the vital and doable need to bring change at the FDA to allow much earlier approval of promising investigational drugs. This is clearly seen in 24 states so far having past Right to Try legislation.

Tens of thousands of lives could be saved and extended with changes at the FDA, and this could definitely be done without sacrificing good science.

Below is some input from the Abigail Alliance.

I strongly urge you to take progressive doable lifesaving action on this non-partisan issue!

Frank Burroughs  
President  
Abigail Alliance for Better Access to Developmental Drugs

• Frank Burroughs is president of the Abigail Alliance for Better Access to Developmental Drugs, which since 2001 has been pushing the FDA and the U.S. Congress to bring about much needed change to save thousands of lives by getting promising investigational drugs for serious life-threatening illness approved much earlier. His daughter, Abigail, was unable to get access to an investigational drug that was performing well in early clinical trials to treat head and neck cancer. The drug was approved for general use to treat that type of cancer 4.5 years after Abigail's 2001 death. A few hours after Abigail died Burroughs decided he would keep working to expand early access to developmental drugs. "Why should I quit now?" he asked. "There are other people as precious as Abigail."

• Some say the FDA's compassionate use methods work. In reality, they work badly. Currently only 1,000 to 1,200 patients receive FDA approved Individual IND access (compassionate use) annually because most physicians cannot spend the required 100 hours to complete the application. If and when the new FDA shortened form is implemented, that number could potentially quadruple to 4,000 patients. Sadly this represents only a small percentage of patients who need access. Despite the proposed shortened FDA application, many FDA obstacles remain.



• The Abigail Alliance for Better Access to Developmental Drugs has 14 years' experience advocating for earlier access and earlier approval of promising investigational drugs. We have heard from thousands of patients with no further FDA approved options left in their battle to live. These patients do not want indiscriminate access to drugs. These patients and their physicians seek access to investigational drugs with high promise. It may be years before these promising drugs receive FDA approval.

• This statement comes from our [www.abigail-alliance.org](http://www.abigail-alliance.org) homepage:

"Every drug for cancer and other serious life-threatening illness the Abigail Alliance has pushed for earlier access to and earlier approval of over the past fourteen years is now approved by the FDA, unfortunately years after patients tried in vain to get access and therefore died. Not one drug we pushed for earlier access to and earlier approval of failed to make it through the clinical trial process."

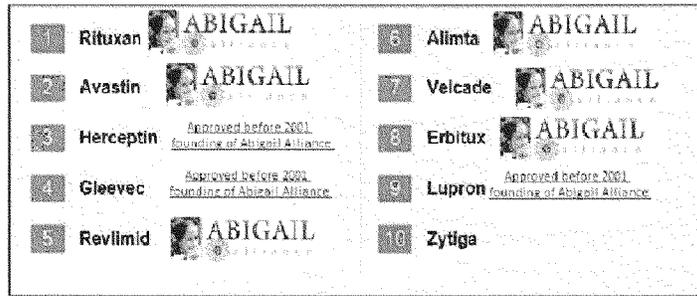
Thousands of lives could have been saved with earlier access and earlier approval.

**Patients fighting for their lives need the 'Right to Try'**  
Of the ten most widely used cancer drugs, the Abigail Alliance pushed for earlier approval of 6 of them!  
(3 were approved before the Abigail Alliance existed)

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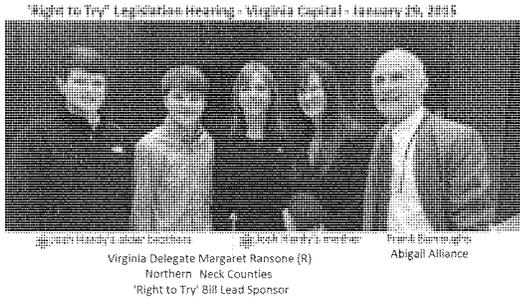
## FiercePharma Top 10 best-selling cancer drugs of 2013

May 29, 2014 Carly Helfand



Note: Abigail Alliance has pushed for earlier access and earlier approval of drugs for serious life-threatening illnesses other than cancer drugs that are now approved by the FDA.

- As the FDA's Science and Technology Advisory Board confirmed in 2007, the FDA could get drugs approved much sooner if the FDA updated its scientific and statistical tools. The Board strongly recommended changes in clinical trial designs and options for a provisional approval mechanism for promising investigational drugs. That report was written nine years ago. The FDA has not yet adopted these recommendations.
- There have been times when investigational drugs have demonstrated significant efficacy early in the clinical trial process, even as soon as Phase 1 and Phase 2 trials. One example from 1999 was a Phase 1 trial for the cancer drug Gleevec for CML leukemia that had 30 of 31 patients in the trial go into remission. Although approved faster than most drugs, there were many people who died waiting for Gleevec's approval. Today, there are similarly promising drugs for Duchene Muscular Dystrophy and ALS. They too may require years for approval.
- There are rare times when the Abigail Alliance and others are able to apply pressure to help a few patients fighting for their lives. Below is an example of one of these successes. Access to the promising investigational drug Josh needed saved his life! Unfortunately only 41 other patients could get the Drug, while others had to wait in vain.



✱  
After much effort, Josh Hardy's (Fredericksburg, VA) 7 year-old life was saved, because he was able to get a promising developmental drug. More children and adult could be saved if we can continue to bring about more much needed change at the FDA. Josh just turned 9!



**This begs the question, what about the children and adults that died, because they could not get this lifesaving drug!**

**Myths**

- *Right to Try would result in a 'Dallas Buyers Club' environment.*

Definitely not true. Efforts to get earlier access and earlier approval of promising lifesaving drugs would be limited to drugs that are in FDA approved clinical trials and are showing significant efficacy. What is very interesting is that the thousands of patients the Abigail Alliance for Better Access to Developmental Drugs has heard from over the past fourteen years are trying to get drugs that are showing significant promise in early clinical trials and are designed for their disease. By the way these are people who have tried and have been unable to get into clinical trials. Only 3% of people who try to get into clinical trials for lifesaving drugs are able to do so.



- *Earlier access to drugs would hurt clinical trial enrollment.*

Not true. Because of the long efforts of the Abigail Alliance for Better Access to Developmental Drugs the FDA is now designing more and more trials for serious life-threatening illnesses that do not have placebo arms. A patient in the clinical trial would be getting the drug along with those outside the clinical trial.

If there is a placebo arm, access to drugs outside clinical trials could be limited to those who have tried and could not get into a trial.

As pointed out in bullet four on page 1, in 2007 the FDA's own Science and Technology Advisory Board recommended earlier access to promising investigational drugs for patients who could not get into clinical trials. Additionally it should be noted that the board's report was very critical of the FDA not using more modern tools and techniques in their clinical trial designs and drug review process, which includes trials designed without placebos.

- *What if a company cannot provide enough drugs to meet the need of patients?*

This can happen, but the few programs (expanded access) that have been run in the past, use a lottery system. One well know third party that has run these programs in the patient advocacy group NORD (National Organization for Rare Disorders).





February 24, 2016

Dear Chairman Johnson and Ranking Member Carper,

Thank you for addressing the issue of barriers to new treatments by holding Thursday's hearing on Connecting Patients to New and Potential Life Saving Treatments. As the nation's largest member-based organization working exclusively on advancing safe and legal access to medical cannabis for patients and researchers, we are all too familiar with research and access.

While agencies within the federal government, such as the Food and Drug Administration, the Drug Enforcement Agency, and others, have been slow to address cannabinoid-based therapies, 40 states have sought to protect patients who use medical cannabis products under the supervision of their physician. Unfortunately, these patients must break federal law in order to find relief and wellness through medical cannabis products. Whether it be in the raw, dried flower form, or extracts for high concentration of certain cannabinoids (including CBD, THC, THCA, and others), federal law prevents patients from accessing these therapies and prevents researchers from learning more about how these products can best treat patients.

Attached, you will find stories of American families who use varying cannabinoid profiles to treat their conditions. Americans for Safe Access (ASA) urges the Chairman and the Committee to take a look at the complete range of cannabinoid profiles when examining barriers to access and research. Limiting THC and THCA from patients only further imposes these barriers. While low-THC, high-CBD extracts will no doubt help a great many patients, many more will be left without relief simply due to the bias against other parts of the cannabis plant.

Many of the families who submitted their stories do not wish to have their names attached to their stories. This is understandable, to admit success as a medical cannabis patient is to admit that you are breaking federal law. This same force prevents many patients from even seeking this potentially lifesaving therapy. Nobody should be forced to choose between breaking federal law or going without potentially lifesaving medicine.

Physicians should have every tool available that can help them treat their patients. If a licensed physician determines in their medical opinion that the potential benefits of a therapy outweigh the potential risks, the patient should be able to undergo that option. We urge the Committee to explore these options. ASA supports the Compassionate Access, Research Expansion, and Respect States (CAREERS) Act, (S.683) because it addresses federal barriers to the full range of cannabinoid profiles.

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**National Office**

1806 Vernon St. NW, Suite 100, Washington DC 20009  
PHONE: 202.857.4272 FAX: 202.857.4273

**California Office**

770 L Street, Suite 950, Sacramento, CA 95814  
PHONE: 916.449.3975

**General Information**

WEB: [www.AmericansForSafeAccess.org](http://www.AmericansForSafeAccess.org)  
TOLLFREE: 888.929.4367

We thank you for receiving these stories and considering them as you contemplate means to lift the federal barriers to cannabinoid therapy.

Sincerely,

Michael Liszewski,  
Government Affairs Director

Beth Collins,  
Communications and Outreach Director

---

**National Office**  
1806 Vernon St. NW, Suite 100, Washington DC 20009  
PHONE: 202.857.4272 FAX: 202.857.4273

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TOLLFREE: 888.929.4367

February 24, 16

Sen. Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs

328 Hart Senate Office Building  
Washington, DC 20510

Dear Chairman,

Medical cannabis has helped my 6-year old son's epilepsy in ways that FDA-approved pharmaceuticals have failed. He had tried 6 different FDA-approved anti-seizure pharmaceuticals, in addition to the ketogenic diet and steroids. He saw 8 different neurologists, including those at Johns Hopkins world-renowned Pediatric Epilepsy Center and Massachusetts General. He used to take 12 different pills every single day.

All of those solutions did not help stop the seizures. He had stitches 7 times from seizure related injuries. Since he was diagnosed at age 1 1/2, he has had over 14,000 seizures.

When my son went on CBD-oil, we noticed an improvement in learning, but no change in his seizure control. Eight days after starting THCa, my son went seizure free and continues to be seizure free for 15 months and counting. He has been seizure free and pharmaceutical free for a week now. His education team and everyone who knows him are truly amazed with his improvement in his ability to learn and participate in the world.

Our state has a legal medical cannabis law that is being implemented. We look forward to being able to give our son the life-saving THCa oil through the legal program. We hope the Federal government will also allow access to this treatment that does not make our son high. We hope to be able to travel outside the state without fear of persecution.

Think for just one moment what it would be like to walk in our son's shoes and please open your hearts and your minds to allow him to get legal, safe access he needs as soon as possible to this life-changing medicine.

Sincerely,

Mom of 6-year old with epilepsy

CC: Sen. Tom Carper

[date]

Sen. Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs

328 Hart Senate Office Building  
Washington, DC 20510

Dear Chairman,

I am writing you asking for medical cannabis to be rescheduled so I can get a law passed to get this medicine here in Iowa. I suffer from chronic back pain and I was diagnosed with scoliosis. I sought out other forms of relief and cannabis eased my suffering. This started was back in 1996 and here it is 2016 and its still an on going issue. I used mostly the dried flowers as my medicine to relief my pain.

The issues with the current state and federal laws regarding medical cannabis and cannabis in general is not only that we have people in jail right now with less than a gram of cannabis, there is no room for the hardened criminals, but also I have noticed a lot of people are leaving their state of Iowa for extended periods of time and even for good because cannabis is not recognized as a legitimate and helpful medicine.

I am able to attest that this medicine does work, and if you and the people in power see the benefits of this simple but helpful plant, not only health wise but the revenue that comes from it, I don't know exactly why it has not been already approved.

Do the right thing and stop the suffering in Iowa.

On a side note July 2014 to June 2015 in Colorado medical cannabis netted almost \$70 million dollars in taxes.... Take that into consideration as you make this **VERY IMPORTANT** decision to save the lives of people who are suffering, and expand the range of people who could be saved from this.

Thank you for your time, and I hope you make the right decision not just for me but for all Iowans who are suffering.

Sincerely,

Chris Albright  
Boone, Iowa

CC: Sen. Tom Carper

2/23/2016

Sen. Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs

328 Hart Senate Office Building  
Washington, DC 20510

Dear Chairman,

My name is Janel McDaniel. I am a 34 year old seizure patient who didn't develop this until I was 31 years old. Think about it from my life. I drove, went to theme parks, was completely healthy until that fateful morning in July 2012 when my life forever changed. When I first got out of the hospital, I was completely sedated for 16+ hours a day. The doctors said "my brain needed to rest" until we knew what happened. I was on 4 medications to keep me asleep. I wasn't allowed to be left alone. I couldn't care for my young kids. We had to sell our house and move in with my in-laws so someone could watch me at all times. The seizures were horrible. We had to give up our independence as a family, give up our home, and not to mention the burden financially and emotionally seizures cause!

Fast forward 3 years later, I have been on 10+ medicines, all FDA approved. I have always worked in the medical field so I knew that I was "supposed to do exactly what the doctor said." I worsened. I couldn't move and would sleep for 24-48 hours after each seizure. My husband held his breathe wondering if this one would be the "final" one as nothing was helping. We removed stress, I couldn't work, I took my meds as prescribed, etc. Anything and everything the doctors suggested we did to try to make them stop. After all, I have no family history or contributing factors as

to why they started. I still worsened and the severity worsened to where I was told last year that I have a 45-50% of dying in my sleep if we can't get control. So more meds were added and back into the hospital I went.

I was then introduced to medical cannabis. At first, I was skeptical. After all, my medical training told me different and I've never even smoked a cigarette, much less done any drugs. It was a far concept for me. But when you are faced with watching your kids grow up or dying, I chose to be here as long as I can. I have tried 4 strains of cannabis oil. The 2 that can be shipped didn't control me. After all, they were developed with kids in mind and that's ok. I then tried a strain with an 18:1 ratio out of CO. I felt amazing! So I started weaning off the Keppra 2000mg, Trokendi XR 600mg, Valium 20mg, and Vimpat 600mg that I took daily. Amazing enough, I was able to wean off ALL meds and still have seizure control on R4. Then I couldn't get access to R4 any longer so I found a place similar in CA. This involves driving to CA, breaking the law, and no testing but it was the strain I need so I had to try.

The first month, I had a few seizures. The first thing I noticed was my short term memory returned and people said I wasn't repeating myself like I was. I felt better but not 100% because I was having break through seizures. My type of seizures changed immediately. I went from 5+ minute seizures where I was unconscious to seizures less than 20 seconds and the major difference is I could hear people in the room, although I still couldn't see them. This helped comfort level wise since I never knew before. I remember thinking this is a miracle! I was still having some break through seizures so it was recommended that I add thca. I am one of the few that regular thc as a rescue triggers cluster seizures in me. I felt like I was normal again. Day after day passed after starting the thca with the oil. 30 days seizure free came!! I was for sure I would drive again and be able to go back to nursing. After all, I can't

be running an IV on someone and have a drop seizure. I was able to return to work, although not nursing yet, and most importantly, I was able to function as a mother, the only true title I ever wanted in life.

FDA approval for medicine is something I've learned means nothing. As a nurse that worked Pediatrics, I see what they are doing. The FDA approved Tamiflu for ages 2 weeks old and up but yet you can't give Tylenol before 6 weeks old and Motrin before 6 months old! Then OxyContin for 11 year olds? A while back Loratab was not recommended for kids because of the respiratory depressant effect yet OxyContin? OTC cough meds are still not recommended for under age 2 yet Tamiflu is? That is unbelievable. Then I started researching. Cocaine and methamphetamine are schedule 2!! Yes you read that right!! I struggled as a nurse to go against what I was taught but it opened my eyes to how twisted things are. Do you know how things are removed from the FDA schedule? People die! That's insane!!

I can't fathom how people can't understand. Nicotine and alcohol kill hundreds of thousands a day. Cannabis-0.

Now Georgia strips in state cultivation, which was someone like mine last hope. See, my last batch from CA was bad. It made me violently sick! I can't even tell you everything that happened because I don't remember until 5 days later. But I'm desperate. Desperate to live to watch my kids grow. Moving out of state is not an option for me. I share custody of my oldest child with my ex-husband and I won't leave my son behind. So my choices are to keep breaking the law (which I have never done before now), stop cannabis oil and go back to how I was, or beg for mercy! I chose mercy and grace. I respect the law but I love my kids. How do you choose? I've now had the experience of a bad batch of cannabis and I never want to feel it again! It was scary.

No medicines controlled me, but cannabis has given me longer periods of normalcy. Normalcy-a word that so many take for granted yet I have to pray and strive for! Life, liberty, and pursuit of happiness. Inalienable rights we were given by our founding fathers. Why am I and so many other being denied this by keeping us sick with seizure meds?

I didn't ask to get sick but i ask for the medicine to help me. Allow me to be an adult. Don't let my worst fear of death happen when there are other choices. Fear of change affects us all including me. But this is a change that saves lives! All laws were meant to be re-examined. Please reconsider. Don't wait until it's too late.

Sincerely,

Janel McDaniel  
Flowery Branch, GA

CC: Sen. Tom Carper

February 22, 2016

Sen. Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs

328 Hart Senate Office Building  
Washington, DC 20510

Dear Chairman,

I am a resident of Massachusetts and I am writing today about medical marijuana and legalization. I have researched medical marijuana since it became legal in Massachusetts. I am a chronic sufferer of pain, severe muscle spasm, nerve injury, and a long list of allergies to things in the everyday environment including mold, mildew, dust mites, and multiple-chemical sensitivity to name a few. In 2014, as a direct result of too much prescription medication for pain I landed in the hospital ER ICU overnight. That was a wake-up call that led me to start a dialogue with my long-time personal physician about the possible benefits of treatment with medical marijuana. One of the things that I learned in my personal research was about the wide variety of medical and quality of life benefits to cannabis. Nonetheless, I have come to realize that the benefits and uses of cannabis do not always qualify for a prescription. As a law abiding and upstanding citizen, I believe that this makes removing legal barriers to medical and scientific research critical. As a nation, we seek to improve the quality of life for all citizens, and insure our laws truly reflect public policy throughout America. However, here is how the current conflict between state and federal laws regarding medical cannabis affects me, I have learned that even if my doctor prescribed medical marijuana, or when it becomes legal under the current legislative initiatives in Massachusetts I still would not have access because I live in Federal public housing. My lease is subject to Federal laws concerning marijuana, and my understanding is that would give my housing authority a cause to evict me for marijuana use or possession.

That is why I am writing in support of Americans for Safe Access and submitting my story for them to present at the hearing on "Connecting Patients with New and Potentially Lifesaving Treatments." It is clear that the American people are committed to legalization and reform. The list of states legalizing cannabis for personal and medical use is steadily growing. The legislative direction of these states and the majority of their citizens make it clear that the current legal status of cannabis at the Federal level is at odds with the vast majority of Americans and their elected officials.

Moreover, the medical communities from the doctors who recommend and prescribe cannabis to our top Federal regulators are making it clear that cannabis has a long and growing list of medical applications from opioid treatment to combating deadly seizures in adults and helpless children. A

global community of researchers and doctors is producing an endless flow of data proving that cannabis is an untapped resource that we have only just begun to exploit to its fullest potential.

Shortly after my hospital stay, I lost my job. Over the past two years, I have completed a training program through my state unemployment assistance office. Now that I am re-entering the job market obtaining the treatment of my choice would leave me fearful of losing my job because of medical cannabis treatment. The existing conflict between state and federal requirements leaves employers with no choice except to report and terminate patients for cannabis use. So please, look at the facts relative to the legalization issues and honestly weigh the cost of legalization with the benefits to society, patients, and the Government's interest. We are the government's ultimate beneficiary or victim in the decisions that you make to support, or not support, legalization and reform.

The things that I have learned about the benefits and uses of cannabis over the past years have made me an advocate for legalization. I follow the battles of ordinary law abiding hard working Americans as they struggle with outdated laws, misguided law enforcement, and misinformed bureaucrats. I cannot express how sad it makes me to read story after story about children and elderly patients losing their battles with illnesses that researchers have already proven are treatable with cannabis. I do not understand how my federal government can argue endlessly on principle while children and their parents in states across America suffer without treatment as doctors and legislators plead with the DEA, FDA, and Congress to act. I hope that you will act in support of Federal cannabis legalization for me, and millions of Americans. It is time to stop the needless suffering, it is time to stop ruining American lives, and it is time to stop ruining American families.

Sincerely,

Curtis Chambers  
Wayland, MA.

CC: Sen. Tom Carper

February 24, 2016

Senator Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs  
328 Hart Senate Office Building  
Washington, DC 20510

Dear Chairman,

This letter is to ask for your help in addressing the FDA's barriers to accessing medical cannabis for seriously ill patients and patients with chronic conditions--including epilepsy--and their families.

Our 11 year old daughter Rachel has intractable (drug-resistant) epilepsy. She has both big seizures that don't end on their own (every one of her big seizures is a medical emergency necessitating use of a rescue medication--Diasat, a Federal Schedule IV controlled substance), little seizures (atypically atypical absence--otherwise known as dialeptic seizures), a continuous spike in her frontal lobe, and two kinds of subclinical seizures. She can have up to 50 seizures a day of the sort we can see; her subclinical seizures--which we can't see--are in the too many to count range.

Rachel is under the very best of care--being treated by an experienced epileptologist who is also a medical school professor and who works out of a Children's Hospital with a Level 4 Epilepsy Center (the highest rating). Despite this excellent care, Rachel's epilepsy has not been able to be successfully controlled by current antiepileptic drugs (AED's). Her very experienced epileptologist calls her his poster child for what can go wrong with AED's. Three trials of AED's have resulted in a classic drug eruption, the beginnings of DRESS Syndrome (which carries a 10% mortality rate), and severe behavioral issues--simply put, under one of the AED's our normally very sweet, loving child became hostile, standoffish, and aggressive (yelling at us, throwing things at us, and literally attacking us physically). The fourth trial of an AED (her current medication--which is a Federal Schedule V drug) has resulted in long term severe nausea and intestinal pain. None of these drugs stopped her seizures. In fact, each one has simply exacerbated Rachel's seizures to varying degrees.

Because of her AED related rashes, many other AED's can't be tried because of the very real risk (documented with medical studies) of cross-sensitivity and the likelihood that she'll develop another serious rash--perhaps one with an even higher mortality rate. Her doctor says her case is very unusual, very complex, and very challenging. Despite all her seizures, she is a very normal, very bright,

very social, and very upbeat little girl. She just wants to be able to have a normal childhood and worry about normal childhood things. Cannabis could be so helpful in achieving that.

Rachel's epileptologist has talked to us about about medical cannabis. Cannabis would NOT present the difficulties that the other AED's present in terms of rashes. Its mode of action is totally different from other AED's. It helps the brain find the balance between excitation and inhibition--and unlike normal AED's, cannabis works through secondary pathways in the brain, not primary ones. It's a gentler, kinder medication. But we can't access cannabis in the state of Alabama at this point without fear of criminal prosecution.

We have no idea what the future holds for Rachel. We've already pursued genetic testing through Baylor University; they found no explanation for her epilepsy. Rachel will begin more extensive testing this summer to see if she could be a surgical candidate, but only 2% of children prove to be good candidates. We are starting to realize that if her epilepsy continues to be intractable that we may have to consider moving to a state where cannabis can be more easily accessed. This would be very sad as my husband is a law professor who would have to leave his job; our family and friends are here in Alabama where we've been for nearly 30 years. The thought of trying to smuggle bottles home across state lines is disturbing. We don't want to have to break the law to help our child have a chance at normal life.

Of course, if medical cannabis were rescheduled so it were no longer a Schedule I drug, it would help immensely. Families like ours need your help. Please help us access cannabis for our children!

Sincerely,

Desiree Smolin  
Birmingham, Alabama

CC: Senator Tom Carper

February 24, 2016

Sen. Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs

328 Hart Senate Office Building  
Washington, DC 20510

Dear Chairman,

Our family moved to Colorado in March of 2013. My husband and I had reached the end of Emily's pharmaceutical rope. She had failed over 14. There were no more meds that we could try. Her neuro said this is the best we can do. The best they can do was four antiepileptic drugs scheduled, a special highly control diet called the ketogenic diet, and 3 prn (as needed) benzodiazepines that she took daily. Emily was only 3 and was having over 100-200 seizures per day. The worst made her oxygen plummet to the 50-60's and she would gag and vomit as she violently flailed on the living room floor. She was in a palliative care program through our local hospice. She was not a brain surgery candidate. We had no hope. When we saw kids having success on cannabis oil in Colorado we knew we had to try. Bankrupt, jobless, and scared we moved. We were alone and isolated from family.

It was so hard on us but our love for our beautiful girl outweighed our fear. Emily's worst seizure stopped on April 2, 2013 with her first dose of cannabis oil. It was a 14:1 ratio of cbd:thc. As time went on the company who made Emily oil kept increasing the ratio to wean out the thc so it could be classified as hemp and be shipped. Emily lost more and more seizure control as the ratio got higher. We started adding thc back in and regained the seizure control that we lost. Fast forward to 3 years later. Emily's seizures are great. Less than 10-15 split second seizure per day. She is on zero seizure medications. Just cannabis oil. She doesn't sleep well in spite of trialling many prescription sleep medications. I decided to try just thc at night to see if it helped her sleep. It helped her sleep a little better but the biggest thing we noticed was her seizures stopped! After the first week my husband and Emily's day nurse kept looking at each other in shock! Did she just go a week with out a single seizure?! She went 28 days before she had a small little myoclonic jerk. She is averaging 2-3 weeks between seizures now and they are usually just a split second jerk.

Emily now only takes a small dose of a high thc low cbd oil each night.

While this is amazing and her developmental progress has been great lately too it's hard because we can't take her thc oil out of the state. Colorado is our island now. When she used "hemp" oil we could travel but now that hemp didn't help we are forced to stay put if we want to control her seizures.

I wish everyone had safe access to the full spectrum of cannabis oil. Had we not been in a legal state and we able to try a high thc oil Emily may not be doing as well as she is.

I am so thankful for her medication.

Sincerely,

Erica Rollins  
Colorado Springs, Colorado

CC: Sen. Tom Carper

February 24, 2016

Sen. Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs

328 Hart Senate Office Building  
Washington, DC 20510

Dear Chairman,

Jennifer Collins of Fairfax, Virginia is 16 years old and suffers from Jeavons syndrome and can have up to 300 or more absence seizures a day. Her seizures would often cluster and cause tonic clonic seizures as well. She tried and failed 15 anti-epileptic medications, but either they didn't work, or the side-effects were unbearable.

These side effects of her medication included rages, cognitive functioning issues, depression, weight gain, and ovarian issues, to name a few. Her rages, caused by her medication, had gotten so bad, that on several occasions her parents had to call 911 to help me subdue her. This was not the happy-go-lucky child everyone knew and loved, and it was devastating for her. She couldn't control it, and she wanted to hurt herself.

Out of options, her mother spoke with Jen's neurologist about trying cannabis as a treatment, and he said, "if I could legally obtain this for you here, I would. It is worth a try." So, in December of 2013 to Jennifer and her mother moved to Colorado, separated from her father, sister, extended family, friends, and support community to give her the opportunity to try cannabis.

The Collins family didn't make this decision lightly. They left to give Jennifer the opportunity to find relief from her seizures, and the harmful side effects of her medications through medical cannabis. They stayed in Colorado for on year.

While in Colorado, Jennifer started taking non-psychoactive Tetrahydrocannabinolic acid (THCa) oil, a tiny amount administered by a syringe under her tongue three times a day. Not only did her absence seizures lessen drastically and her tonic clonic seizures disappear, but she was able to lower the doses of her pharmaceutical medications. The rages stopped, the thoughts of suicide stopped, she lost the 30 pounds she had gained upon starting medication, and her cognition and school grades improved.

The stress of living apart from her father, sister, friends and family was too much for Jen, who fought so bravely to fit in and make friends in a somewhat unwelcoming environment. So the family was again faced with a heart breaking decision. They chose to go back to Virginia and fight for the right to take her

oil in Virginia. They and put their faith in their lawmakers to pass a law that would allow her take the medicine that helps her in the home where she grew up, surrounded by the people that love her.

Jennifer fought hard for the bills that Senator Dave Marsden and Delegate Dave Albo wrote to give people like her with intractable epilepsy the ability to take Cannabidiol oil (CBD) or THCa to treat their seizures without fear of prosecution. The bills were passed and signed into law by Governor Terry McAuliffe in February of 2015.

Unfortunately, the current law does not provide for any form of production and distribution of the cannabis oils Jen and others like her in Virginia need. So, once again she is working on helping pass Senator Marsden's bill, SB701 that will allow tightly controlled production of CBD and THCa oils in the state. In addition, she has been speaking to members of the U.S. Congress trying to get the Senate and House CARERS Act bills passed. The CARERS Act would, among other things, reschedule cannabis to schedule 2. It is now a schedule 1 drug (reserved for the most dangerous drugs that are deemed to have no medicinal value) and remove some of the barriers to important research on this plant.

Jennifer has been an inspiration to many people, especially those suffering from intractable epilepsy who need this medication. She has not had a tonic clonic seizure since starting cannabis oil two years ago. In addition, she was able to wean her pharmaceutical medications down to 1/12 of one, and 1/3 of the other and no longer needs rescue medication. Jennifer should not have to fight so hard to legally take a medicine that has improved her life so much.

Sincerely,

Beth Collins  
Fairfax, VA

CC: Sen. Tom Carper

February 22, 2016

Sen. Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs

328 Hart Senate Office Building  
Washington, DC 20510

Dear Chairman,

I suffer from Severe Chronic Pain due to Degenerative Disc Disease, Cervical Spondylosis, Stenosis and Arthritis. I have had 5 spinal fusion surgeries (fused from C-4 to T-5) and also have a spinal cord stimulator implanted in my neck, and it's battery pack in my back. None of these surgeries have helped with my pain. Opioid "Pain Killers" and Muscle Relaxers have also been useless and caused terrible side effects, such as Agitation, Depression and Disruption to Sleep due to violent muscle jerks.

I have been to Surgeons and Pain Management and All have told me "There is Nothing More We Can Do For You". I searched the Internet for any answers and the only thing I found, over and over was Medical Marijuana. I have Never used an Illegal Drug and had never even gotten Drunk.

I am a 45 year old Husband and Father of 2 Wonderful Teens. I am Retired on Disability because I can no longer sit at a computer without being in sheer agony. This has placed me in a very Depressing and Desperate Situation. For the past 8 years, I have been unable to take part in many family activities, missing out on trips, concerts and vacations, even Movies became too painful to endure.

Last year, I went to one of my Doctors and discussed Medical Cannabis and was told that it was being worked on in Maryland but could be over a year before Dispensaries are opened. One of the Nurses Bluntly asked "Why don't you just try it? Then you would know to pursue it when it is available." I took her advise and purchase a very small amount to see for myself. I only took a few puffs and soon was feeling relaxed pain relief!! For the first time in over 7 years I experienced ZERO Pain while sitting in my Recliner!!

I never dreamed I would See Marijuana (Cannabis) as a "Medication" but after So Many Failed Procedures and Pharmaceuticals that had horrible side effects, there is No Other Option. Medical Cannabis is not yet fully Legal in Maryland, but is the Only thing that has given me Hope! Decriminalizing it is all fine and good, but I still have to FIND my "Medicine" in a not so safe way, and buy tiny amounts that are quite expensive. There is no way to know what is in what I get, let alone, if it is a strain that will help me. Even though todays batch worked, the next time may be something totally different. I have dealt with ones that make my heart race to ones that make me extremely lazy and some that give very little relief. Spending that kind of money on a useless strain is very frustrating. I look forward to the day a dispensary opens here so I can get the High CBD Strain that I need, but for now, I will do what I Need to do to achieve relief.

Last year a dear friend of my family committed suicide. He was a 71 year old Husband and Father that was suffering from advancing stages of Parkinson's Disease. I admitted to my wife that I, unfortunately, could understand the mentality that brings a person to that awful decision, because I had been Way Too Close to that Edge. Cannabis Pulled Me Back From That Edge!!

There was No Hope!! I am only going to get worse. Doctors have failed me. Surgeons have failed me. Pain Medications have failed me, causing horrible side effect, such as severe myoclonic jerks, from narcotic pain medicine and muscle relaxers. While falling asleep, I would Jump and smash my hand into my nightstand or even hit myself in the face. I have also dealt with extreme mood swings that scared my family. Even Advanced Medical Technologies have failed me. The Spinal cord stimulator did not offer any relief to the worst areas of my pain. Being Repeatedly Told "There is Nothing I Can Do For You" takes a person to a Terrible Mental State...

Medical Cannabis has allowed me to go out for a couple hours at a time before I am unable to stand the pain. I was recently able to attend my Daughter's Marching Band Competitions without being in excruciating pain. I have also been able to go out to restaurants and movies again!!! I am getting to Live Again and my wife told me: "I HAVE MY HUSBAND BACK!" All from something I Absolutely Despised!!! Cannabis IS the Miracle Medicine everyone has been looking for!! The Government needs to Recognize That!!

Sincerely,

Stephen T. Qualey  
Millersville, Maryland

CC: Sen. Tom Carper

February 21, 2016

Sen. Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs

328 Hart Senate Office Building  
Washington, DC 20510

Dear Chairman,

Hi my name is Raymond F Smith I had a bad accident a few yrs back in which I lost my 6 yr old son. I accidentally backed over him and took his life. I was devastated. I used marijuana for post traumatic stress syndrome. It was a life saver as I was raising my 2 boys by myself at the time. It helped me forget about everything but what was important at the time. It helped me run my business and perform my daily duties with out losing it and the repeat of that days occurring nightmare. PTSD is for real and marijuana was the only thing that eased the pain of my loss.

The side effects of marijuana are not physically disabling and yes you can still function fully and get through your daily lives and be vary productive. Marijuana is a God send. It is all natural and the chemical in it matches a chemical in our brain, and by being able to enhance that chemical gives instance release from the pressure of the bad thoughts in your mind. I thank God for this wonder drug and I have had to use it illegally thus causing me to have a run in with the law because of it being illegal. I live in Burlington Iowa and pray that the legislators will get on board and read the research that is proven by using this natural drug.

Sincerely,

Raymond F Smith  
12673 Flint Bottom Rd Burlington Iowa 52601  
CC: Sen. Tom Carper

Tuesday, February 23, 2016

Sen. Ron Johnson  
Chairman  
Senate Committee on Homeland Security and Governmental Affairs

328 Hart Senate Office Building  
Washington, DC 20510

Dear Chairman,

It is with great honor that I have the opportunity to share with you the success my daughter has had with cannabis. At 6 weeks old, our sweet Magdalyn began having seizures. By 4 ½ months old, we were told she probably wouldn't live very long. She tried pharmaceutical after pharmaceutical, with minimal impact on her seizures, yet devastating to her development. Statistically, she had less than .8% chance of finding a pharmaceutical that would effectively treat her seizures. At 17 months, out of options, we decided to move across the country. We relocated to Colorado, away from family and a tremendous support system at our church in Tennessee. That was the toughest but best decision we ever made. Though she has yet to find complete seizure freedom, she is thriving.

When we relocated, Maggie had over 500 seizures per day and significant global developmental delays. Nearly any movement she made was a seizure of some sort. She was critical. We saw an instant response to starting her on Charlotte's Web oil. Her digestion picked up and she began to vocalize more. We continued to slowly wean her off the pharmaceuticals. We added THC-A oil to her regimen and her cognition picked up. Over the past 2 years, she has been able to express herself, develop more and more control with her body, and her seizures have decreased by over 80%! That is phenomenal given her prior critical condition. Most recently, we began using a transdermal THC patch that has provided even further seizure relief.

After substantial exposure to both pharmaceuticals and supplements, as well as over 2 years of administering cannabis to our daughter, I am convinced that cannabis works much more like a supplement than a pharmaceutical. The treatment continually needs to be varied in order to support her body's systems, versus chemically altering her body. It is an individualized medicine.

Unfortunately the federal and varied state laws create a major predicament when wanting to visit family and friends throughout the country. It is outlandish to me that we are limited in our ability to travel and could face prosecution solely for helping our daughter find more seizure relief.



We are beyond blessed for the opportunity that we have had to simply enjoy life with our now 3 ½ year old daughter. The reality that she is in preschool this year, and we haven't had to bury her yet is a testament to just how beneficial cannabis oil is. As a family, we continue to pray for legislators' clarity and education on this issue.

Sincerely,

Rachael Selmeski  
Castle Rock, CO

CC: Sen. Tom Carper

**Post-Hearing Questions for the Record  
Submitted to Ms. Darcy Olsen  
From Senator Claire McCaskill**

**“Connecting Patients to New and Potential Life Saving  
Treatments”**

**February 25, 2016**

- Q. How can the FDA improve the Accelerated Approval process to ensure access to life-saving treatments, while also maintaining public safety?

Under the Accelerated Approval process, the actual research time may be shorter than the standard FDA approval process. However, Accelerated Approval does not reduce the time delay in the negotiations that take place between the sponsors and the FDA on what is required to be considered for a review. This process can take many months or, in some cases, years. (This time delay is not officially tracked by the FDA.)

The obstacle seems to be the FDA interpretation of what is sufficient to be considered for an acceptable NDA filing, as well as what constitutes a positive review under the Accelerated Approval pathway. In order to further improve the Accelerated Approval process, steps should be taken to reduce the time spent on the negotiations that take place between the sponsors and the FDA on what is required to be considered for review which does not contribute as significantly to patient safety (compared to actual safety testing). The parameters for what is sufficient for an NDA filing and what constitutes a positive review could be defined legislatively, giving both the FDA and NDA applicants clear parameters for both.

Another distinction from the standard FDA approval process is that, under Accelerated Approval, post-marketing study of clinical outcomes must be conducted and must show meaningful therapeutic benefit over existing treatments (or placebos). If, according to the FDA, a meaningful therapeutic benefit is not shown, the drug can then be rejected.

The ability of the FDA to reject a drug post-approval under the Accelerated Approval process should be more closely examined. Possible reforms could include creating a less-restrictive definition of "meaningful therapeutic

value." This would not impact patient safety but would offer physicians more available treatments for patients.

A particular treatment might be rejected because it only helped 10 percent of patients. But rapid advances in medicine might now show, for example, that the same treatment helping 80 percent of patients with a specific genetic makeup.

Distinct but related designations that are intended to accelerate the FDA drug approval process include Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval.

Q. How have fast tracked drugs been specifically beneficial to adults and children with chronic conditions?

Of the 76 Fast Track drug approvals that occurred from 1998 through June 1, 2010, more than half (43) of the approvals were for the treatment of HIV. While most treatments are not specifically indicated for children (resulting in the vast majority of treatments for children prescribed off-label), only one approval during this time period was for pediatric patients (relapsed or refractory acute lymphoblastic leukemia).

Of the six novel drugs approved under Accelerated approval in 2015, five were for cancer diseases (of which there are more than 200): Alecensa (advanced (metastatic) ALK-positive non-small cell lung cancer), Darzalex (multiple myeloma), Farydak (multiple myeloma), Ibrance (advanced (metastatic) breast cancer), and Tagrisso (advanced non-small cell lung cancer).

One question that deserves further investigation is whether the Fast Track designation is being under-utilized for rare and terminal diseases (other than cancer).

## EXPLORING A RIGHT TO TRY FOR TERMINALLY ILL PATIENTS

THURSDAY, SEPTEMBER 22, 2016

U.S. SENATE,  
COMMITTEE ON HOMELAND SECURITY  
AND GOVERNMENTAL AFFAIRS,  
*Washington, DC.*

The Committee met, pursuant to notice, at 10:04 a.m., in room SD-342, Dirksen Senate Office Building, Hon. Ron Johnson, Chairman of the Committee, presiding.

Present: Senators Johnson, Paul, Lankford, Ayotte, Ernst, Sasse, Carper, McCaskill, Tester, and Peters.

### OPENING STATEMENT OF CHAIRMAN JOHNSON

Chairman JOHNSON. Good morning. This hearing of the Senate Committee on Homeland Security and Governmental Affairs is called to order. I want to welcome all of our witnesses and all of our audience members.

This is the second hearing we are holding on issues related to a bill I introduced called “Right to Try,” and I will ask unanimous consent (UC) to have my written statement entered in the record.<sup>1</sup> I will keep my comments brief because I want to show about a 3½-minute video as my true opening statement.

On Saturday, I attended a Walk for Amyotrophic Lateral Sclerosis (ALS) in Appleton, Wisconsin. I think that so many of us first heard about ALS as Lou Gehrig’s disease, and then later, on Tom Watson’s caddy. And, in my own personal experience, a member of our Lourdes High School family, Doug Perzorski, was diagnosed with ALS. His wife, Meg, and their children—unfortunately, we lost Doug a couple of years ago.

And, then as a U.S. Senator, a couple of years ago, I met a young mother of three, Trickett Wendler, and I had just met with the Goldwater Institute, and I knew of their efforts trying to pass “Right-to-Try” bills in States like California and elsewhere. Just by mentioning my interest and my support for “Right to Try,” tears started streaming down Trickett’s face.

On Saturday, I met a number of patients fighting ALS, and their families fighting with them. There was a family—and three of the siblings were suffering from Familial ALS (FALS). One had had it for 15 years—it is a slightly different condition when it is that kind of hereditary ALS.

<sup>1</sup>The prepared statement of Senator Johnson appear in the Appendix on page 281.

We have Matt Bellina. We also have Frank Mongiello, who provided such incredible testimony when we had our press release on this, and so, Frank, welcome to you. In a nutshell, this effort—if it were up to me, I would not call it “Right to Try.” I would call it “Right to Hope.”

And so, what I would like to do now is offer a 3½-minute video by Dr. Ebrahim Delpassand. I consider Dr. Delpassand a whistleblower. He is a courageous doctor. He is board-certified in nuclear medicine. He has a residency at Baylor, where he had his residency at Baylor College of Medicine, and was formerly at the University of Texas MD Anderson Cancer Center (MD Anderson) for 12 years, where he was the chief of clinical nuclear medicine. In 2003, he joined the private oncology center Excel Diagnostics. He is an adjunct professor at the University of Texas Medical Branch—a highly qualified doctor.

In 2005, he began investigation for a new drug to treat neuroendocrine cancer—carcinoid cancer. A newer version was later available, which meant there was another approval process from 2007 to 2010. In August 2010, he began treating patients with a therapeutic agent called Lu-177 Octreotate. In March 2015, he treated 143 of the 150 patients allowed. He requested the Food and Drug Administration’s (FDA’s) permission to expand the trial and add another 100 patients. By this point, the manufacturer had completed its multicenter trial and was in the follow-up phase to observe the progression of the condition. In other words, the clinical trials had completed enrollment. The FDA cited commercialization concerns in denying the request.

So, I would like to just play the video now.

[Videotape shown.]

Now, I consider Dr. Delpassand a hero. I consider him a whistleblower. He is taking great risk operating under Texas’ “Right-to-Try” law, trying to save his patients’ lives, but also giving and offering his patients hope.

Now, I spoke with the representatives of the ALS community, here. Obviously, Dr. Delpassand is dealing with cancer patients. We also have Jordan and Laura McLinn. Jordan has Duchenne Muscular Dystrophy (DMD). Now, I was overjoyed on Monday to find out that the FDA finally approved a drug to give these little boys with DMD their right to try—their right to hope. So, that is really what this is all about.

Now, next week, I will be asking the U.S. Senate to approve the “Right-to-Try” bill under a unanimous consent request. We have cleared it on our side—and, obviously, one of the goals of this Committee is to provide powerful testimony and to convince every U.S. Senator, if they are not willing to cosponsor it—I would certainly love their cosponsorship of this very simple bill that just allows these State “Right-to-Try” bills to operate and that allow heroes like Dr. Delpassand to give their patients hope. If my Democratic colleagues and other Republican colleagues that have not cosponsored it are not willing to cosponsor it, please do not object so we can pass this bill and so we can give these patients and their families the right to hope.

With that, I will turn it over to Senator Carper.

**OPENING STATEMENT OF SENATOR CARPER<sup>1</sup>**

Senator CARPER. Thank you so much Mr. Chairman and thank you for calling this hearing today. I appreciate your willingness to continue a conversation about what we all know is an important issue that is critical for Americans seeking access to potentially lifesaving treatment. I also want to thank you and your staff for the ongoing work that we are engaged in to try and move the ball forward and to find ways to help patients gain expedited access to experimental therapies, including through a forthcoming Government Accountability Office (GAO) report on these issues. I especially want to thank our witnesses. It is a great honor to welcome you here. I especially want to say to Matt Bellina, Lieutenant Commander (Retired), an A-6 pilot, Navy salutes Navy this morning. And, I am delighted to see you here. It is a real treat to meet you.

I also want to single out, if I could, Andrew McFadyen's wife, Ellen, and their son, Isaac, who is being treated for Mucopolysaccharidosis (MPS), and his brother, whose name is Gabriel. Gabe, it is nice of you to be here with your mom and dad.

And, to all of our other witnesses that are here, thank you for joining us. It is great to see you.

Before I begin my formal statement, I just want to take a moment and mention my appreciation for the Chairman for sharing the video that we have just seen and I look forward to learning more about this physician's experience. My understanding is that, in what would seem to be similar situations, the FDA has approved over 99 percent of patient applications for expanded access to these new experimental treatments. In fact, I understand the FDA has even granted drug approvals based solely on expanded access data, even for drugs that may be in Stage II trials—or even in Stage I trials. The FDA, as you know, by law, is precluded from discussing the details of any drug under review, but, if the doctor that we have just heard from today were here, I would ask him why he did not appear to use the expanded access program, which has worked quickly and efficiently for so many patients and their doctors. With that in mind, I would like to ask unanimous consent that we place an FDA fact sheet<sup>2</sup> on expanded access, along with the recently updated application form, in the record.

Chairman JOHNSON. Without objection.

Senator CARPER. Thank you.

My understanding is the application form for expedited access is a form that previously took hours to complete, I have heard as much as 10 hours—maybe even more. The expedited updated application form, I am told, takes 45 minutes or so, which has been one of the barriers for folks to actually take advantage of this opportunity.

But, today we are going to have an opportunity to hear from the FDA, State representatives, patients, loved ones, and other advocates on ways we could improve access to experimental medical treatments—something we all want to do. These individuals and their families have faced some of the most difficult and painful

<sup>1</sup> The prepared statement of Senator Carper appears in the Appendix on page 282.

<sup>2</sup> The FDA Fact sheet submitted by Senator Carper appear in the Appendix on page 314.

challenges anyone could face. They deserve to be heard—and they deserve better access to experimental treatments.

We will also have an opportunity today to review the Chairman's legislation, S. 2912, which he has alluded to, the Trickett Wendler "Right-to-Try" Act. I appreciate the intent of Senator Johnson's bill—I think we all do—and I, certainly, support expanding access to experimental therapies for terminally ill patients.

We must keep in mind, however, that there is, already, what I understand to be an effective framework in place at the FDA for giving patients access to experimental drugs while those drugs are still being tested. The agency has given an extraordinary level of attention to the requests of patients with life-threatening conditions. In fact, I am told it has approved, as I said earlier, more than 99 percent of requests for emergency treatment between 2010 and 2015. The agency has also taken constructive steps to greatly simplify its application process and further improve and streamline patients' access to experimental treatments.

Despite the high approval rates and ongoing reforms, I understand that the FDA believes that more can be done and is continuing to work to further improve patient access to experimental treatments—and we applaud that. I hope to learn about some of those steps today, as well as some additional ideas for how to ensure that all patients in need have the information and the resources needed to access experimental medicines.

For terminally ill patients and their loved ones, safe and effective treatments cannot come quickly enough. That is why we need to do everything we can to give patients, doctors, and the companies that make these drugs the tools they need to participate in clinical trials, utilize the FDA's expanded access programs, and develop new treatments as safely, effectively, and quickly as possible. I hope that our Committee can help with these efforts and work with patients, health care providers, the pharmaceutical industry, and the FDA to ensure that all patients and their families can access safe and effective treatments as quickly as possible.

Again, I want to thank our witnesses and their families for joining us today, and for your willingness to share your stories and put forward possible solutions to these challenging issues.

Thank you so much.

Chairman JOHNSON. Thank you, Senator Carper.

I will note that the video that we played is just a condensed version of a 20-minute video that we will enter into the record and that will be available on our website. Dr. Delpassand wanted to be here—but he had a medical emergency, I guess, with his mother—so he could have answered those questions.

It is the tradition of this Committee to swear in witnesses, so if you will all rise and raise your right hand. Do you swear the testimony you will give before this Committee will be the truth, the whole truth, and nothing but the truth, so help you, God?

Mr. BELLINA. Yes.

Mr. CALDERON. Yes.

Mr. NEELY. Yes.

Mr. GARR. Yes.

Mr. MCFADYEN. Yes.

Chairman JOHNSON. Thank you. Please be seated.

Our first witness is Matthew Bellina. Mr. Bellina is a former U.S. Navy aviator, retiring at the rank of Lieutenant Commander. He received his commission in 2005 after graduating from Virginia Polytechnic Institute and State University (Virginia Tech). In April 2014, he was diagnosed with ALS. He is a husband and a father of two boys, with another on the way. Mr. Bellina.

Senator CARPER. And, if any of your family members are here and you would like to introduce them, please do. And, that is for all of the witnesses.

**TESTIMONY OF MATTHEW BELLINA,<sup>1</sup> LIEUTENANT  
COMMANDER, U.S. NAVY (RETIRED)**

Mr. BELLINA. Thank you so much, Senators. And, thank you for having me. I would like to introduce my family. My kids are the boys that were making noise while you were speaking—and I apologize.

Senator CARPER. I would have been afraid, when my boys were their ages, to have brought them to a hearing like this. [Laughter.]

Mr. BELLINA. Yes, it was risky, but I did not want them to miss it.

Senator CARPER. They are doing great.

Mr. BELLINA. It is Caitlin, JP, and Kip sitting back there.

Senator CARPER. Would you all raise your hands? Would you raise your hands, please, kids? There you go.

Mr. BELLINA. And there is an unnamed baby on the way as well.

Senator CARPER. That is good.

Chairman JOHNSON. Go ahead, Matt.

Mr. BELLINA. Thank you, Senator.

So, last night, when I was laying in bed, I was uncharacteristically nervous about this. Senator Carper, as somebody who has worked in naval aviation, you can understand. We are not usually nervous about things. But, I felt a great burden to speak on behalf of all terminal patients. How do you do that? And, then, a kind of calm washed over me because I realized that this is not a class or a group of people that we can all lump together. We are talking about individuals, and they have individual needs, individual hopes, and individual dreams. And, I do not have the right to speak on their behalf or to make decisions for them. And, neither does anybody else in this room.

I think the first thing I want to clarify is that I am proud of the FDA's "Gold Standard." I am proud of what the FDA does. I am proud that American medicine is the best in the world. And, I would never, ever want them to relax those standards for any reason. I think that that is an important distinction. We are not trying to undermine the FDA.

This is a situation where we are asking for a very specific carve-out for a very small exception that does not necessarily—well, it does not cost us any money. I am not asking to build a wall. I am talking about making an exception for people that really need it.

I am so happy, Senator Carper, that you mentioned compassionate use. I would like to commend the FDA. I think that they have done an excellent job of doing everything, within their regu-

<sup>1</sup>The prepared statement of Mr. Bellina appears in the Appendix on page 284.

latory power, to approve things. But, unfortunately, the data has a bit of a sample bias. I think there were 1,000 approved this year. There were 12,000 in France, if that gives you any idea. There were not that many people applying, and I think that it has a lot to do with the reporting requirement. No pharmaceutical company in their right mind would give me a drug compassionately, because, if I have an adverse event—which, I am an ALS patient, let us face it, I probably will—they have to report that to the FDA, and it is going to jeopardize their standing and their trial.

We are dealing, in this case, with heterogeneous diseases. There is not a single cause. ALS is a perfect example. There are, I think, 39 known genetic mutations for ALS. That only makes up 10 percent of the overall cases. The other 90 percent are sporadic—and they are largely veterans. We do not know why. People who have worked in aviation are about eight times as likely to get ALS.

So, when you run an FDA trial, as we are doing them now, you are throwing, at best, 400 people into a room together, giving them a small molecule, and hoping to get a result. Well, the data is kind of garbage in, garbage out. We are not getting good data. And, we need to move toward personalized medicine, in these cases.

I feel that, “Right to Try” may not be, exactly, the end goal, but it is a first down. We are moving the marker toward doctors, patients, and pharmaceuticals being able to look at patients as individual people. And, I think that is a really important step. It is an ideological thing. I have heard the argument that we will risk side effects. But, as you can tell, I am struggling here. At some point in the near future, I am going to suffocate under the weight of my chest. So, what difference, at this point, does it make for me to have a side effect?

And so, I think that, when you are talking about toenail fungus or psoriasis—yes, we need to be concerned about that. But, where I am sitting—it is a totally different story.

The other thing some bioethicists have talked about is, “false hope.” Do we want to give terminal patients “false hope?” Well, I do not really think there is such a thing, because right now we have no hope, so it is either hope or no hope. This bill, it does not do everything, but it moves us in the direction of having a little bit of hope. And, I think that it is very consistent with what the FDA is doing right now. I commend them. The Sarepta approval was fantastic. But, we need to open things up for the market to be able to kind of correct for itself and allow the pharmaceutical companies to not have to worry about negative action against them if they are trying to do something good.

Chairman JOHNSON. Thank you, Matt.

Mr. BELLINA. Thank you.

Chairman JOHNSON. Our next witness is Assemblyman Ian Calderon. Assemblyman Calderon is the majority leader in the California State Assembly, where he was first elected to represent the 57th Assembly District in November 2012.

He serves as the Chair of the Select Committee on Youth and California’s Future and Co-Chair of the Legislative Technology and Innovation Caucus. He has previously worked at Hurley International and is a field representative for the California Assembly. Assemblyman Calderon.

**TESTIMONY OF THE HONORABLE IAN C. CALDERON,<sup>1</sup>  
MAJORITY LEADER, STATE ASSEMBLY, STATE OF CALIFORNIA**

Mr. CALDERON. Thank you, Chairman Johnson, Ranking Member Carper, and Members of the Committee for inviting me here today. I am honored to testify before you on the “Right to Try” for terminally ill patients.

As Majority Leader of the California State Assembly, I am fortunate to work on a variety of public policy issues every year. This year, alone, I have sent bills to the Governor dealing with issues ranging from ensuring that financial literacy is part of the high school curriculum to setting minimum fines for piracy violations. While each bill I work on is a piece of policy I believe in strongly, my work on “Right-to-Try” legislation, over the last 2 years, has truly given me purpose as an elected official. The fight to allow terminally ill patients to seek investigational drugs and treatments not yet approved by the FDA is something I am immensely proud to be a part of in California. And, I thank you for giving me the opportunity to talk about it today.

In January 2015, many of the policy conversations in California centered around “Death with Dignity.” If you recall, this was mere months after Brittany Maynard, the young woman diagnosed with brain cancer, had moved from California to Oregon in order to utilize Oregon’s “Death-with-Dignity” law. While researching Oregon’s law and its possible application in California, it struck me that this conversation needed to include policy prescriptions to make it easier for these terminally ill patients to fight to save or extend their lives. It was then that I came across the “Right-to-Try” movement, and subsequently introduced Assembly Bill 159. For me, “Right to Try” was a logical companion to “Death with Dignity.” I never saw the two issues as incompatible. I did not want to limit the options for those diagnosed with a terminal illness only to death—albeit a more controlled one. I felt strongly that, if we were going to pass “Death with Dignity,” and thus make it easier for terminally ill patients to die in California, that we should also make it easier for these terminally ill patients to fight to live, by giving them access to potentially lifesaving drugs and treatments that have been deemed safe—but are not yet approved by the FDA.

As the first iteration of California’s “Right-to-Try” legislation made its way through the legislative process, I had the privilege of meeting David Huntley. David was a professor emeritus at San Diego State University, an accomplished Ironman triathlete, and an, obviously, loved husband and father. David was also diagnosed with ALS, more commonly known as Lou Gehrig’s disease. It is a death sentence given our current lack of understanding of the disease—but there are ways to combat the speed at which it progresses and the pain that it causes. Shortly after his diagnosis, David learned that there was a promising new drug called GM604 that was still in the clinical trial process at the FDA and, thus, had not yet been approved. He sought access to this drug, but was denied. So, David spent the latter part of his life fighting to give patients, like himself, a chance. David agreed to fly up to Sacramento in April of last year to testify with me before the California Assem-

<sup>1</sup>The prepared statement of Mr. Calderon appears in the Appendix on page 286.

bly Health Committee. This was the first committee hearing on the “Right to Try” in California. David’s testimony and clear understanding of the pitfalls of the current experimental drug access paradigm were instrumental in getting us past the first legislative hurdle.

It was evident that David was in a tremendous amount of pain—yet he was determined that he be there for the “Right-to-Try” legislation and that it pass in his home State. Just 3 months after testifying, on July 4, 2015, David Huntley succumbed to ALS and passed away. He came to Sacramento to testify for a measure he knew would be too late to help himself, but that would ensure that future terminally ill patients have the access to potentially life-saving medication that he had been denied. That kind of selflessness is rare—and I will never forget his dedication.

With David’s help, “Right to Try” passed the Assembly Health Committee. But, it still faced intense scrutiny from five more committees in the State Assembly and the State Senate. Though this was only last year, it was early in the “Right-to-Try” movement. The bill went through a rigorous public hearing process, where we sought to improve upon the “Right-to-Try” legislation that had been introduced in other States. Each committee, in concert with the myriad of stakeholder groups—and in deference to concerns that felt unique to California—included amendments to the legislation. Throughout the Committee process, we worked on—and eventually added—several amendments to alleviate concerns about having proper oversight patient protections. We added Institutional Review Board (IRB) oversight of a physician’s recommendation, in order to ensure that patients are fully aware of the potential side effects of any investigational drug they may consume. We also added the requirement that a consulting physician confirm the primary physician’s diagnosis that the patient is terminally ill as well as inserted reporting requirements into the California Department of Public Health (CDPH) to further increase oversight. And, similar to the difference I see in Senator Johnson’s “Right-to-Try” bill versus the House’s version, we clarified that the legislation would not create a private cause of action against the prescribing physician or drug manufacturer—and this was instrumental in removing the opposition of the California Medical Association (CMA).

While we were not able to completely remove all opposition to California’s “Right-to-Try” bill, through the public hearing process, we did work to address many of these concerns, without compromising the strong intent of the bill. When my “Right-to-Try” bill reached the Governor’s desk last year, I was satisfied that, due to its strong patient protections and robust oversight requirements, it was one of the most comprehensive “Right-to-Try” pieces of legislation in the country.

The Governor ultimately vetoed the bill. And, in his message, he acknowledged that the FDA was in the process of streamlining its Expanded Access application and wanted to grant the agency the time to do so—with the hope that this new application would make the process unnecessary. Thirty one other States have passed “Right-to-Try” legislation. I am happy to have been a part of the impetus that spurred the FDA to streamline the application. However, these new regulations—announced in June of this year—only

deal with streamlining the physician's portion of the application. This is an improvement, but the process does nothing to shorten the manufacturer's portion and the data required by the application or to reduce the 30 days the FDA has to decide. A thousand people are approved each year by the FDA to get access to these drugs, but considering the fact that 564,000 Americans are expected to die from cancer, alone, this year, the small number of people navigating the FDA's Expanded Use program speaks to the program's failure to actually help terminally ill patients obtain access to lifesaving treatment. These patients do not have the luxury to wait for an onerous, bureaucratic process. These are the reasons why "Right-to-Try" legislation is so important, and, in the midst of a battle with a life-threatening illness, it is much easier for a patient to deal with their own doctor rather than a large and impersonal government agency.

At the beginning of this year, I reintroduced the bill in California. Fortunately, with all of the protections we added last year, it sailed through the legislature. It now sits on the Governor's desk, where I am hopeful it merits a signature, adding California as the 32nd State to enact this legislation.

Members, I thank you for giving me the opportunity to share my effort to bring "Right to Try" to California. I applaud the effort on the Federal level to do the same nationwide. I hope the Federal Government does not stop there. We need Federal legislation that expedites the FDA's drug approval process. It should not take, in today's technology age, 10 to 15 years to approve a new drug that will produce lifesaving treatments. In the meantime, I commend the Federal effort to encourage the States to essentially adopt methods to work around the FDA.

"Right to Try," at its core, is simple, and it speaks to a very basic human right. If your parent, your child, or even you are faced with a terminal illness, there should be a process in place for you to seek potentially lifesaving treatments—and the government should not impede that. This bill received unanimous bipartisan support in the California State Assembly—all Democrats and all Republicans—and it is extremely important to pass it on the Federal level because it gives us, as a State, the opportunity to have these laws on the books while also, at the same time, freeing up the drug manufacturers, allowing them to give the drug to these terminally ill patients.

Members, thank you for your time.

Chairman JOHNSON. Thank you, Assemblyman Calderon.

Our next witness is State Representative Jim Neely. Representative Neely represents the 8th State House District in the Missouri House of Representatives. He was first elected in November 2012. He is also a physician at Cameron Region Medical Center and a veteran of the United States Army. He also previously served for over a decade on the Cameron School Board. Representative Neely.

**TESTIMONY OF THE HONORABLE JIM NEELY, D.O.,<sup>1</sup> MEMBER,  
HOUSE OF REPRESENTATIVES, STATE OF MISSOURI**

Dr. NEELY. Good morning. Thank you. Mr. Chairman and Members of the Committee, again, my name is Jim Neely. I am a physician, State representative, and, more importantly, a dad. I want to go on record in support of S. 2912 because terminally ill patients do not have time to wait for the FDA to improve investigational treatments.

I have been practicing medicine for over 30 years. Over that time, I have seen patients with medical conditions and issues of life that have been very challenging to deal with, from multiple myeloma, multiple sclerosis (MS), ALS, to acquired immunodeficiency syndrome (AIDS).

In 1985, I had my first AIDS patient. I was practicing medicine in Florida at the time. My first AIDS patient, he was debilitated, frail. He was hopeless. A year later, he died. He was not eligible for any clinical trials. They did not approve the first antiretroviral (ARV) agent until a year later.

Throughout my medical career, I have been troubled by laws that restrict suffering patients' access to investigational treatment. As a physician, my practice is guided by evidence. I understand the importance of our clinical trial system. However, terminally ill patients deserve the option to try investigational treatments after they have exhausted all approved treatment options and they are no longer eligible for clinical trials.

As I began considering the issues as a State legislator, my daughter Kristina was diagnosed with Stage IV colon cancer. She had four children at the time and was pregnant with the fifth, which severely limited her eligibility for clinical trials. From a research perspective, I understand the importance of studying uniform groups of patients, but there has to be room for compassion for patients like our daughter.

Before she passed away, just last year, she was adamant, I quote, treatments "should not be up to somebody that has no involvement in my care." I believe this bill goes a long way to providing more options for terminally ill patients and their physicians.

A friend of mine, Ross Nichols, testified on our bill, in Missouri, on "Right to Try." It passed unanimously out of the Senate and out of our House. It passed 152-1. The one who voted no never votes yes. This gentleman, Ross, he had glioblastoma (GBM), the most aggressive—the most common brain tumor. Ross knew that the experimental treatments he was likely to receive would not save his life. But he still enrolled in clinical trials. He explained, "My number one job right now is being a dad. I will do whatever I can do to extend that." Ross told the committee that he was testifying for the bill because he wanted people in Missouri to have access to the same treatments that were available to him at the research institutions that he could afford to travel to. He was right.

Many people fighting for their life cannot afford to spend what could be their final months traveling across the country in order to receive investigational treatments. I am glad Ross was able to travel and receive treatments that gave him hope, but he should not

<sup>1</sup>The prepared statement of Mr. Neely appears in the Appendix on page 292.

have had to travel. Ross passed away in February 2015. I am glad his hope for other patients lives on with this bill.

Rick Suozzi, father of the late Kim Suozzi, also came to testify in support of our “Right-to-Try” bill in Missouri. His daughter was diagnosed with glioblastoma at the age of 21 in her final semester at Truman State University. Kim knew her diagnosis was a death sentence, but she went to extraordinary lengths for a small chance to survive. She traveled to the top-notch cancer institutes like Dana Farber Cancer Institute, UCLA, Duke, the University of Texas MD Anderson Cancer Center (MD Anderson). Kim enrolled in three trials in the last 6 months of her life. She was no longer eligible for clinical trials. She lied to research doctors about her treatment history in order to make herself eligible. Can any of us blame her?

My time is up. I thank you for giving me the opportunity. I believe government should create opportunities for people to care for each other. This bill knocks down some of those barriers. I appreciate the opportunity to be here today. It is an honor. Thank you. This is a bill for people. Thank you.

Chairman JOHNSON. Thank you, Dr. Neely. We are so sorry for your loss, but thank you for your testimony.

Our next witness is Richard Garr. Mr. Garr is the co-founder of Neuralstem, Inc., which develops therapies involving brain and spinal cord stem cells, including a treatment for ALS currently in clinical trials. He was previously president and Chief Executive Officer (CEO) of the company. Prior to Neuralstem, he was an attorney at Beli, Weil, & Jacobs, the B&G Companies, and the Circle Management Companies. He is also the founder of the First Star Foundation, The Starlight Foundation Mid-Atlantic chapter, and a past honorary chairman of the Brain Tumor Society. Mr. Garr.

**TESTIMONY OF RICHARD GARR,<sup>1</sup> FORMER PRESIDENT AND CHIEF EXECUTIVE OFFICER, NEURALSTEM, INC.**

Mr. GARR. Thank you. I would like to thank the Committee for this opportunity to testify in support of this Act.

As president and CEO of a biopharmaceutical company developing treatments for currently incurable diseases, as a member of the advisory board that helped craft the model “Right-to-Try” act which has been making its way through the States, and as the father of a son diagnosed with a brain tumor, I have been involved in the scientific, FDA regulatory, business, legislative, and patient advocacy arenas germane to this issue for over two decades. S. 2912 is a good bill that will provide hope and comfort to many patients diagnosed with fatal diseases and it will accelerate the effort to find cures for currently incurable diseases.

There are issues—and I would like to spend my limited time here, today, talking about them.

An issue we hear is that this is going to foist unsafe medicines on an unsuspecting public. Nothing could be further from the truth. This bill relies on FDA oversight. As you know, any drug that can be administered under this has to have gone through an FDA Phase I trial and has to continue to be in the FDA queue, which

<sup>1</sup>The prepared statement of Mr. Garr appears in the Appendix on page 296.

is a very important point. So, if a company pulls a drug out of the FDA process for any reason—safety or otherwise—it is no longer eligible to be administered under this Act.

I also think it needs to be pointed out that, companies do not develop drugs for incurable diseases without spending an enormous amount of time and money. This is not an undertaking you go into lightly. At Neuralstem, it took us at least \$50 million and 10 years just to get into our first trial for ALS. So, in addition to the FDA safety data, which you get from the trials and which are required for a doctor to administer this drug, there is always a large body of pre-clinical safety data—such as animal data, in vitro, and in vivo data. And so, there is a lot of safety data for these drugs.

I would also—as other people have said here—like to debunk the myth that this is somehow an anti-FDA bill. Nothing could be further from the truth. The heart of this bill is the safety net that continuing FDA oversight provides—an oversight, as everyone has said, that is universally acknowledged as the gold standard for the world. And, I would point out here that even proponents of the “Right-to-Try” movement, such as the Goldwater Institute, who probably believe that “Right to Try” is based on a constitutional principle and disagree with the idea of Federal preemption, have insisted on the FDA oversight principle of safety in all of the 31 Acts so far that have gotten through the States. This is not an anti-FDA bill.

I would like to address your issue, Senator Carper, briefly. We did two trials for ALS. We will be starting a third, hopefully, in the not too distant future—but, probably, in Japan for regulatory reasons. So, we treated 40 patients—15 in the first trial. It took us 18 months to transplant those—to do those 15 surgeries. We had at least—and I am just thinking of my own personal emails at night—600 people who asked if they could have it on a compassionate use basis. It cost us \$150,000 per patient—and that is without charging anything for ourselves—for each patient in that trial. So, the reason that the FDA’s compassionate use vehicle, or tool, is not applicable is that is a tool, but it is a tool for a very specific use—and maybe about 1,000 people a year can do it.

In a case like ours—and I would tell you that all of the products that are being developed for incurable diseases are not cheap pills. They are all cell therapy or gene cell, monoclonal antibodies. It is very expensive technology. And, the fact is we could not do any compassionate use—we could not possibly meet the need. We did not have the money and we did not have the time or the resources. Maybe GlaxoSmithKline can do it for a cancer drug. But, they are not developing these drugs. The biotechnology industry is developing these experimental medicines. And so, another part of this that has to be addressed—and the States will have to do it—is you have to let the companies charge for this—and you cannot do that under your existing compassionate use guidelines with the FDA. There are very strict limits on cost. And, actual cost for our product—for me to send our cell guy up to Charles River Labs in Pennsylvania, to follow the cells, to do what we do, and to ship them to the surgeon has nothing to do with the \$50 million that it costs us to get to that point. And so, there is something that just does not work there.

I see that I am running out of time, so I do want to mention one last thing, and that is—as you are hearing from everybody here, this is a “Right-to-Try” Act, not a “Right-to-Cure” Act. And, what the doctors who deal with the patients and the caregivers will tell you, almost across the board in all of these diseases—not just ALS—is that people with fatal diagnoses—and this bill only applies to drugs for fatal diseases. People with fatal diagnoses have a sense of hopelessness and their caregivers do also. And, many of them feel that they have lost control of their lives. They want to go down fighting. They want to help research. No one who gets an experimental drug—even if we are all hoping that it can work—we do not develop drugs that we do not think are going to work. But, the fact is, over 90 percent of them fail—even those that get to late-stage trials.

So, the industry is meticulous in educating patients about the realities of what is going to happen. And, they still want to go through it. Yes, they have hope and they want to help the research—and this will accelerate research. And so, I think it is also an extremely important part of these “Right-to-Try” Acts that you give people back some control of their lives in a place where science is telling them they have lost control and that is why they have this fatal diagnosis.

Thank you for the time.

Chairman JOHNSON. Thank you, Mr. Garr.

Our final witness is Andrew McFadyen. Mr. McFadyen is the executive director of The Isaac Foundation, a nonprofit focused on funding and supporting research into finding a cure for Mucopolysaccharidoses (MPS), a rare and progressive disease affecting his eldest son. As part of his work, he is a member of the New York University (NYU) Langone Medical Center Working Group on Compassionate Use and Pre-Approval Access. He is also an eighth grade teacher in Kingston, Ontario and a guest lecturer at Queen’s University Faculty of Education. Mr. McFadyen.

**TESTIMONY OF ANDREW MCFADYEN,<sup>1</sup> EXECUTIVE DIRECTOR,  
THE ISAAC FOUNDATION**

Mr. MCFADYEN. Thank you. And, I want to actually begin by just welcoming my kids, Isaac and Gabriel. They are my inspiration in all that I do. And, I wanted to use a little bit of my time as well to recognize you, Matthew. Your story is incredibly heartbreaking. Your family is just beautiful. And, you are an inspiration to me and I am glad that you are here.

So, good morning. I am the executive director of The Isaac Foundation, an organization based in Canada that is dedicated to providing advisory and support to patients dealing with a wide range of disorders and needing access to rare disease treatments. Our work pushes international boundaries, with the bulk of our efforts taking place in Canada and the United States. I am also a member of the NYU Working Group on Compassionate Use and Pre-Approval Access, where we are making a concerted effort to improve and address the issues around access to experimental medications.

<sup>1</sup>The prepared statement of Mr. McFayden appears in the Appendix on page 299.

I am very proud to say that at The Isaac Foundation we have never, ever been unsuccessful in gaining access to rare disease treatments for children in Canada. And, our work, directly, with pharmaceutical companies here in the United States is helping countless patients see similar results as well.

Now, as I stated, my organization is incredibly dear to me because it is named after my son—my hero and the bravest person I know—Isaac McFadyen, who is here behind me today and who suffers from MPS Type VI.

When Isaac was diagnosed, we were told that he was going to live a life of pain and suffering. Every bone, tissue, organ, and muscle in his body—with the exception of his brain—would be ravaged by his disease until he eventually succumbed to the condition—probably in his early to late teens.

For 10 years, he has battled—we have battled together—to stave off the inevitable. And, we have been lucky. In 2006, we were able to gain a new life-prolonging treatment—one that was approved here by the FDA, but not by Health Canada—to fight his disease. Isaac is now 12 years old—and the 12 that we see today is very different than the 12 we were told to prepare for.

So, I fully understand the world that our families are living in and I understand the unbearable burden that a terminal diagnosis brings to a family. I understand because I live each and every day staring down the mortality of my son. I understand because I have walked this lonely road searching for hope when all seemed lost. I have been there—and I am still there each and every day as I continue to work tirelessly to find a cure for Isaac before the clock runs out.

Now, as I said, Isaac is one of the lucky ones. Unfortunately, little Jack Fowler in the picture here is not. Jack was diagnosed with a version of MPS similar to the type that Isaac has—except Jack has the tragic misfortune of having his disease attack his brain. The disease will progress rapidly and steal everything that makes Jack Fowler Jack Fowler—his mobility, his words, his thoughts—his everything—before finally taking Jack Fowler away from us.

Now, there is a drug that can prevent this from happening, but Jack barely missed out on qualifying for the clinical trial and he was not able to obtain the drug under the FDA's expanded access program because, despite his physician, the hospital, the hospital review board, and the FDA all supporting his case, Shire Pharmaceuticals blocked access to the drug. Today, hope is all but lost for his parents as they watch their son slip away.

But, how can hope be lost for Jack Fowler when he lives in a State where "Right-to-Try" legislation is in place? The Goldwater Institute has done a marvelous job of promoting "Right-to-Try" laws as being the last chance for people to extend their lives. Very pointedly, they claim that "Right-to-Try" legislation "restores life-saving hope back to those who have lost it." This utopian vision of access to medications for millions of Americans who need them is laudable. However, the cruel reality with "Right-to-Try" laws is that it will not grant patients the immediate access to the treatments they desperately need—the and it never has.

Looking past the myths that "Right-to-Try" proponents state ad nauseam and looking past this legislation's potential to create an

unequal access to medication, the simple fact is that this legislation, crafted to give people like Jack Fowler his fair shot of simply being alive, does not work. Although over 183 million Americans, including Jack Fowler, are currently living within the boundaries governed by “Right-to-Try” laws, providing them with, as the Goldwater Institute claims, immediate access to the medical treatments they need, there continues to be no concrete evidence of a patient ever receiving a life-saving medication under “Right-to-Try” legislation that they otherwise would not have received under the FDA’s expanded access program.

In truth, “Right to Try” is a misnomer and provides nothing to patients in need, except a misguided belief that help has arrived. A more apt title would be “Right to Ask” because this is the only entitled right the legislation actually gives patients.

There are ways forward. Over the past few months, companies like Janssen and BioMarin are crafting new approaches while working within existing FDA programs and guidelines to expeditiously and fairly provide access to those in need—and it is working.

So, recognizing that we are all here to work toward the same outcome, I hope that we can move now and that we can keep moving until everyone in this room and everyone throughout the country can look the parents of Jack Fowler in the eyes and tell them that help is on the way, that help is here, and that Jack will get to realize his simple dream of being alive.

Thank you.

Chairman JOHNSON. Thank you, Mr. McFadyen. And welcome, Isaac.

I have been told that Frank Mongiello is in the audience and he would like to make a brief statement. If we can assist Frank, get him up to a microphone. We have some staff coming down.

#### **TESTIMONY OF ERIC AND FRANK MONGIELLO**

Mr. ERIC MONGIELLO. So, first I would like to start off by reading a quote from Mahatma Gandhi, and it—

Chairman JOHNSON. And you are Frank’s son? Can you just introduce yourself quickly?

Mr. ERIC MONGIELLO. I am Eric Mongiello. This is my dad right here, Frank Mongiello.

So, starting with this quote: “You may never know what results come of your actions, but if you do nothing, there will be no results.”

Basically, what is that meaning? We do not have the luxury of time to wait around until this bill gets passed. Every day is another day off my dad’s life, and others with terminal illnesses. Me, personally, I do not want to have to grow up without a father. I do not want my little brother and my siblings to have to grow up without him. And, with the “Right to Try,” this will give us hope. We have no hope right now. And, this is very important to me because, as long as we have a fighting chance, then I know whatever happens, whether it helps or not, that at least we tried, and at least we did something instead of sitting by the side and waiting for the inevitable. Thank you.

Chairman JOHNSON. Thank you. Frank.

Mr. FRANK MONGIELLO. Thank you very much for having this hearing.

My ALS is progressing every day [unclear]. We do not have the luxury of time.

All we are asking for here is a basic inalienable right to live every [unclear]. I do not want to die, but I want to be able to fight for my life, and if that means taking a drug that might not be proven by the FDA, I am OK with that.

It is my life. I should have the right to fight for it. Thank you.

Chairman JOHNSON. Thank you, Frank.

Frank made a statement when we had a press conference on this. And, Frank has a beautiful family and he is just asking for that right to hope.

Mr. Garr, I will start with the questioning. Can you respond a little bit to Mr. McFadyen? Why would Shire block access to—can you just kind of explain that?

Mr. GARR. I am not from Shire, so I will not speak for them.

Chairman JOHNSON. I understand, but I mean, can you—

Mr. GARR. In general, sure, and I would like to address this claim, which is that nobody has been treated with “Right to Try.” The reason no one has been treated with “Right to Try” is that this bill has not passed, right? As you put your industry hat on, all of the issues that have to be addressed, in terms of whether the FDA can use negative information to withhold your approval in the regular approval process—that is the reason, right? This bill, specifically, prohibits the FDA from doing that. When you design a trial, you eliminate as much of the variables as possible to match your evidence—your pre-clinical evidence—and you create an experiment. Correct? And then, when you go to “Right to Try” or compassionate use, you start treating people, as the doctor said, that are outside of that.

And so, it is very difficult, as a company, after you have just spent 10 years and \$1 billion, or whatever it is Shire spent on their drug, to get to a point and then say, “OK, we know that if this goes into patients that do not meet the inclusion criteria, there could be problems.” So, they have an obligation to their shareholders to get their drug approved. That is probably what they told themselves. I do not think I agree with it, but that is what the obligation is. And, no company, I will tell you—and he confirmed that, right? No company will feel comfortable going through this. When you go through the compassionate use process with the FDA, that limited tool, you have some protection. Under the current State “Right-to-Try” Acts, you have none.

Chairman JOHNSON. And, that is basically the reason. You have the 31 States that have passed this, but because you have no protections at the Federal level, anybody like Dr. Delpassand is taking a huge risk. That is why I call Dr. Delpassand a real hero. He is taking an enormous risk with his career treating these patients and giving them hope. So, we really need the Federal law in order for the State laws to actually kick in. And, that is really, I think, what the strategy was—to show the support for “Right to Try” in the States— but until the Federal Government acts, the State laws have not been effective.

Mr. GARR. Absolutely.

Chairman JOHNSON. Assemblyman Calderon, first of all, what party affiliation are you?

Mr. CALDERON. I am a Democrat.

Chairman JOHNSON. And, again, this had very strong bipartisan support. You made the statement—and this is in terms of the simplicity of what we are asking for here—patients have the right to die in certain jurisdictions, and yet they do not have the “Right to Try.” Where is the logic in that?

Mr. CALDERON. I do not know. That is why I felt, once I got the bill to the Governor’s desk, that it would merit a signature—because of the State at the time dealing with the “Death-with-Dignity” law. However, the Governor vetoed and we have been working with his office and we are hopeful that we will get a signature this year.

Chairman JOHNSON. Can somebody explain, again, the statistics of 99 percent of expanded use being approved—1,000 patients versus how many would be, potentially, looking at this? Matt, I see—

Mr. BELLINA. Senator Johnson, if I could weigh in on that. So, before you apply for compassionate use, as a terminal patient, you go and talk to your doctor and say, “What do you think about this thing?” And, they look at you as a person, it is between you and your doctor—it is your body. And, they say, “Yes, I think that could help you,” or, “No, there is not enough data,” or whatever.

If they think it is a good idea, the next thing you are going to do is call the company, and you are going to say, “Hey, you are in a Phase IIb trial with this drug, and I want to try it.” And, I am going to tell you, from personal experience, about 50 times, you are not going to get a response.

Chairman JOHNSON. So, you personally, have made those calls?

Mr. BELLINA. I have made those calls, personally. And, I cannot get into an FDA trial because I do not meet exclusion criteria. I have had the disease for too long. So, there is literally no way for me to get these drugs. As Mr. Garr said, I mean, they are not going to risk giving me a drug and risk me having an adverse event. They would have to report that to the FDA. They have already spent—who knows—maybe \$100 million at this point.

Chairman JOHNSON. Does anybody have any kind of statistic regarding , how many Matts are out there, that have made those 50 calls, in comparison to the 1,000 successful applications of expanded use or expanded access?

Mr. BELLINA. Senator, I think that is, again, something we will never know simply because it never gets to the government at that point. You are talking about a gmail account to a gmail account. This is not under any kind of regulation. These are just people reaching out to people in these companies—and there is no way to quantify that.

Chairman JOHNSON. Yes.

Mr. CALDERON. Senator, if I may, I was elected to the California State Assembly when I was 27 years old. I am 30 now. I am the youngest majority leader in the history of the State of California. But, I am also a Millennial, and part of my generation—everybody is trying to say, “Well, how do we get them engaged? How do we get them to care about our political process?” A lot of it is just our

perception that government just has this inability to reach these common sense ideas. Why would you not allow someone who is terminally ill the ability to try and fight to save their own life? It is beyond logic to me.

Chairman JOHNSON. So, having fought this successfully legislatively, what was the primary argument against—I mean, in the end, you knocked down all of those walls because you passed this almost unanimously, correct?

Mr. CALDERON. Absolutely.

Chairman JOHNSON. Just one person voted no.

Mr. CALDERON. And, in terms of the opposition, the problem was more, a question of whether there was liability. All that my bill did, really, was give people the ability to try and ask for the drug. That is all the intent of the original bill was. But, given the opposition, we added all of these patient protections and oversight. By the time the bill got to the Governor, the reason why the Governor vetoed it is because, within the expanded access, the FDA was working on an expedited way to get access to those drugs.

But, look, let us be honest. If I had a terminal illness, I would want to live. I am probably not going to want to deal with the FDA, because how do you figure that out? I do not even know—I am authoring the bill in California. I do not even know where I would go. I guess I would just go online and google how I would even apply for the program. But, contrast that with the State having a law on the books where you can just talk to your own doctor and say, “Hey, Doc, I am terminally ill. I want to fight to live. I do not care what it takes. Give me anything that is going to allow me to stay on this Earth longer.” Or, if it is for my kids or a parent.

Chairman JOHNSON. But, you were able to overcome the objections, and our bill also overcomes those same objections, basically?

Mr. CALDERON. Absolutely.

Chairman JOHNSON. Just very quickly, Dr. Neely—a similar situation. What objections—why did anybody oppose this in Missouri?

Mr. NEELY. In the State of Missouri, nobody had any issues. Everybody was all on board. It was about taking care of people. I think, at our level, it is all about taking care of people. And, I think that is what we have done.

I might add we had—one of my staff physicians at Cameron came down with ALS in 2014 right after Missouri passed their “Right-to-Try” legislation, and I was telling him about it, and the trials that were going on for ALS in the San Francisco area. Again, he was in his early 70s. He had been practicing medicine for 40 years. He did not want to have to deal with the government.

Chairman JOHNSON. OK. Senator Carper, are you ready?

Senator CARPER. I am.

Chairman JOHNSON. Senator Carper.

Senator CARPER. Thank you again. Matt, gosh, about 15 years ago, my brother-in-law was diagnosed with ALS, and so, we lived what you are going through.

My mother passed away about 8 years ago—Alzheimer’s. Her mother, her grandmother, her sister. My guess is everyone on this panel could tell a story. Everyone.

Andrew, let me ask you a question. I do not know how familiar you are with the changes that have been made in the approval process at the FDA to expedite access to experimental treatments. But, my understanding is that there had been a lot of criticism, in the past, of the FDA. The FDA has been responsive to those criticisms. Could you just walk us through some of that? And, I will ask Dr. Lurie the same question later. But, are you familiar with that?

Mr. MCFADYEN. Yes, I am, actually. I understand that they have made changes. They released guidance, in June, talking about issues that could take place—adverse events and how impact clinical trials. At the same time, they updated their application form. It has been said—I have heard it often—that it takes 100 hours to fill out this form—and that is just not the case. It takes 100 hours for the company, before they apply to the FDA, to fill out those forms. The old form, it did take a few hours to do. We went through it with Jack Fowler. We looked at it long and hard with Jack Fowler. I did it, myself, and it did not take that long.

The new changes in place are looking at about 45 minutes for those forms to be filled out, and, it is not filled out by the patient. It is filled out by the doctor. It is the exact same thing. You do go to your doctor, and you ask to have access to this drug. The doctor sends it to the FDA and it needs to be sponsored by the companies.

The same holds true for “Right to Try.” You go to your doctor, you ask, and you have to get the company on board to do this. So, even if this passes expeditiously at the Federal level, nothing really changes with respect to access when it comes to the companies agreeing or not agreeing to provide. And, I know the FDA has done a really good job of getting that form changed. It took a little while, but that application process is changed.

I also want to note that they did release, in that guidance, some information for companies, so that companies were not as adverse to providing these drugs for patients. And, they said very categorically in that guidance that adverse events that take place will not have a bearing on the clinical trial process. To support that, they released an audit, and in that audit, they were able to show that expanded access was not derailing clinical trials by any stretch of the imagination.

There are still things that they could do. They still have a ways to go. I would recommend that they do another audit and look at the drugs that have passed and have a look at which adverse events took place during those clinical trials for compassionate use, as the drug was being passed, and how those adverse events really impacted the discussion—the approval process discussion. And, our hunch with our group at NYU Medical Center is that the people making these decisions understand that the people accessing these drugs under compassionate use, expanded access are the sickest of the sick. They are not your healthy sick people that get into the trials and they take that into account when they are looking at approving these drugs.

Senator CARPER. So, let me see if I understand this. It is a question I just asked of my staff. If the FDA approved anybody who applied, who filled out this form, whether it is 45 minutes or whatever it takes to fill it out—and I understand it is filled out not by

the patient and not by the patient's family, but by the patient's physician. Is that correct?

Mr. MCFADYEN. That is right.

Senator CARPER. So, the notion that—and I think it was Dr. Neely who said these words, and I think he was quoting his daughter, "Treatment should not be up to somebody who has no involvement in my medical treatment." But, the person who actually submits and signs, fills out and completes the document that goes to the FDA is the physician of the patient. Is that right?

Mr. MCFADYEN. That is right.

Senator CARPER. OK. So, let me see if I understand this. The FDA could approve access to experimental drugs to everybody who applies, whether it is in Stage I, Stage II, or Stage III. And, that does not mean that a patient is going to have access to those treatments. OK. I understand you are saying that is correct. So, then, if this legislation does not really get at the heart of the problem and the changes that the FDA has made—and I think they are significant and in the right direction—do not completely solve the problem, what should we do legislatively? I think you may have said this, but I just want to ask you to say it again. If this does not work—this legislation does not work—and if the FDA reforms are insufficient, what do we need to do? Or, is it something that maybe is beyond—

Mr. MCFADYEN. Well, I think, first and foremost, we need to pass the 21st Century Cures Act. That will pave a quicker pathway—

Senator CARPER. You say the 21st Century Cures Act?

Mr. MCFADYEN. That is right, yes.

Senator CARPER. Is that Senator Alexander's legislation?

Mr. MCFADYEN. I believe so.

Senator CARPER. I think so, yes.

Mr. MCFADYEN. I think that needs to be passed. I also think at the same time we need—

Senator CARPER. And, tell us why.

Mr. MCFADYEN. Well, it is going to pave the way to have access to drugs approved a lot quicker. At the same time, I think we need to pass the Andrea Sloan CURE Act where—that forces companies to actually state online their expanded access, compassionate use policies—the criteria for inclusion. It will also force companies to have one point of contact at the company for somebody like Matthew to call and say, listen, I do not want a gmail address. I want—at Johnson & Johnson's (J&J's) website—and I want that one person to get back to me, immediately. If an application for compassionate use with a company is denied, it forces the company to explain exactly why. It actually lifts a level of secrecy at the company level.

At the FDA, they really need to do a better job of communicating to the pharmaceutical industry exactly what adverse events do to the clinical trial process. In our study at NYU, we have seen that it does not actually impact it. But, Matthew is right. Only 1,200 or 1,300 applications land at the FDA to be signed off on, and although 99 percent of those are approved, that is still only a small representation of the people that need access.

So, if “Right-to-Try” legislation gets passed at the Federal level, just as it has at State levels, we are not going to see the dramatic shift tomorrow that we hope to see. We just are not.

I talked to a lot of industry folks before I came down here. I spent 16 hours a day for the past week talking to an unbelievable amount of companies throughout the United States—companies that I deal with seeking access as well as companies that I have never talked to before. And, they are as afraid of adverse events outside of the clinical trial setting taking place under expanded access as they are under “Right-to-Try” legislation. And, although the FDA cannot hold adverse events against the company and against the clinical trial because they do not have to be reported to them, there is a very good chance that adverse events under “Right to Try” will still be reported. It will be reported in the media. Companies that trade publicly have to include reports about anything that could impact the approval or the development of a new drug to the U.S. Securities and Exchange Commission (SEC). Oftentimes, those reports fall into shareholders’ hands, which fall into the general public’s hands, which get reported in the media.

And so, it is a very real issue for them under both “Right to Try” and expanded access. And so, what we really need to do is work with these companies to ask how we can come together to make the changes that we need in order to provide access for our patients, in the now, so that we can have true help.

Senator CARPER. Thank you so much.

Chairman JOHNSON. Senator Paul.

#### OPENING STATEMENT OF SENATOR PAUL

Senator PAUL. I would like to start with a question for the Chairman. You said that there are plans to try to have this pass by unanimous consent?

Chairman JOHNSON. I would like to do that next week.

Senator PAUL. OK. And, you have no objections on our side of the aisle?

Chairman JOHNSON. That is what we are hearing.

Senator PAUL. OK. And—

Chairman JOHNSON. Maybe I do.

Senator PAUL. No. Have you heard any public objections on the other side of the aisle?

Chairman JOHNSON. No, I have not.

Senator PAUL. OK.

Chairman JOHNSON. But, I do not have a whole lot of cosponsors. I have one.

Senator PAUL. Right. But, I think it is important to know that that is coming up, and I think it is important to know that our process is somewhat secretive, in the sense that people do not have to reveal when they are blocking legislation like this. But, it can be pushed, and people can inquire who the opponents are, and I think if people are going to oppose it, I think they ought to publicly oppose it and, if they have reasons, put those reasons forward. But, I think that the holds or the blocking of this should not be secret. And, I think every attempt should be made to make sure that that is an open process and that we know who wants to stop the legislation.

Chairman JOHNSON. That is why I will go down to the floor of the Senate next week and ask for unanimous consent. And, hopefully, whoever has an objection will come down and tell us what the objection is.

Senator PAUL. Right. With that being said, I think that there are a couple of things to think about if we want to place our faith in the FDA doing things in an expeditious way.

The recent controversy over the epinephrine auto-injector (EpiPen) costing \$600, well, there has been a generic out there that applied in 2009. So, 7 years later, we have not gotten an approval, and it is over, I think, frivolous sort of complaints. Basically, it injects the drug. It injects the right dose. It works. And, yet the FDA is saying, "Well, it is not identical to the EpiPen device." And so, for technical reasons, it is being held up. At least that is what I have heard in the press—7 years. So, I think we should not place a lot of faith in some sort of expeditious process. In fact, I think the whole FDA process needs to be overhauled, not just for people who are terminally ill but for everything. We do a miserable job at the length of time of trying to approve drugs in our country. So, if we are going to wait back and say, "Oh, well, everything is just swimmingly well, just be patient," I think that is a big mistake.

I think the biggest part of the debate here, though, is over whether the compassionate use program works. And, I think that needs to continue to be driven home, whether it works or it does not work. And, I have learned a lot today about whether it works or it does not work. I think the fact that we have patients calling drug companies and they are not eligible but are not showing up in any statistic, it is not measurable, maybe, how large the number of ineligible patients is.

My political director's sister has pulmonary fibrosis. Her drug is not approved here. She actually is in a clinical trial because she lives in New York. But, if she lived in Bowling Green, Kentucky, my guess is it would be a little bit harder to get into one of these trials because we do not have a major university. But, the drug she is using in her trial has been on the market for 10 years in Japan. Why in the world do we not use drugs that have been on the market to the general public? A Phase III trial might have 1,000 patients. How many people live in Japan? A hundred million people? It is a rare disease, but maybe there are 10,000 people in Japan using the drug. Why are we not using that data? We give the FDA the option to use the data, but they choose not to. And, this is the problem. We come to this legislation—it comes forward, and I will try to put a word in that the FDA should or shall do this, and everybody will say, "Well, let us just give them the option of using it, let us trust the FDA to do the right thing."

Well, no, the FDA does what they have always done—and that is slow-ball and slow-roll things, and so, we have instance after instance—we do not have like thousands of instances of the FDA saying, "We got it done". We have thousands of instances of it taking 5 and 10 years.

But, we also have to look at the whole FDA process. The EpiPen has a 38-year patent. Why in the world would we do that? They tweak their patent on the device. OK, it delivers it slightly faster, quicker, or differently, the needle is slightly longer—and we give

them another 10 years. The EpiPen is 38 years. They got the approval in 1987. The injector was actually approved in the 1970s. And, their patent is not going to run out until 2025.

The other thing I have learned, today—or was reinforced for me is—Matthew talking about the individualization of treatment. We may be entering into an age, if we are not already there, where we are never going to have 1,000 people get the same treatment because it is going to be individualized to their exact genetic disorder if it is some gene that is wrong in his body. Maybe the treatment is going to be specific to him. There are never going to be 1,000. But, ultimately, the way I look at this issue is, look, we live in a free country. My goodness, shouldn't people be free to try? And, will it always work? No. But, I mean, ultimately, if you have ALS, my guess is that you also want trials to go on. It is not like you are against trials to go on to see what actually works. But, if we prevent the trials and we prevent people from trying, we will never know.

So, I commend the Chairman for putting this forward and wish you the best of success.

Chairman JOHNSON. Thank you, Senator Paul. I do want to point out that Senator Donnelly and Senator Manchin are the two Democrat cosponsors we have.

Mr. Garr, you talked about the ability of “Right to Try” to accelerate research. Can you just kind of speak to that? And, I want to keep this relatively short and then I will give Senator Carper a chance. I want to ask that question. But, then I also want to get you guys thinking about this. Where is the real harm? Obviously, Mr. McFadyen, you are not for this, but what is the harm of this? I am not saying it is a panacea. I am not saying it is going to work great. You have the problem of determining the cost of these things—incredibly expensive. But, what is the harm in doing this, in terms of—versus the benefit of giving people hope? But, again, talk about the accelerated research.

Mr. GARR. Sure. We did, as I said, 15 patients in the first trial and 25 patients in the second trial. If we had delivered this drug through a “Right-to-Try” opportunity in any of the States that passed it, it would have been the exact same surgeons doing the exact same surgery with the exact same product. In fatal diseases, there are no healthy volunteer trials, right? So, every patient, every bit of data you get is important. And what I would also say is that no company looks at a drug and says, “Gee, my market for this is the label I get from the trial,” right? The very specific narrow group. No. Everyone looks at the development and says, “OK, this is how we can create a trial and get this passed. And then, how do we expand the label?” Right?

And so, every pharmaceutical company—all of your companies in Delaware, right?—all have the same mantra, today, which is, “Fail fast.” Right? They do not want to spend \$2 billion in 10 years to find out it does not work. Right? More data is always better. More data is always better. It always accelerates research.

And, I would also just like to point out that there is a relatively easy answer. In Japan—and we have moved all of our cell therapy there—they adopted a law where, if you have a fatal disease, you can do a trial, and as long as it passes the safety test and shows

some reason to believe it could work—not statistically significant efficacy. The trials are not powered to show efficacy. But, they have to show safety. They then give you a transitional approval. You can then commercialize for 5 years—even 7 years—while you continue to do trials and continue to collect data. That gives access to everybody who wants it with a minimum safety net of safety established. And, I will tell you, it has taken the whole cell therapy industry and turned the map upside down and pushed everyone to Japan. Right?

Now, the 21st Century Cures Act is kind of a kinder, gentler, and weaker model of that, but it does not come right out and do what the Japanese did. That is the way you solve this problem if you really want to.

Chairman JOHNSON. And, of course, with “Right to Try”, you only get drugs that have passed Phase I, which is the safety standard.

Mr. GARR. Very safe.

Chairman JOHNSON. Assemblyman Calderon, you have been trying to jump in here.

Mr. CALDERON. Thank you, Senator. I think there needs to be an important distinction made when it comes to access, because we are looking at access, right now, in terms of being able to get the drug—but that is not necessarily the case. You also have to look at access in terms of time. If you are given a diagnosis of a year to live with a terminal illness, well, right now the new expedited process, all they did was shorten the time for the application from 100 hours to 45 minutes. But, there is still a 30-day waiting period. And, now say that application is returned with a misspelling. Maybe they forgot to fill something out. You send it back, and the 30 days starts all over again. If you are given a year to live, 30 days is your life. And, the point is that with my bill in the legislature—in the assembly—you could do that within a week. That is why State laws, in terms of “Right to Try”, are so important.

Mr. MCFADYEN. And, can I just address that? I am sorry to interrupt. It is not 30 days for the FDA to get these applications back. Sometimes, it is just overnight. Sometimes, for compassionate use, expanded access, it is done over the telephone. So, it is not 30 days. They are not going to care about a misplaced “I” or an “I” before an “e.” That is not how this works. It does get done in a very rapid fashion.

Chairman JOHNSON. And yet, can you explain why Dr. Delpassand could not expand his own trial to patients that needed the therapy?

Mr. MCFADYEN. No, with a 3-minute video I cannot.

Chairman JOHNSON. Go and look at the 20-minute video.

Mr. MCFADYEN. I will. I most certainly will.

Chairman JOHNSON. Give him a call.

Mr. MCFADYEN. But, what I will say is that he is in the 1 percent that did not get to move forward. So, when 99 percent do, there is access through that. It is not the FDA that we continue to vilify here. It really is the matter of the companies not providing access.

Chairman JOHNSON. Matt, do you have something?

Mr. BELLINA. Yes, Senator, thank you. We are all hovering around something—a great example that I really think illustrates

what we are all talking about here. There is a drug out of Japan that has been approved for ALS for about 2 years now. It is called Radicut. And, to the credit of the FDA, the company applied for a new drug application (NDA) based on Japanese data. You have about 10 years of trials and 2 years of market. And, the FDA accepted the NDA—

Senator CARPER. I am sorry, NDA?

Mr. BELLINA. New drug application. Sorry, Senator.

Senator CARPER. Thank you.

Mr. BELLINA. So, the company, Mitsubishi Tanabe Pharmaceuticals, asked for a 6-month review out of respect to the FDA. The FDA came back and said, "We will look at it, but we need 10 months." This is a drug that has been essentially in humans for about 12 years and, in that 10 months, we are going to lose about 5,000 ALS patients. Excuse me. So, you can see—I am sorry. I get a little emotional about that. That drug should be, in my opinion, already in a Phase IV market study, and it really illustrates—

Senator PAUL. And, how far are we into that? How far are we into that 10-month cycle?

Mr. BELLINA. We are about 4 weeks in, Senator.

Chairman JOHNSON. Does anybody else want to quickly comment before I turn it over to Senator Carper?

[No response.]

Senator Carper.

Senator CARPER. Mr. Garr, you mentioned that the expanded access program at the FDA limits what a company can charge patients for treatment. How do "Right-to-Try" laws ensure that patients can afford their treatments?

Mr. GARR. Yes. All of the issues around cost and access are unresolved on this, but they are no different than they are for approved drugs. Right? So, in other words, how do we know that everybody can afford Genentech's new vaccine? I mean, we have the exact same issues for these unapproved drugs that we have for approved drugs. So, yes, there are issues. They are all resolvable. There are people in this industry who just spend all day, every day working on those answers. I cannot tell you right now what our therapy would have cost an ALS patient. I know what it costs us to do a trial, right? I cannot tell you that. But, the fact is that whether we are doing it under a compassionate use, where we have to give it to them basically without charging, we have to try and get the surgeons not to charge, and we have to try and get the anesthesiologist not to charge, and go through that whole process—or if we figure out what everybody is going to charge for a particular thing, that is no different than it will be when it becomes an approved drug.

Senator CARPER. I am going to ask you to hold it right there. What help, Mr. Garr, should be offered to patients and to pharmaceutical companies to ensure that patients can afford these drugs, and then, that companies can sustainably provide the treatments that patients are seeking?

Mr. GARR. I think there are two basic things that have to happen. First, companies have to be able to charge for it—and, yes, there will be companies that still will not do it. There will be companies that will not offer their drugs. There is nothing in this Act

which forces companies to offer their drug under compassionate use or under “Right to Try.”

And, the second thing is there are, I believe, the last time I looked at it, about a dozen States that have already passed laws that require insurance companies to cover experimental treatments for certain types of cancer. So, if you are in a cancer trial in Kansas, for instance—right?—and it is at least a Phase II trial and you have to pay for it, it is just like it was an approved drug, in terms of the insurance company. I think that is the second part of the answer. Again, the market has to work. The insurance industry, we have all kinds of people working on drug pricing and approvals throughout this entire industry. And, I would add that we are an industry that is 100 percent based on the presumption that all of these issues can be addressed. People may not like the way they are addressed. Not everybody is happy with the answers. But, in the end, who gets drugs, what they are paid for, and who pays for them—we work that out for every approved drug on the market. So, there is no reason we cannot work that out for unapproved drugs also.

Senator CARPER. Thank you very much.

Mr. McFadyen, you have worked on behalf of patients. You mentioned patients and families. As a patient advocate, I just want to thank you for what you do. And also, Ellen, for your support as well, as his wife, trying to help individuals gain access for rare disease treatments. Have you ever worked with a patient who has received drugs under a “Right-to-Try” law?

Mr. MCFADYEN. No, not at all. And, that is what we continue to say, that there is no concrete evidence of patients ever receiving a medication under “Right to Try” in the United States that they otherwise would not have received under expanded access laws. And, there are 137 million people that have access—supposed access—under “Right to Try,” and there is no evidence that it is working—that it is moving forward. So, in my personal experience, no.

I can tell you that, the disease families that I represent—the rare disease folks—many of them are watching the live feed right now, and we are all united in the belief that, should legislation be passed, today, the landscape for them looking at access to medications, tomorrow, will not have changed. It is not the programs that are the issue right now. It is the companies and their fears under expanded access and adverse events—but also under “Right to Try.”

Senator CARPER. Just a follow-up question, if I could, Mr. McFadyen. What has been your experience, if any, in working with the FDA on behalf of patients seeking access to experimental medicines?

Mr. MCFADYEN. Yes, I have actually had a very good working relationship with the FDA—they have been very responsive to our needs. Richard Klein is the patient support liaison director at the FDA, and he returns emails—actually, I was shocked at how quickly I got responses from them, at first, and I am not anymore. They get information back to us very quickly. They help walk us through situations where we need information and that sort of thing. They are currently putting in place sort of a personal concierge service

to help physicians fill out that 45-minute form to make sure that it is done right so that they can have that on-the-phone conversation review—an overnight review type of thing. And, from what I understand, as well, your next witness, Dr. Lurie, is seen within the patient advocacy community as somebody who is a patient advocate at heart with the FDA and who really wants to try and advance access to medications for my kids—for our patients—as fast as possible.

Senator CARPER. I understand that Johnson & Johnson recently established a new program to help patients secure, I think, number one, information to experimental treatments but also access to those experimental treatments. I do not know if you are familiar with their program, but if you are, could you talk about it, please?

Mr. MCFADYEN. Yes, actually, Johnson & Johnson looked at this issue of access to medications long and hard and understood that things needed to move forward quickly. And so, what they put in place was something they called “CompAC.” They take all of the expanded access and compassionate use requests for one certain drug. It is a trial program right now that has just run its course and it is going to be expanding soon. And, they take those applications, and they send them on to a group at NYU Medical Center that looks at these applications. The applications are free of bias, so decisionmakers in that 10-person committee, which is made up of medical ethicists, researchers, physicians, and that sort of thing—Art Caplan leads that group. They look at those applications, and they make a recommendation back to J&J on whether a patient should be approved or denied access to that experimental drug.

Last year, alone, in the 6 months that it was on, I think they took in 100 or so applications. Sixty two of them were approved. Sixty of them were recommended by the committee to move forward back to J&J, and after that recommendation for 60, two more got in a little bit more medical information to the company, and they were approved. The other ones that were not approved were not approved because the patients had not exhausted all other avenues of available treatments.

And so, they used this program to make it extremely expedited and free from bias from pharmaceutical eyes based on costs, etc. And, they allowed others to recommend for them. It could be a pivotal turning point for companies, with respect to access to medications, because if this is a model that they can use and use successfully—a big company like J&J—and they are going to expand this process in the very near future for other drugs and that sort of thing. That is what we really need to do.

Taking that example, I know BioMarin Pharmaceuticals just announced an early access program for a disease that I actually deal with quite extensively, Batten disease. Batten disease is one of the worst childhood diseases I have ever seen. Over the course of a year or two, patients lose all mobility, all access to their extremities, and they enter a vegetative state and pass away very quickly. BioMarin, after Phase I–II, opened up an early access program. They are trying to get as much of the drug out as is feasibly possible for these patients, and they are taking a similar path forward to J&J by allowing the investigators to have their own committee

and their own set of ethics and criteria. So, they are not making the decisions anymore—and I am seeing this happen more and more with pharmaceutical companies looking at the problems that currently do exist with access to medications.

Senator CARPER. Thank you so much.

Chairman JOHNSON. Senator Paul.

Senator PAUL. I just have a really quick question. I wanted to reemphasize something Mr. Garr said and make sure I understand it. Under the compassionate use program, no money can change hands—not even for costs or anything?

Mr. GARR. No, there are mechanisms for recouping some costs, but the way they define cost is very different than the way a company thinks of it. A good example is ours. We literally have to send a cell technician up to Charles River Lab in Pennsylvania, have him work there for a day, do what he has to do, and ship the cells somewhere else, right? That is a very tiny part of the opportunity costs we lose when our Chief Science Officer (CSO) has to spend 24 hours being a cell technician.

Senator PAUL. Right. And, I guess the only other point I would like to make, quickly, is that, if you allow for profitability, I am all for that because profitability does drive innovation. There was an economist after World War II, Joseph Schumpeter, and he put it this way: “The miracle of capitalism is not that queens have silk stockings, but that factory girls do.” But, the way that is driven is, initially, only the queen may be able to afford it. And so, allowing money to go into the development of drugs, both through individuals or through companies, is a good thing. When calculators first came out, no poor person could afford them. Now, you are virtually given a calculator with your phone, basically. When most things are innovated—Lasik surgery came out, it was very expensive. Only the rich could afford it. But within years, if you allow capitalism to work, the price comes down. But, the driving force of innovation is allowing capitalism and pricing to work. And so, I think that is an important distinction between what we are talking about here and the compassionate use program—and a limitation of the compassionate use program.

Thank you.

Chairman JOHNSON. Thank you, Senator Paul. I would also point out, if you are talking about costs, it would be nice if it did not cost, on average, \$2.6 billion to bring a drug successfully to market.

Just really quickly, if anybody has a final—OK, but quickly.

Mr. CALDERON. Thank you, Senator Johnson. Just three quick points.

In terms of the 30 days of the application process—the new expedited application process with the FDA—it is 30 days if the FDA has any questions of the physician or the manufacturer.

In terms of statistics regarding “Right-to-Try” legislation, today, any statistics that you would gather from “Right-to-Try” laws, today would be, I believe, inappropriate to use because, when I introduced this bill last year, there were less than 10 States that had this on the books. Now, there are over 30. So, you would not have any properly measurable data to look at.

Chairman JOHNSON. And, until the Federal legislation provides that overall protection, they are not going to work. It does not sur-

prise me at all. There are not very many people like Dr. Delpassand who are willing to take that risk.

Mr. CALDERON. Right. And, in terms of costs, well, what is the other alternative, having to move to another country in order to get access to these drugs? And so, in terms of costs, well, yes, it is going to be more expensive even if you have to move to another State that has "Right-to-Try" laws on the books. It is better to stay in your own State to have that opportunity to do it at home.

Chairman JOHNSON. Quickly, anybody else? Mr. Garr. Oh, I am sorry. Mr. Neely.

Mr. NEELY. Yes, I think, just after this access, this is an avenue that we need. Patients need it and the doctors need it. Thank you.

Chairman JOHNSON. Matt.

Mr. BELLINA. Yes, Senator. I think that Andrew has done a really good job of laying out the obstacles, and I think there really is a lot of work that is going to need to be done even after the passage of this legislation. But, I think that you brought up a great point. What is the overt risk? What is the downside of this legislation? I think, you don't not try for a first down because it is not in the end zone—if anybody is into football. So, that would be my one question.

Chairman JOHNSON. Thank you, Matt.

Just very briefly.

Mr. MCFADYEN. It will be very brief. Senator Paul is no longer here, but I did want to address the idea of access. With all due respect, my son can wait until he can save up and afford a calculator. He cannot afford \$200,000-a-year or \$300,000-a-year drugs that can be charged under "Right-to-Try" legislation. Direct costs are direct costs and providing access should not be about making money.

Chairman JOHNSON. Again, I just want to thank all of the panelists and I appreciate your testimony. With that, we will call our next panel, Dr. Lurie. Thank you.

Senator CARPER. Thank you all.

[Pause.]

Chairman JOHNSON. Dr. Lurie, it is our tradition to swear in witnesses, so if you will please rise? Do you swear the testimony you will give before this Committee will be the truth, the whole truth, and nothing but the truth, so help you, God?

Dr. LURIE. I do.

Chairman JOHNSON. Please be seated.

Our next witness is Dr. Peter Lurie. He is the Associate Commissioner for Public Health Strategy and Analysis in the Office of the Commissioner at the Food and Drug Administration. Prior to that, Dr. Lurie was Senior Advisor in the Office of Policy and Planning. Before coming to the FDA, he was deputy director of Public Citizen's Health Research Group. He had an earlier academic career at the University of California, San Francisco (UCSF), and the University of Michigan (UM). Dr. Lurie.

**TESTIMONY OF PETER LURIE, M.D., M.P.H.,<sup>1</sup> ASSOCIATE COMMISSIONER FOR PUBLIC HEALTH STRATEGY AND ANALYSIS, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**

Dr. LURIE. Good morning. Mr. Chairman, Ranking Member Carper, and Members of the Committee, I am Peter Lurie, as you have heard, with the Office of Public Health Strategy and Analysis at the FDA. Thank you for the opportunity to be here to discuss expanded access to investigational products.

As a physician, I have personally witnessed the suffering—and we have heard much about that today in really heart-wrenching testimony—and I have witnessed the dilemmas facing patients and their families when they are confronted with serious or life-threatening conditions and have limited treatment options. In these circumstances, investigational products may be their only hope and the FDA recognizes that. In many instances, patients with life-threatening diseases are more willing to accept the risks associated with investigational products than other patients would—especially if they have no other available options.

And, that is why, for over two decades, the FDA has had in place a system to help patients gain access to investigational products. And, it is functioning well. The treating physician must first approach the pharmaceutical company. If the company agrees to the physician's request, the physician can then apply to the FDA for permission to proceed. Should they do so, they are highly likely to be allowed to proceed. The FDA has authorized more than 99 percent of single patient expanded access requests between 2010 and 2015. And, despite what we have heard, emergency requests are usually granted immediately over the telephone and non-emergency requests are processed in a median of 4 days. The 30 days means that the application can proceed without the FDA if we exceed 30 days. It does not take 30 days. It takes either the same day for emergencies or a median of 4 days for non-emergencies.

Now, access to investigational products requires the active cooperation of the treating physician, the FDA, and the industry. It appears that pharmaceutical companies turn down considerably more applications from physicians than does the agency. Mr. McFadyen spoke to this when he gave you the data from the Johnson & Johnson experience. They have turned down 98 applications for one drug in a 6-month period. Now, the FDA has turned down 66 applications—fewer, for all of the drugs that are out there, among the thousands that it has received. So, they have turned down 98. We have turned down only 66. And so, on this, I think Mr. Garr's testimony was very much on point as well.

Now, we continue to work avidly to improve the expanded access program because everything can be improved. The FDA established an expedited telephone process for daytime and after-hours emergency requests for expanded access—and you have heard about the success of that program. In 2009, we revised the application regulations to make the process and the responsibilities of physicians clearer.

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<sup>1</sup>The prepared statement of Mr. Lurie appears in the Appendix on page 307.

In June 2016, in response to feedback from physicians that completing the two expanded access forms was time-consuming, the FDA developed and released a new simple form for individual patient expanded access—and here it is. And, I am proud to say, I led the group that pulled this together. The form is estimated to take only 45 minutes to complete and requires just a single attachment, whereas, the previous form required up to eight.

At the same time that we put out this new form, we released step-by-step instructions on how to complete it and two additional guidances—one of which addressed the charging issue. Simultaneously, we revamped our expanded access website and we produced fact sheets for physicians and patients.

However, even patients with serious or life-threatening conditions require protection from unnecessary risks, particularly because, in general, the products that they are seeking through expanded access are unapproved—and may never be approved. Moreover, the FDA is concerned about the ability of unscrupulous individuals to exploit such vulnerable patients—and we see this. Thus, with every request, the FDA must determine that the potential patient benefit from the investigational drug justifies the potential risks, in the context of the disease, to be treated. And, that is why, even as we permit more than 99 percent of applications to proceed, we make meaningful changes to about 11 percent of them, generally to ensure patient safety, including changes in dosing, safety monitoring, and informed consent.

The FDA's expanded access process strikes a careful balance between helping to facilitate patient access to investigational therapies and the need to protect patients and promote the public health through science-based regulations—as Mr. Bellina points out. Upsetting this balance has the potential to expose patients to unreasonable risks and stymie the development of medical products that could benefit us all.

To sum up, the FDA's expanded access program allows almost all applications to proceed. It improves many of the applications that we receive and it does so expeditiously. At the same time, it protects vulnerable patients from potential harm from drugs that may not be effective and from exploitation by unscrupulous individuals. It also maintains the integrity of the clinical trials process because, in the end, the very best way to hasten access for patients to safe and effective drugs—for the largest number of patients, not just those in expanded access programs—is to get the drug approved.

That concludes my comments. I am happy to take any questions you may have.

Chairman JOHNSON. Thank you, Dr. Lurie.

You talked about undue risk. It is true, under this bill, that these drugs will have already passed Phase I, which has basically certified the safety of the drug. Can you reconcile those? What is the added risk if the FDA has already said it is a safe drug?

Dr. LURIE. We have not, sir. At the end of Phase I, we have only seen a few dozen patients being treated. And so, although we have some preliminary information about safety, we are far from certain that this is a safe drug. We still have Phase II to go through, where we gather additional safety information, followed by Phase III, in which we get still more. So, Phase I is a very long way from estab-

lishing effectiveness and it is also a long way from establishing safety.

Chairman JOHNSON. Well, you never completely establish safety. I mean, even once a drug is totally approved, you are going to continue to do that monitoring.

Dr. LURIE. Certainly, but there is a world of difference between a couple of dozen patients and the many hundreds to thousands who will, ultimately, be exposed during Phase III trials.

Chairman JOHNSON. Can you explain why Dr. Delpassand was not able to increase the number of patients he was able to treat? Now, here is a situation where the manufacturer has actually agreed to provide the drug.

Dr. LURIE. Right.

Chairman JOHNSON. I would assume—it seems to be the real stumbling block in whether it is expanded access or “Right to Try” that—because companies do not have protections against adverse effects—they do not have liability protection. I want to talk a little bit about the restrictions, in terms of being able to charge patients. But do you know what is pulling off, in terms of down there in Texas?

Dr. LURIE. I really cannot speak to that, sir. I have only seen the video for the first time this morning, so I cannot speak to the details of that. And, as I think you understand, these are pre-market drugs and the FDA is restricted in its ability to be able to discuss them.

Chairman JOHNSON. Can you understand just the human frustration, though, when you have a doctor apparently, again, working with patients, having access to a drug, treating, getting up to his limit of 150 patients, and having another almost 100 patients there that he thinks can benefit—and, I am sorry, bureaucrats in Washington, D.C., saying, “No, we are not going to let those extra 100 patients have that hope”? Can you speak to that?

Dr. LURIE. Yes, well, in principle, I could understand that. I cannot speak to his situation, but I can speak to the general situation, which is that, 99 percent of the time, when a doctor tries to get access for their patients, they succeed. And, the times that they do not, I must tell you, are really outlier situations. I mean, those are the situations where we—meaning our medical reviewers, who know as much as anybody about the drug, right? They know more than the doctor because we have seen the information coming in, perhaps from foreign countries, and unpublished results—we see that stuff. So, we may have additional information, and so, based on that, we may believe the drug is unsafe. Based on that, we may believe that there is no reasonable hope that the drug will work. Or, we may know that the company is not making the drug in a way that is safe for patients.

Those are the outlier reasons. That is 1 percent, right? Most of the time they are going through, but, when they do not, it is usually a fairly flagrant thing because we do not exercise that authority very often.

Chairman JOHNSON. What is the FDA’s intention, in terms of how it deals with someone like Dr. Delpassand, who is operating under Texas’ “Right-to-Try” law? Is there going to be any enforcement action against doctors that have the courage to do that?

Dr. LURIE. Yes, well, Senator I cannot really speak to what enforcement action we might take. We are a science-based organization—and we are interested in data. And, to the extent that data is generated—and that it might come to our attention—we are interested in the data that there might be.

Chairman JOHNSON. In your testimony, you use the phrase “exploit vulnerable patients.” Can you talk about what you mean by exploiting vulnerable patients—people, like Matt, who are trying to get access to a drug to give themselves some hope?

Dr. LURIE. Yes. Look, we understand that patients, like Matt, are looking for hope. We understand that. We understand how desperate they can be. But, it is that very desperation that makes them vulnerable to exploitation. All someone needs to do—

Chairman JOHNSON. Can I say, who are you—who is the FDA—to make that decision for them?

I am sorry. Who are you to tell Matt that you are going to protect him from exploitation when he has no further hope?

Dr. LURIE. Well, Senator, with respect, I feel like that is the very responsibility with which this Congress has charged us. I think we have been asked to look after patients—and we feel that that is exactly the responsibility that we are exercising.

Chairman JOHNSON. I have no further questions.

Senator CARPER. I want to dwell on the last question that the Chairman asked. In your testimony, I thought I heard you say the words “protect patients against unscrupulous individuals who might want to take advantage of those people.” Do you have any examples of that you might be able to share with us, either on the record or here, today?

Dr. LURIE. Well, Senator, as I said, the problem is that we cannot go into specific applications. But, I think that someone just has to take a look at the Internet and see the kinds of things that are being hawked there, and how often they focus on very desperate patients, to realize that this is a very real issue.

Senator CARPER. Alright. Thank you. Matt raised, earlier, when he was testifying—I think it was Matt who mentioned an ALS drug that had been approved, in Japan, maybe a couple of years ago—2 years ago—and that there was an effort to see if that drug could be made available here. I think, initially, the FDA said it needed 6 months to look at this—6 months—and then, they said, “No, we need 10 months.” Could you just talk about 6 months as opposed to 10 months—and, when you have some country, like Japan, that has been allowing a drug like this to be used for a couple of years? What is the approval process like at the FDA? How can we expedite that? Or can we?

Dr. LURIE. OK, so I think there are two issues. First is the 6 months versus the 10 months. So, those are goals that are in what is called our “user fee legislation.” They are the product of negotiation between the FDA and industry. And, there is a priority review process and a standard review process. The priority review is for those that would be expected to show a particular benefit—and that is 6 months. Otherwise, it is 10 months. About half go through each. That is the rough proportion between the two. That is legislation, in the end, that is ratified by the Congress—so we follow those. We have to get 90 percent—best we can—90 percent of the

applications for priority review in 6 months and for standard review in 10 months. And, we have met those goals now for a number of years.

So, that is the way it works. There is a definition. The FDA has guidance on it that explains the difference between the two. And, I expect that we did our best to follow that guidance in deciding how to assign that particular drug.

Now, with respect to the issue of Japan or foreign countries, in general, I think, there is an old story about how the FDA is slow and how drugs are on the market in foreign countries and American patients cannot get access to them. That is a very old story and, frankly, an outdated story. It just simply is not true.

Now, 57 percent of all drugs in the last several years that have come on the market have come on the market in this country first. Now, there are about 200 countries in this world, and—

Senator CARPER. That is over half of all of the drugs?

Dr. LURIE. Yes, over half of them. They are in 200 countries and one country is first most of the time.

Senator CARPER. And, that is us?

Dr. LURIE. And, that is us. And, just to be colloquial about it, if you go back to the Olympic Games and you look at how the Americans did, everybody said, "Well, what a great success. The Americans brought home this treasure trove of gold medals," which they did—and everybody is proud of that. But, they only won 12 percent of the gold medals. I mean, the FDA is doing better than that.

Senator CARPER. OK. Thank you.

Dr. Lurie, let me just ask—the FDA has released information to clarify that outcomes in expanded access cases are not treated the same way outcomes from clinical trials are treated. Do adverse events from expanded access cases ultimately affect the final outcome of the FDA's review of that drug? The FDA has approved almost 100 percent of expanded access applications, as you have mentioned. But has the FDA ever put a hold on an ongoing clinical trial as a result of an adverse event from a patient using expanded access? And, how quickly were these holds resolved?

Dr. LURIE. OK. So, let me answer that question sort of generally and then specifically.

The general answer is that our folks—our medical officers, who are experts at reviewing drugs—they understand that the expanded access situation is very different from the conventional clinical trial situation. The patients who are in it are different in expanded access. They are more likely to be sick. They are more likely to have other conditions. They are more likely to be on other drugs. There is no comparison group—right?—in general, in the expanded access program as well.

So, we know that any particular adverse event that comes in should be treated, in most cases, as an anecdote and should be afforded the appropriate weight, which, frankly, is not a very high weight, because it is just not—it is so atypical. And so, for that reason, I think that people should place some trust in the fact that medical officers can distinguish between these two very different sets of circumstances.

Now, we know that people are worried about it. We have heard this concern raised several times during the previous panel. And,

in fact, in one of the three guidances that I mentioned we released back in June, we addressed this question, specifically, in the so-called question and answer (Q&A) guidance. It is one of the three. Question 25 is about exactly this question. We explain how the FDA's medical officers understand the context and will apply the appropriate weight. Now, that is the general answer.

The specific answer is that we took this question seriously enough that we tried to gather some actual data. We went back 10 years and we looked at all of the applications that had come in. There were about 11,000 of them. And, they were—I am simplifying, slightly, here—for about 1,000 drugs—1,033, to be exact. And, we asked ourselves how many times had an adverse event that occurred in expanded access resulted in what we call a “clinical hold” on an application—right?—an ongoing manufacturer's application. Out of 1,033, over 10 years, we found two. OK? They were partial holds. Once the issues were resolved, then the program was allowed to continue.

So, we do understand this issue. We would not overweight these anecdotal pieces of information. But, we need to have that information all the same. OK?

What we do not want is a circumstance where the FDA does not receive an adverse event report. Or, if they receive it, they are forced to ignore it. I mean, for a scientific agency, it is just terrible for us to have, perhaps, in rare cases, valid scientific information and then, have to ignore it. Let us say the drug comes on the market, and then, after approval, when thousands of people start to get the drug, that very same adverse event now occurs and we knew about it back then, but we could not address it? I mean, we will probably be right here before this Committee again.

Senator CARPER. Thank you. If this legislation is not—it is well intentioned, very well intentioned legislation.

Dr. LURIE. Yes, sir.

Senator CARPER. If this is not the answer to this challenge, this conundrum that we face, what should we do that we have not done?

Dr. LURIE. Well, I think that some people have talked about some transparency on the part of the pharmaceutical industry. I do think that would be helpful. Johnson & Johnson has been a leader. I think more and more we are seeing companies put their expanded access policies, either in general or with respect to particular drugs, on their websites. I think those things really help. We are, as some others mentioned, exploring the possibility of a navigator to help folks get through the process.

As was also said, we have folks who are committed to doing that—who are dedicated to just that—day in and day out. And, they hold people's hands through this process. They understand which companies have drugs that are available through expanded access. They understand which parts of the FDA have jurisdiction over that drug. They understand what form needs to be filled out and how to do it. And, they hold your hand through the whole process.

So, we are reforming ourselves, internally, to make things better. The form is the biggest symbol of that, to be sure. And, I should say, parenthetically, 100 hours—I mean, as was pointed out, the

form was kind of a repurposed form. It had been for commercial purposes before. And, our form indeed said 100 hours. But, nobody believed that it actually took the 100 hours. I mean, do you know any doctor—or does your doctor ever spend 2½ weeks on you? Right? A hundred hours? It is inconceivable. So, that was never happening. OK? But now, all the same, we took the criticism seriously. And, to the extent that that misinformation had dissuaded people from applying, we have gone and reformed the form. It took a bunch of work. It is now done and people are starting to use it.

Senator CARPER. Mr. Chairman, I would just say that the folks at the FDA have a hard job. A hard job. Thank you for doing it.  
Chairman JOHNSON. Senator Lankford.

#### OPENING STATEMENT OF SENATOR LANKFORD

Senator LANKFORD. Dr. Lurie, thank you for being here. Let me pick up where you just left off there with the 100 hours for the form. It is my understanding that the 100 hours was not the time needed to complete the form, rather, it was the time needed to gather the information required for the form. The form was pretty straightforward, just as a checklist, but the form implied that it would take 100 hours to gather the information needed for the form. Is that accurate or not accurate?

Dr. LURIE. That is right. Under the Paperwork Reduction Act (PRA), when we make these estimates, the estimate that now says—on the back of this form, 45 minutes, it is not just, literally, filling it out. It is all of the associated materials, all of the attachments, and so on and so forth. And, I want to tell you, I took a look at that form. I am a physician and I work at the FDA. And, I thought, if you are a medical doctor (M.D.) out there, who is working hard and dealing with expanded access on a frequent basis, it was pretty intimidating. I agree with that. And, that is why we pulled together this group—exactly to address that concern.

Senator LANKFORD. So, the 45 minutes is not just completing the form. It is gathering information—

Dr. LURIE. Oh, it is everything.

Senator LANKFORD. It is everything required.

Dr. LURIE. It is everything. And, whereas before, there was a lot of additional information to collect—

Senator LANKFORD. Right, because it was just a two-page form before as well.

Dr. LURIE. Right.

Senator LANKFORD. So the form is not longer or shorter. The difference is the amount of information required to get in it?

Dr. LURIE. It is, in fact, shorter, in the sense that there used to be 26-odd fields and it is down to 11 fields.

Senator LANKFORD. Right.

Dr. LURIE. What we did was we took all of the information that was in the attachments and we brought them right into the form. So, it is now one-stop shopping essentially. The only thing that you now need to attach—and there used to be eight attachments. The only thing you now need to attach is the letter from the company. Right? And, of course, you have to get that first—and we have al-

ready heard, repeatedly, about the difficulties that doctors sometimes have in securing that, from the companies, for their patients.

Senator LANKFORD. OK. Talk to me about the internal conversation about acceptable risk. This has been one of the conversations to say at what point, as you go through the studies—one, two, and three, and the whole process—is the number, the percentage, there, of risk. So, help us understand that better.

Dr. LURIE. Well, certainly there is no way to discuss it, in percentages per se, but what someone can say is that people at the FDA understand that risk is something that varies according to the severity of the illness and the availability of other successful treatments for that condition. So, when we come up with something that is invariably fatal, we treat that differently. If we, instead, are presented with a drug that is to treat allergic rhinitis—right?—that is a totally different matter. And, this whole program is about serious and life-threatening illnesses for which there are no acceptable therapies as an alternative, right?

So, we are already in that box from the get-go, here, and so, it is not a very high bar—and that is expressed, mathematically, as the 99-percent approval rate.

Senator LANKFORD. Right. But, you were discussing, earlier, while we are in this box, the difference between the efficacy and then the safety issues as well—and talking about the first stage of it, then getting on to the second stage, we are getting more and more on efficacy and its own effectiveness and trying to evaluate that. At what point do you see through this process that someone is terminally ill and begins to see some effect that the risk outweighs that? That is pretty much the crux of this conversation.

Dr. LURIE. Right.

Senator LANKFORD. When the first level is done and patients hear the stories—or people that are not patients hear the stories—this seems to be effective, but then there is the pause to say, “We are going to go through multiple other areas.” How can we quickly get people in there that want to be able to take a higher risk knowing that stages two and three have not been done?

Dr. LURIE. Yes, well, again, the answer is almost always. I mean—99 percent—we almost always, in this bucket, are going to say that the potential for benefit outweighs the risk. It is in the very rare circumstance that we say no.

I would caution, though, that there is a lot of information that is out there about the claimed effectiveness of drugs—some of which gets a lot of press attention—and some of that simply is not so. Some of it is just not accurate information. And, it ends up creating a lot of noise, which is very difficult for us to refute.

Senator LANKFORD. What about the double blind studies? Once you start going through the process on a terminal illness and you deal with those folks that are getting the placebos and you see the individuals that are getting the drugs and see a rapid response.

Dr. LURIE. Right.

Senator LANKFORD. How do you all deal with the moral issues and the ethical issues of leaving those that are getting the placebo—knowing that they are in a terminal status, as opposed to trying to shift them over?

Dr. LURIE. OK. So there—

Senator LANKFORD. This is a science versus ethics conversation.

Dr. LURIE. I understand, absolutely, and so, there are kind of two elements to that. First is outside of the FDA, and the other is inside of the FDA. The outside of the FDA is that, in any significant randomized controlled trial, with or without a placebo, there is a committee that meets on a periodic basis called the Data Safety Monitoring Board (DSMB). And, they take a peek at the data, maybe every 6 months, to see what is going on, because what you would not want—as I think you are concerned about—is that people were in some long-term trial going on for years and years and years, and it turns out that back at 6 months you knew that people were getting seriously damaged by the drug and it continued for 2½ years more. Or, that after 6 months, there is such incredible evidence of effectiveness that you might as well have stopped right there and then, and you did not, and years went by, and people were still in the placebo group and the drug was not approved, right? Nobody wants that.

So, these Data Safety Monitoring Boards look in approximately every 6 months. They have rules about on which grounds they will stop the trial. And, if you meet that threshold, the trial is stopped, the blind is broken, and the data is made available. Right? So, that is how that works.

Now, with respect to the FDA, it does not happen especially often, but it does happen. There are some drugs that are just gangbusters, right? Many of the drugs we have, they help, but then, occasionally, you come along with something that just is hugely beneficial. And, we have a category for them. We have four expedited programs, and one of them is called breakthrough. And, if you turn out to have a drug that does that—something that is really so remarkable—then you get the breakthrough therapy, and with that comes a series of advantages that should get you to market sooner, because the last thing the FDA wants is to have in its files some drug that could make a huge difference to patients and people not getting it. That would be terrible.

Senator LANKFORD. OK, so the 6-month time period, obviously, for someone who has 1 year or 2 years—or they are feeling profound effects of the drug that is diminishing, whether it is the ability to walk or the ability to be able to speak, whatever it may be—the 6-month time period on the double blind to be able to come back and evaluate it seems like a long time in those situations.

Dr. LURIE. No. That is a different matter, Senator. So, the 6 months is the amount of time—now the trial is done where we start talking 6 months. The trial is done. Perhaps, it has been stopped by the DSMB, perhaps not. But, the 6 months is from the time that the application is presented to the FDA until the time at which we make a decision. OK? That is a different matter and that does take a certain amount of time. It used to be, when these things were not done electronically, we would get literally a roomful of boxes of information, right? Huge amounts of stuff that we had to make our way through. And, I should say, parenthetically, that the FDA is the only agency in the world who gets that raw data, right? There is nobody else in the world who does.

Senator LANKFORD. But what I am trying to figure out is while the study is ongoing—

Dr. LURIE. Right.

Senator LANKFORD. Maybe I misspoke on this earlier. While the study is ongoing and you are seeing an effect for those that are receiving the drug and they are receiving benefit—their speech is improving, their muscular function is improving, their organs, or whatever it may be—and those that are in the placebo are not.

Dr. LURIE. Right.

Senator LANKFORD. And, you see a significant number there—I am talking about during the study—the ethical conversation to say, “I have people in this study that are terminal,” and that you are allowing the study to be able to go through, to the end, when you see an obvious effect.

Dr. LURIE. Right. But, what I am trying to explain is that the FDA is not involved, in general, at that point, right? This is the company who has sponsored the trial—

Senator LANKFORD. But, does the FDA require a double blind study to be able to go through the process?

Dr. LURIE. Well, it depends on the nature of the drug, the condition, et cetera, et cetera. But, the point is that there is a control, and that control is the DSMB. And, the people who hire the DSMB, in effect, are the companies whose drug would come to market. So, the conversation that you are worried about—and it is a completely reasonable one, and it is what the DSMB is there to address—is something that is taking place before the product is presented to the FDA. Right?

Senator LANKFORD. Right.

Dr. LURIE. It is with the company at that point.

Senator LANKFORD. Right.

Dr. LURIE. And, the very concern that you are worried about is what the DSMB is for.

Senator LANKFORD. Well, I am concerned that the FDA has a requirement and that they are trying to fulfill that requirement to be able to get the drug to market, but that it may inadvertently doom some child or some adult to be stuck in a situation where they are receiving the placebo when there is a benefit—

Dr. LURIE. No, the FDA wants—

Senator LANKFORD. I understand that it is a rare thing to be able to see a rapid benefit like—

Dr. LURIE. Right. No. The FDA, wants there to be DSMBs. The FDA does not want people to go out and collect data for longer than is necessary to establish safety and effectiveness. And, if we can figure it out even earlier than expected, that is wonderful. We say, “stop the trial, please present the data, and come to the FDA.” If it is that great, there is a fair chance it will wind up in priority review. But, we do not want patients stuck in clinical trials that are just adding new patients—right?—and not really any meaningful new information about safety and effectiveness. If that is what is happening, we want the trial stopped. We want to see the data as soon as possible.

Senator LANKFORD. Mr. Chairman, may I ask one more question on this?

Chairman JOHNSON. Sure.

Senator LANKFORD. My question is about the toolkit licensing that has been proposed out there when you are dealing with a drug

that has been permitted for a certain organ, but, instead, opening it up for a certain type of treatment, for instance, a cancer treatment. So, it is actually a certain cancer. It has been approved for, maybe, the stomach, but this is trying to move to another area—and I have heard this ongoing conversation. I will tell you, I am not a physician, but I wanted to ask about where that is moving in the conversation.

Dr. LURIE. Senator, I am not prepared to discuss that today, but I am happy to look into it further and bring you back some answers.

Senator LANKFORD. OK. I would be glad to be able to get that, because that may broaden out and accelerate some of the process as well.

Dr. LURIE. OK.

Senator LANKFORD. Thank you, Mr. Chairman.

Chairman JOHNSON. Thank you, Senator Lankford.

I think we have spent too much time on this 100 hours, but I will point out, on January 4, 2015, you wrote an article in a blog, and here is a quote: “We estimate that physicians will be able to complete the finalized version of the form in just 45 minutes as compared to the 100 hours listed on the previous form.” Again, this was in February 2015.

Dr. LURIE. Right.

Chairman JOHNSON. It took you 16 months to get that new form out there. And, both of those are estimates, right? I mean, was it really 100 hours before?

Dr. LURIE. No. Again—

Chairman JOHNSON. And, now it is only 45 minutes?

Dr. LURIE. The 100 hours was estimating something different, right? It was estimating the amount of time to fill out a commercial Investigational New Drug (IND), as we call them, the application to administer the drug to patients. So, it was estimating something different.

When we went out and developed the estimate for this, I went out and I actually found people—physicians, within the Federal Government, partly in the FDA—we went to the Centers for Disease Control and Prevention (CDC) and we went to the National Institute of Health (NIH). We said, “Tell us how long it takes.”

Chairman JOHNSON. The bottom line is that for the previous expanded access form, the FDA estimated it took 100 hours to fill it out—

Dr. LURIE. No, I would not say that—

Chairman JOHNSON. Then, it took you 16 months to come up with a shorter form. And, now you are saying it takes 45 minutes. I am just kind of pointing out the FDA takes a little while to do these things.

Dr. LURIE. Well, Senator, look, I am the guy who put the group together, so I am happy to take the criticism home. But, I will say this: Under the way our processes work—and I think it is a process with which you are familiar—we have to put out a draft guidance, which we did in February 2015. We have to wait a certain number of days for comments to come in. We have to review those comments.

Now, what we decided to do this time was not only to just finalize that draft guidance, which is related to this form, we also decided to do more while we were at it. So we did not do one. We did three guidances.

Chairman JOHNSON. That is fine. Again, we are spending too much time on this one form—100 hours. I want to get to the real crux of the problem here, because I think we are confusing the approval rate versus the ability of a patient like Matt to actually get a drug and have the “Right to Try.” So, a 99-percent approval rate is one thing, but what is holding up, for example, Matt trying to contact a manufacturer 50 times to have access? And, from my standpoint, there are three things standing in the way of manufacturers actually taking his phone call and making their drugs available under some kind of expanded access or “Right to Try.”

First of all it is just the cost of providing it. These are companies. They are responsible to shareholders, and as Senator Paul was talking about, there is a profit motive that drives innovation and drives some of these discoveries. That cannot be minimized. Next, it is just the adverse effect and the effect of that—and you spoke to that earlier. The other thing is liability protection. So, there is an enormous impediment for manufacturers to agree to make these drugs available to somebody like Matt.

I guess I would just like you to speak to all three of those elements again. The cost. Companies develop drugs because, in the end, they are reporting to shareholders and they have to make a profit. So, it is difficult for companies to just give things away. A lot of them do. And, again, it is a \$2.6 billion cost, on average, for a successful drug—and that entails the cost of trying to develop all of the other drugs that fail.

So, first of all, talk about the cost. Under the current system, expanded access, what is the allowable rate of reimbursement versus what is it actually cost to manufacturers? And, just give us a generalization of that.

Dr. LURIE. So, one of the three guidances which I was referring to is exactly on that point, and what we say in it is that you can recover, under expanded access, the direct cost of providing the drug. And, the reason for that—and this is the place that we reached after taking comment from the public—is that you do not want to set it so high that some unscrupulous person might charge an arm and a leg to some vulnerable patient, right? So, that was the balance that we struck—and it seemed to be acceptable to most people.

Chairman JOHNSON. So, again, companies can get that direct cost.

Dr. LURIE. Yes.

Chairman JOHNSON. And that would include surgeons, as we are hearing from—

Dr. LURIE. Yes.

Chairman JOHNSON. OK.

Dr. LURIE. They can get the direct cost, correct.

Chairman JOHNSON. Now talk about just the liability. One of the things our bill offers is liability protection, which I do believe people, like Matt, Frank, and people in the audience, would sign a stack of liability waivers if they could have access.

Dr. LURIE. Right. I am afraid you are straying beyond my area of expertise at this point.

Chairman JOHNSON. So, under expanded access, do you know one way or the other whether there is liability protection?

Dr. LURIE. I cannot speak to that, Senator.

Chairman JOHNSON. And, then speak again to the adverse impact—or the adverse effect—and how that really is going to weigh into a manufacturer's decision of whether or not they want to take that call from Matt and make a drug available.

Dr. LURIE. Right. Well, we are hoping that they pay attention to the study that we published, because I think it is immensely reassuring. I mean, 2 out of 1,000 drugs were put on clinical hold—and only temporarily. I think from that, if I were a manufacturer, I would say, "Well, that is really pretty reassuring." And, quite honestly, if I were a manufacturer, I would want to know about the adverse effects that my drugs might cause sooner rather than later. I would not want to have my drug on the market because some adverse effect was ignored during expanded access—only to have it recur, where you might face liability when the drug is actually on the market.

But, Senator, we see some other reasons why the companies hold back—and I think you have heard a lot of testimony about how frequently that happens. And, I pointed out how one company has turned down, in 6 months, more than the FDA turned down in 5 years for all drugs.

Chairman JOHNSON. But, tell me why. Do you have any idea why that one company turned—was it because of lack of liability protection? Was it because of the concern about adverse effect? Was it because the direct cost really did not reimburse them properly? Do you have any idea why they turned them down?

Dr. LURIE. Sorry. Why the company—

Chairman JOHNSON. Correct. Do you have any idea what the rationale was?

Dr. LURIE. Why do companies turn them down?

Chairman JOHNSON. Yes. I mentioned three reasons. Do you have additional—

Dr. LURIE. I do. And, one is—and this sound totally banal, but it is true—there may not be enough drug around, OK? And, the companies are not in the business of making massive quantities of drugs for products that may never be approved. And, remember that lots of these expanded access products will never be approved, right?

Chairman JOHNSON. Some of these drugs are extremely expensive to manufacture, correct?

Dr. LURIE. Some of them are. And, you would not want to be making excess amounts of those if your product was never going to be approved. So, what they tend to do is to make an amount, maybe a little bit of excess, that will support the clinical trial. And, that is the second part of my answer.

The companies agree with us that the best way to get safe and effective drugs to people is through the clinical trial process—and they do not want to see that undermined in any way. And, we agree with them because we think, in the end, that is how you do it. Then, you are sure. And, it is not one patient at a time, as com-

elling as one patient is. There are thousands of patients behind them who we also need to think about. And, for them, it is the clinical trial process that will be lifesaving in some cases.

Chairman JOHNSON. So, let me finish out, just kind of going back to the question that Senator Lankford was talking about in regard to breakthrough drugs. Once again, here is the FDA making decisions for people—and, every drug is different and every situation is different. But, again, I just put myself in the position of a parent with a child, where you see over the years, through a clinical trial, that a drug, like the drug that was just approved for DMD is having a positive impact. And, your only access is to do a clinical trial, thinking that your child is maybe getting just saline. There has to be some way to give those parents the right to just, actually, make sure they get the drug. Do you understand that?

Dr. LURIE. I do, Senator.

Chairman JOHNSON. When it all comes right down to it, going back to the assemblyman from California, talking about, you have the right to die, why not the “Right to Try.” There is just something, in terms of the FDA making these decisions for parents and patients, that we have to come to grips with to let individuals make that decision—rather than have the FDA make it for them. At a certain point—and, again, from my standpoint, we are talking about once you have gone through Phase I, because there is a certain level of safety that has been agreed to. Again, you always are assessing a drug for safety even way past approval. You are always looking for that. I guess just respond to that.

Dr. LURIE. Well, it is hard to say that the FDA is making those decisions for people when we approve 99 percent of our applications. I mean, to me, if I am looking at a process—

Chairman JOHNSON. But, again, that is not talking about all of the impediments for people even in applying.

Dr. LURIE. Right, but that is not us, sir.

Chairman JOHNSON. Well, it is the adverse impact. It is the approval process. It is all of those things. You are a part of that whole process.

Dr. LURIE. I think we do need to keep the approval process and the expanded access process, separate in this conversation. And, there are efforts that Congress is discussing about the approval process, but that seems, to me, a different matter here. And, we should not really mix them together.

With regard to expanded access, we do understand how patients feel. And, it is for that reason—and, taking into account risk and benefit in their particular context—how desperate they can be—that is the reason they practically all get approved.

Chairman JOHNSON. So, we have 31 States— maybe with California passing it, 32 States—with these “Right-to-Try” laws on the books. And, all we are trying to do is get the Federal Government to kind of stay out of the way so that those “Right-to-Try” laws will actually work in the States. But, you cannot tell me one way or the other whether the FDA is going to allow those States’ “Right-to-Try” laws to work.

Dr. LURIE. Well, again, the Agency does not have a position on any of those bills or, for that matter, the Federal one. But, I will say this: If I were looking at a process—a multi-step process with

multiple collaborators and partners—industry, the doctor, the FDA, and so on—and I looked at a part of that process that approved 99 percent of applications—that improved many of those that we got and did so quickly, I probably would not be looking at that part as the part to reform.

Chairman JOHNSON. Thank you, Dr. Lurie.

Dr. LURIE. Thank you.

Chairman JOHNSON. The hearing record will remain open for 15 days until October 7, at 5 p.m., for the submission of statements and questions for the record. This hearing is adjourned.

[Whereupon, at 12:22 p.m., the Committee was adjourned.]

## A P P E N D I X

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### **Opening Statement of Chairman Johnson “Exploring a Right to Try for Terminally Ill Patients” September 22, 2016**

Good morning and welcome.

As members of Congress, we meet dozens of people every day – all with different stories. And it is one of our greatest privileges that when we are entrusted with these stories, we have a unique ability to act.

More than two years ago, Trickett Wendler entrusted me with her story. People would say she was suffering from ALS, but really she was fighting ALS. She was tirelessly advocating for any hope that could help her and others win their fight against a disease with a near certain outcome. She was fighting for the right to try to save her own life.

Trickett passed away on March 18, 2015.

In February of this year, I met then six-year-old Jordan McLinn, full of life and curiosity. A nearly 100 percent fatal form of muscular dystrophy is robbing him of his strength, and soon he won't be able to walk, brush his teeth or hug his mother.

Yet there was hope. A promising treatment was in the pipeline for FDA approval. And thankfully, just this week approval was granted; but only after months of unnecessary delays and years of study and trials – delays that mean Jordan and others may never regain muscle function they lost waiting for the federal government's permission to use a treatment almost everyone agreed was safe and could potentially save their lives.

For Jordan, Trickett and retired Navy pilot Matt Bellina, who now fights his own battle with ALS, I introduced the Trickett Wendler Right to Try Act of 2016. It simply says patients, who have no alternative and are facing death, should have the ability to try to save their own lives – the right to hope.

The bill is really a federal counterpart to the incredible bipartisan movement that has led to adoption of Right to Try laws in 31 states. But it's unclear what effect those state laws have until we make certain the federal government will respect them.

Despite the legal uncertainty there are doctors willing to jeopardize their practice to give patients needed, but unfortunately unapproved, treatments. One of them is Houston oncologist Dr. Ebrahim Delpassand. Even though the FDA has told him no, he bravely continues to treat patients under his state's law. Now nearly 80 patients, whose chance of survival would be, as he puts it, “close to none,” are alive thanks to his treatment.

For the millions of patients fighting for a chance to try, we must do what we can to help them. Right to Try is not a cure, and it's not a miracle, but it is a way to hold on to hope.

**Statement of Ranking Member Tom Carper**  
**“Exploring a Right to Try for Terminally Ill Patients”**  
**September 22, 2016**

Thank you, Mr. Chairman, for calling this hearing today. I appreciate your willingness to continue a conversation about an important issue that is critical for Americans seeking access to potentially lifesaving treatments. I also want to thank you and your staff for the ongoing work that we are engaged in to try and move the ball forward and find ways to help patients gain access to experimental therapies, including through a forthcoming GAO report on these issues. I also want to thank our witnesses, especially Representative Neely, Mr. Matthew Bellina, Mr. Richard Garr, and Mr. Andrew McFadyen for their willingness to share their personal stories with us.

Before I begin my formal statement I would just like to mention my appreciation for the Chairman sharing this video. I look forward to learning more about this physician’s experience. My understanding is that in what would seem to be similar situations, the U.S. Food and Drug Administration (FDA) has approved over 99 percent of patient applications for expanded access to these new experimental treatments. In fact, I understand the FDA has even granted drug approvals based solely on expanded access data. The FDA is, by law, precluded from discussing the details of any drug under review, but if the doctor was with us today, I would ask him why he did not appear to use the expanded access program which has worked quickly and efficiently for so many patients and their doctors. With that in mind I would like to ask unanimous consent that we place an FDA fact sheet on expanded access along with the recently updated application form in the record.

Today, we will have an opportunity to hear from the FDA, state representatives, patients, their loved ones, and other advocates on ways we could improve access to experimental medical treatments. These individuals and their families have faced some of the most difficult and painful challenges anyone could face. They deserve to be heard, and they deserve better access to experimental treatments. We will also have an opportunity today to review the Chairman’s Legislation, S. 2912 the Trickett Wendler Right to Try Act. I appreciate the intent of Chairman Johnson’s bill, and certainly support expanding access to experimental therapies to terminally ill patients.

We must keep in mind, however, that there is already what I understand to be an effective framework in place at the FDA that gives patients access to experimental drugs while those drugs are still being tested. The agency has given an extraordinary level of attention to the requests of patients with life-threatening conditions. In fact, I’m told it has approved more than 99 percent of requests for emergency treatments between 2010 and 2015. The agency has also taken constructive steps to greatly simplify its application process and further improve and streamline patients’ access to experimental treatments.

Despite the high approval rates and ongoing reforms, I understand that the FDA believes more can be done and is continuing to work to improve patient access to experimental treatments. I hope to learn more about those steps today, as well as some additional ideas for how to ensure

that all patients in need have the information and resources necessary to access experimental medicines.

For terminally ill patients and their loved ones, safe and effective treatments cannot come quickly enough. That is why we need to do everything we can to give patients, doctors, and the companies that make these drugs the tools they need to participate in clinical trials, utilize the FDA's expanded access programs, and develop new treatments as safely, effectively, and quickly as possible. I hope this committee can help with those efforts and work with patients, health care providers, the pharmaceutical industry, and the FDA to ensure that all patients and their families can access safe and effective treatments as quickly as possible.

I want to close by thanking the witnesses and their families again for their willingness to share their stories and put forward possible solutions to these challenging issues.

**Statement of Matthew Bellina****HSGAC Hearing – September 22, 2016**

As a 32 year old father, U.S. Veteran, and terminally ill ALS patient, I wanted to clear up some misconceptions about S. 2912 and HR 3012—the Right to Try Acts

I should begin by clarifying a key point. No one who supports the federal Right to Try Acts or the state laws they protect wants to undermine the FDA or relax the standards that must be met for drug to be officially approved by the FDA. We simply believe that we can do better at getting promising treatments to sick and dying Americans.

A recent GAO report found that the pace of scientific discovery is stifled by an overly burdensome regulatory environment in the FDA's clinical trial protocol. ALS is a perfect illustration. There are 37 known ALS genetic mutations that make up less than 10% of all cases. The other 90% of ALS patients are suffering from a similar disease (or diseases) of unspecified cause. Under the current regulatory environment, all ALS patients are put into the same clinical trial cohorts in the hopes that one drug might show efficacy in the overall patient population. This is bad science and can never be successful.

Right to Try laws will let doctors look at individual patient biomarkers and work with pharmaceutical companies to use known compounds that target a patient's specific disease profile. This is the future of medicine—and we have the technology, just not the regulations, to allow us to do this now. I cannot speak directly for them, but I surmise this is why the ALS Association recently endorsed S. 2912.

I have heard the argument that this legislation would subject patients to risk and they would have no legal recourse if things go wrong. I have heard the only thing worse than a terminal illness is being terminally ill and suffering a major complication as a guinea pig in an experimental treatment that you had to pay for.

Without any intended insult, I do not believe it is the role of interest groups or bioethicists who have never met me to dictate how I should find value in my remaining days. If some believe that living without hope is superior to living with the risk of side effects that is their personal business.

My motor neurons are dying and without treatment I will suffocate under the weight of my own chest. I am willing to make informed choices with my doctor, based on the individual nature of my disease. Furthermore, any compound that would qualify as a Right to Try drug would already have passed safety trials and be in an active FDA-approved Phase 2 or Phase 3 trial. In other words, the FDA has already deemed the compound worth the risk of further exploration.

Why shouldn't I be given the same right as the limited number of patients lucky enough to get into clinical trials?

I have also heard the argument that the FDA's current compassionate use program already provides patients with the opportunity to try investigational drugs. But this program is severely flawed. The

FDA itself has acknowledged these flaws by attempting to streamline the application process and proposing a new office within the agency to help dying people navigate its bureaucracy.

As long as bureaucrats are making the decisions about which terminal patients are privileged enough to have access to investigational treatments, the academic and scientific integrity of biopharmaceutical research will be inhibited, in the best-case scenario. In the worst-case scenario, we will continue to repeat the same sample bias, which has failed to cure heterogeneous diseases for over 60 years.

I have heard the argument that bypassing the oversight of the FDA is not in the best interest of patients or public health. This is a straw man argument. No one is asking to bypass FDA oversight. Lawmakers must realize that only drugs active in Phase 2 or Phase 3 trials will qualify as Right to Try drugs. The FDA will still have control over what drugs can be bought and sold in the United States. And because the availability of drugs under Right to Try depends on the FDA trail process, the “Gold Standard” remains completely intact.

The greatest weakness of these bills is that many pharmaceutical companies may choose not to participate. If that happens then we have missed a great opportunity, but no one will be overtly harmed. On the other hand, the risk of not passing these bills is that a good drug may languish for 10-14 years in the FDA pipeline and countless Americans will die. Their lives will end without the chance to exercise their Constitutional freedom to make choices regarding their life, liberty, and their own pursuit of happiness.

Testimony of the Honorable Ian C. Calderon

Majority Leader

California State Assembly

Before the

United States Senate

Committee on Homeland Security and Governmental Affairs

“Exploring a Right to Try for Terminally Ill Patients”

September 22, 2016

Thank you Chairman Johnson, Ranking Member Carper, and Members of the Committee for inviting me here today. I am honored to testify before you about Right to Try for terminally ill patients.

As Majority Leader of the California State Assembly, I am fortunate to work on a variety of public policy issues every year. This year alone I've sent bills to the Governor dealing with issues ranging from ensuring that financial literacy is part of the high school curriculum, to setting minimum fines for piracy violations. While each bill I work on is a piece of policy I believe strongly in, my work on Right to Try legislation over the last two years has truly given me purpose as an elected official. The fight to allow terminally ill patients to seek investigational drugs and treatments not yet approved by the FDA is something I'm immensely proud to be a part of in California, and I thank you for giving me the opportunity to talk about it today.

In January of 2015, much of the policy conversations in California centered around "Death with Dignity." If you recall, this was mere months after Brittany Maynard, the young woman diagnosed with brain cancer, had moved from California to Oregon, in order to utilize Oregon's Death with Dignity law. While researching Oregon's law and its possible application in California, it struck me that this conversation needed to include policy prescriptions to make it easier for these terminally ill patients to fight to save or extend their lives as well. It was then that I came across the Right to Try movement, and subsequently introduced Assembly Bill 159. For me, Right to Try was a logical companion to Death with Dignity. I never saw the two issues as incompatible. I didn't want to limit the options for those diagnosed with a terminal illness, to

only death, albeit a more controlled one. I felt strongly that if we were going to pass Death with Dignity, and thus make it easier for terminally ill patients to die in California, that we should also make it easier for these terminally ill patients to fight to live, by giving them access to potentially life-saving drugs and treatments, that have been deemed safe, but not yet approved by the FDA.

As the first iteration of California's Right to Try legislation made its way through the legislative process, I had the privilege of meeting David Huntley. David was a Professor Emeritus at San Diego State University, an accomplished ironman triathlete, and an obviously loved husband and father. David was also diagnosed with ALS, more commonly known as Lou Gehrig's Disease. It's a death sentence given our current lack of understanding of the disease, but there are ways to combat the speed at which it progresses, and the pain it causes. Shortly after his diagnosis, David learned that there was a promising new drug called GM604, that was still in the clinical trial process at the FDA, and thus had not yet been approved. He sought access to this drug, but was denied. So David spent the latter part of his life fighting to give patients like himself a chance. David agreed to fly up to Sacramento in April of last year to testify with me before the California Assembly Health Committee. This was the first committee hearing on Right to Try in California. David's testimony and clear understanding of the pitfalls of the current experimental drug access paradigm was instrumental in getting us past that first legislative hurdle.

It was evident that David was in a tremendous amount of pain, yet he was determined that he be there to help Right to Try legislation pass in his home state. Just three months after testifying, on July 4<sup>th</sup>, 2015, David Huntley succumbed to ALS and passed away. He came to Sacramento to testify, for a measure he knew would be too late to help himself, but to ensure that future

terminally ill patients have the access to potentially life-saving medication he had been denied. That kind of selflessness is rare, and I'll never forget his dedication.

With David's help, Right to Try passed the Assembly Health Committee, but it still faced intense scrutiny from five more Committees in the Assembly and Senate. Though this was only last year, it was early in the Right to Try movement. The bill went through a rigorous public hearing process, where we sought to improve upon the Right to Try legislation that had been introduced in other states. Each Committee, in concert with the myriad of stakeholder groups, and in deference to concerns that felt unique to California, included amendments to the legislation. Throughout the Committee process we worked on, and eventually added, several amendments to alleviate concerns about having proper oversight patient protections. We added Institutional Review Board Oversight of a physician's recommendation, in order to ensure that patients are fully aware of the potential side-effects of any investigational drugs they may consume. We also added a requirement that a consulting physician confirm the primary physicians' diagnosis that the patient is terminally ill, and inserted reporting requirements to the California Department of Public Health, to further increase oversight. And, similar to the difference I see in Senator Johnson's Right to Try bill versus the House's version, we clarified that the legislation would not create a private cause of action against the prescribing physician or drug manufacturer – this was instrumental in removing the opposition of the California Medical Association.

While we weren't able to completely remove all opposition to the California's Right to Try bill, through the public hearing process we did work to address many of their concerns, without compromising the strong intent of my bill. When my Right to Try bill reached the Governor's

desk last year, I was satisfied that due to its strong patient protections and robust oversight requirements, it was one of the most comprehensive versions of Right to Try legislation in the country.

The governor vetoed my bill. In his veto message, he acknowledged that the FDA was in the process of streamlining its Expanded Access application, and wanted to grant the agency the time to do so, with the hope that this new application would make a state process unnecessary. As 31 other states have passed Right to Try legislation, I'm happy to have been a part of the impetus that spurred the FDA to streamline the application. However, these new regulations, announced in June of this year, only deal with streamlining the physician's portion of the application. This is an improvement, but the new process does nothing to shorten the manufacturer's portion and the data required by the application or reduce the 30 days the FDA has to decide. According to statistics furnished by the FDA, roughly 1,000 terminally ill patients make it through the costly and cumbersome application process each year. Considering the fact that 564,000 Americans are expected to die from cancer alone this year, the small number of people navigating the FDA's Expanded Use program speaks to the program's failure to actually help terminally ill patients obtain access to life saving treatment. These patients do not have the luxury of waiting for an onerous, bureaucratic process. This is one of the chief reasons Right to Try Legislation is so important. In the midst of a battle with a life-threatening illness, it is much easier for a patient to deal with their own doctor than a large and impersonal government agency.

At the beginning of this year, I re-introduced Right to Try legislation in California. Fortunately, with all of the protections added via last year's comprehensive public hearing process, Assembly

Bill 1668 had a much smoother path through the State Assembly and Senate. It now sits on the Governor's desk, and I'm hopeful will merit his signature, adding California as the 32<sup>nd</sup> state to enact Right to Try legislation.

Mr. Chairman, members of the Committee, thank you for giving me the opportunity to share my effort to bring Right to Try to California. I applaud any effort at the Federal level to do the same nationwide. I hope the federal government doesn't stop there. We need federal legislation that expedites the FDA's drug approval process. It should not take 10 to 15 years to approve new, life-saving treatments. In the meantime, I commend the federal effort to encourage states to essentially adopt methods to work around the FDA.

Right to try, at its core, is very simple and speaks to a basic human right. If your parent, your child, or even you are faced with a terminal illness, there should be a process in place for you to seek potentially life-saving treatments, and the government should not impede that. Thank you very much for your time.

## Why Patients Need the Right to Try

*Dr. Jim Neely - State Representative - Missouri's 8th District*

Mr. Chairman, members of the committee, my name is Jim Neely. I'm a physician and State Representative from Cameron, Missouri. I'm here to go on the record in support of this bill because terminally-ill patients don't have time to wait for the FDA to approve investigational treatments.

I've been practicing medicine for over 30 years. Over that time, I've seen patients with medical conditions and issues of life that have been very challenging to deal with; from cancer to multiple sclerosis.

I remember treating my first AIDs patient back in 1985 in Florida. After the examination, I walked out of the room with very little idea of how to help him. I regrouped with other physicians, and we agreed, without access to an experimental treatment, he was *completely* hopeless.

There were clinical trials at the time, but he wasn't eligible. We needed more options. The FDA didn't approve the first effective antiretroviral for AIDs until the following year. It was too late.

### ***Disincentives for Compassionate Use***

Throughout my medical career, I've been troubled by the laws that restrict suffering patients' access to investigational treatments. As a physician, my practice is guided by evidence, so I

understand the importance of our clinical trial system; however, terminally-ill patients deserve the option to try investigational treatments after they have exhausted all approved treatment options and are no longer eligible for clinical trials,

As I began considering this issue as a State legislator, my daughter Kristina was diagnosed with Stage 4 colon cancer. She had four children at the time, and was carrying her fifth, which severely limited her eligibility for clinical trials. From a research perspective, I understand the importance of studying a uniform group of patients, but there has to be room for compassion for patients, like my daughter.

Before she passed away, Kristina was adamant that her right to try treatments "shouldn't be up to somebody that has no involvement in my care." I believe this bill goes a long way toward giving more options to terminally-ill patients and their doctors.

#### **Restricted Access Harms Indigent Patients**

A friend of mine, Ross Nichols, came to testify in support of the Right to Try bill we passed in Missouri. At the time, he was receiving treatment at MD Anderson for glioblastoma, the most common and aggressive form of brain cancer. Ross knew that the experimental treatments he received were unlikely to save to his life, but he still sought to enroll in clinical trials, explaining, "my number one job right now is being a dad, and I'll do whatever I can do to try to extend that."

Ross told the committee that he was testifying for the bill because he wanted people in Missouri

to have access to the same treatments that were available to him at the research institutions he could afford to travel to. He was right.

Many people fighting for their life, cannot afford to spend what-could-be their final months traveling across the country in order to receive investigational treatments. I'm glad Ross was able to travel to receive treatment that gave him hope, but he shouldn't have had to. Ross passed away in February of 2015. I'm glad his hope for other patients lives on with this bill.

#### **Restricted Access Strains the Doctor-Patient Relationship**

Rick Suozzi, father of the late Kim Suozzi, also came to testify in support of our right to try bill in Missouri. His daughter was diagnosed with glioblastoma at age 21, during her final semester at Truman State University. Kim knew her diagnosis was a death sentence, but she went to extraordinary lengths for a small chance to survive. She traveled to the top cancer research institutions - Dana Farber, UCLA, MD Anderson, and Duke- just to participate in clinical trials that gave her a glimmer of hope.

Kim enrolled in three trials in the last six months of her life. When she was no longer eligible for clinical trials, she lied to research doctors about her treatment history in order to make herself eligible. Can any of us blame her?

Thank you for giving me the opportunity to share these stories. I believe government should create opportunities for people to care for each other, not erect and maintain barriers. This bill

knocks down some of the major barriers to care that make life even more difficult for terminally-ill patients. With that, I'd be happy to take any questions.

## **In Support of S. 2912**

**Richard Garr**

*Former President and Chief Executive Officer, Neuralstem, Inc.*

US Senate Committee on Homeland Security & Governmental Affairs  
Hearing: Exploring a Right to Try for Terminally Ill Patients

September 22, 2016

I would like to thank the committee for this opportunity to testify in support of S 2912, known as the Trickett Wendler Right to Try Act. As President & CEO of a biopharmaceutical company developing treatments for currently incurable diseases; as a member of the advisory board that helped craft the model right to try act which has been making it's way through the states; and as the father of a son diagnosed with a grapefruit sized brain tumor at age 4; I have been involved in the scientific, FDA regulatory, business, legislative and patient advocacy arenas germane to this issue for over two decades. S. 2912 is a good bill that will provide hope and comfort to many patients diagnosed with fatal diseases; and it will accelerate the effort to find cures for currently incurable diseases.

It is not without its controversies and issues, but I believe many of the criticisms of the bill are the result of misinformation and lack of understanding of how the bill actually will work. I would like to spend my limited time here today setting the record straight and answering these criticisms.

An often heard criticism is that the bill allows unsafe medicines to be foisted on an unsuspecting public. Nothing could be further from the truth. This bill, like **all** of the state passed bills that have preceded it, relies heavily on the proven safety track record of the FDA. No treatment may be administered under this bill unless it has already successfully passed through an FDA safety trial; AND is continuing in the FDA approval process into later stage trials. This insures that there is a continuing evaluation of the safety of any treatment administered under a right to try act. If a company, for any reason, safety or otherwise pulls a drug from the FDA que it is no longer allowed to be administered under the act. I would note that this is not a protection afforded to the public with respect to approved drugs.

I will also point out here that treatments for fatal diseases are obviously extremely difficult to develop. The failure rate is obviously extremely high and so no company enters into such an undertaking lightly. Even in small biotech companies such as Neuralstem, which I had the honor to help found and run for 15 years, we spent tens of millions of dollars over a decade to get our ALS product into the clinic. The body of science required, and sophistication and volume of pre clinical safety data required to simply get into an FDA approved trial is an enormous undertaking. The point is, in addition to a successful phase

one safety trial, there is a large body of pre clinical safety data and manufacturing process purity data behind all of these treatments, by definition; no exceptions. I would also point out that the FDA often continues to request continuing non human safety testing as a drug moves through the approval process and new data becomes available. These are heavily vetted and continually investigated treatments being made available by the act.

I would also like to debunk the myth that this is somehow an "anti FDA" bill. Again, nothing could be further from the truth. As just explained, the bill's heart is the safety net that continuing FDA oversight provides. An oversight by the way, that is universally acknowledged as the gold standard for the world. Even proponents of the Right to Try movement such as the Goldwater Institute, who might believe that the right to try is based on a Constitutional principle, and might disagree with the idea of Federal pre-emption have insisted on this FDA oversight principle on safety. This is not an anti FDA effort.

I would like to address the argument I have heard that this act gives false hope to patients, promising cures. As I mentioned I have been involved in the ALS and brain tumor patient community for a long time; as well as patient and caregiver communities in other currently incurable but not fatal diseases. The biotech and pharmaceutical industry is meticulous about educating patients as to the experimental nature of their treatments in the trial stages. While we are always hopeful that we are on to something substantial, patients are always informed that they are helping to accelerate research, and not being promised a cure. I will also tell you that these diseases are devastating emotionally to patients and their caregivers. They often feel a sense of hopelessness and despair. In ALS, some make their peace with their fate and focus on their remaining time. But many tell you they would like to "go down fighting" and being part of experimental research, whether in a clinical trial setting or through a right to try compassionate use setting, lends an additional sense of purpose to their lives. Having hope for many, is an essential element to improving their quality of life, even if it is a small hope. Patients and caregivers alike know that even every failure brings us closer to an actual cure and their doctors will tell you that that can add great comfort and some sense of control to their lives as they struggle through their illness. The fact that a doctor must administer these treatments ensures that patients have this information before undertaking any treatment. So yes, this is a choice, but it is an informed choice. This is a right to try act, not a right to cure act and all patients will understand this as a result of the mechanisms built into this bill.

I would like to address two areas more related to the "business side" of Right to Try. Yes, companies need to be able to charge for the treatment, and they should be free to set the cost. Almost all new experimental treatments for fatal diseases are going to be modern medicines; cell and/or gene therapies, monoclonal antibodies etc. The ability to apply resources to provide treatments while simultaneously conducting clinical trials will vary from company to company. There can be no "one size fits all" cost formula that would be either fair or productive. Only a company knows its true opportunity costs in such a situation. Indeed, there is nothing in any of the state bills, and of course nothing in this federal bill, that requires a company to make its treatment available under right to try. This too must be decided by the company itself.

I have heard the criticism that actually carrying this out is simply "too hard". That all of the unresolved issues around insurance reimbursement and liability, both professional and product, added to a fear of "rationing" because of scant availability and a host of others make this unworkable. It is true that all of these issues must be addressed, but it also true that we have these exact same issues with respect to approved drugs; and that in fact we are an industry completely based upon the proposition that all of these issues are addressable. There are people in the applicable chairs throughout the space who work on these issues all day every day with respect to approved drugs. This will be no different. Not every resolution will be perfect, and not everyone will be happy with how these issues are resolved, but that is also true with approved drugs; and just as with approved drugs, all of these issues will get resolved.

Finally, I have heard it said that there are already dozens of states that have passed these laws and yet no one is being treated. I can tell you wearing my industry hat that no company will feel comfortable acting under these state laws, until the protections afforded companies under this Federal law are enacted. This Bill is essential to unlocking the promise of all of the Right to Try acts.

Congressional Hearing Written Submission  
Exploring a Right to Try for Terminally Ill Patients

Andrew McFadyen | The Isaac Foundation

September 22, 2016





**The Isaac Foundation** is an organization based in Canada that has dedicated itself to finding a cure for a rare and devastating disease called Mucopolysaccharidosis, or MPS. Our work pushes international boundaries, with the bulk of our advocacy and patient support taking place in Canada and the United States. This is an organization that is very dear to me, because it is named after my son – my hero, and the bravest person I know – Isaac McFadyen, who suffers from MPS Type VI.

When Isaac was diagnosed at the age of 18 months, we were told that he was going to live a life of pain and suffering, and that we would endure many years of heartache and heartbreak. Throughout the course of his life, we were told that Isaac was sure to suffer from heart and airway disease, progressive stiffening of his bones and joints requiring hip and knee replacements and other orthopaedic surgeries, corneal clouding, shortened stature, and a severely shortened lifespan. Essentially, every bone, muscle, organ, and tissue in his body would be ravaged by this disease until he eventually succumbed to the condition, probably in his early to late teens.

During the past decade he's battled – we've battled – to stave off the inevitable. And we've been lucky. In 2006, after a lot of work and determination, we were able to bring a new life-prolonging treatment to Canada – an enzyme replacement therapy that was approved by the FDA but not by Health Canada – to fight his disease. Isaac is now 12 years old, and the 12 that we see today is very different than the 12 we were told to prepare for.

After our success bringing Isaac's treatment to Canada, other families began contacting our organization so that we could help them obtain access to rare disease medications, provide advocacy and support, and walk alongside them throughout their journey. At the time, we knew of only 3 children in Canada fighting this disease, and Isaac gaining access to treatment prior to its approval opened the door for the other children to get the help they needed as well. After another 11 patients were diagnosed, we worked to ensure that all 14 patients in Canada battling MPS VI were receiving access to their life-sustaining medication prior to approval from Health Canada.

I'm proud to say that we've never been unsuccessful gaining access to rare disease treatments for children in Canada, and our work directly with pharmaceutical companies is helping patients see similar results in the United States

Andrew McFadyen,  
Executive Director, The  
Isaac Foundation

These successes brought many more families our way – families battling other forms of MPS, battling other diseases – from Duchenne Muscular Dystrophy, to Batten Disease, to Gaucher Disease, to rare paediatric cancers. Our mission to find a cure for our son became a multi-faceted mission – a mission

that crossed borders and crossed disease families. It became a mission to help those who were suffering from any rare disease and in need, and we've dedicated ourselves to that mission ever since.

Today, I'm proud to say that we've never been unsuccessful gaining access to rare disease treatments for children in Canada, and our work directly with pharmaceutical companies is helping patients see similar results for countless children in the United States. We've achieved this success in part because I understand the world that our families are living in, and I understand the unbearable burden that a potentially terminal diagnosis brings. I understand because I live each and every day facing the mortality of my son. I understand because after 10 years, I still wake up every night and check to be sure that my son is still breathing, crippled by the fear that one day I'll walk in and he won't be. I understand because I've walked this lonely road, searching for Hope when all Hope seemed lost. I've been there - I'm still there - and I continue to work tirelessly to find a cure for him before the clock runs out.

It's because I've been there that I can see the appeal that Right to Try legislation brings to those who have nowhere else to turn. The Goldwater Institute has done a marvellous job of promoting Right to Try laws as being the last chance for people to extend their lives. Very pointedly, Goldwater claims that "Right To Try laws help patients get immediate access to the medical treatments they need before it's too late," and have characterized Right to Try laws as legislation that "restores life-saving hope back to those who've lost it."<sup>1</sup>

This utopian vision of access to medications for millions of Americans who desperately need them is laudable. However, the cruel reality with Right to Try legislation is that it will not grant patients the immediate access to treatments they desperately need.

This utopian vision of access to medications for millions of Americans who desperately need them is laudable. The tagline that my organization uses is "Love, Laughter, and Hope." Love and Laughter because this is what my son and our families give me each and every day. Hope because sometimes that is all you have left. So I understand Hope, and the pull for families to seek that Hope wherever they can find it.

However, the cruel reality with Right to Try legislation is that it will not grant patients the immediate access to treatments they desperately need. Although various forms of Right to Try laws

have been passed in 31 states, there continues to be no concrete evidence of a patient ever receiving a life-saving or life-sustaining medication under Right to Try legislation when they otherwise wouldn't have received it under the existing FDA program. This equates to over 183 million Americans currently living within the boundaries governed with Right to Try laws. Why then, with 57% of Americans having, as Goldwater claims, "immediate access to medical treatments they need", do we

<sup>1</sup> "About Right to Try - Give Terminal Patients the Right to Try." 2015. 15 Sep. 2016 <<http://righttotry.org/about-right-to-try/>>

still have no data or evidence to prove these state laws are actually doing what they purport to do? The answer is simple – they aren't.

Indeed, legislation does not guarantee access to investigational therapies for those in need – it never has. Right to Try legislation provides nothing to patients except the “right not to be barred from seeking access to experimental products.”<sup>2</sup> Legislation has, however, created a misguided belief among vulnerable patients that the help they have been desperately searching for has arrived. Right to Try is a misnomer, implying an entitlement to patients: “If a person asks, someone or some entity has a duty to provide.”<sup>3</sup>

A more apt title would be “Right to Ask”, because this is the only entitlement Right to Try legislation provides patients. This right to ask has been given to patients in need since 1987 through the FDA's Expanded Access Program. For both the FDA program and Right to Try laws, pharmaceutical companies are under no obligation to make their investigational drugs available to patients.<sup>4</sup> Thus, investigating what disincentives prevent companies from deciding to make their drugs available and what incentives could be put in place to change these decisions would be a more fruitful approach than legislating a theoretical “Right to Try”.

Some States' Right to Try legislation also have the potential to create unequal access to medications for patients. Under the FDA's current Expanded Access program, pharmaceutical companies are only allowed to charge patients direct costs and select indirect costs associated with providing access to patients. Such charges must be approved by the FDA and serve to protect patients from being taken advantage of by pharmaceutical companies.<sup>5</sup> Most often, companies chose not to charge patients. Under State Right to Try legislation, companies can charge patients as they see fit, except in Texas, where the law requires that companies provide their investigational drugs for free. This would create a situation in which vulnerable patients may pay exorbitant prices for unproven therapies, acting out of desperation. Furthermore, patients trying to access drugs under Right to Try laws may find themselves in the precarious position of losing access to home health care, hospice care, or even insurance.<sup>6</sup>

<sup>2</sup> Bateman-House, Alison et al. "Right-to-Try Laws: Hope, Hype, and Unintended Consequences." *Annals of internal medicine* 163.10 (2015): 796-797.

<sup>3</sup> Bateman-House, Alison et al. "Right-to-Try Laws: Hope, Hype, and Unintended Consequences." *Annals of internal medicine* 163.10 (2015): 796-797.

<sup>4</sup> Rubin, Rita. "Experts critical of America's right-to-try drug laws." *The Lancet* 386.10001 (2015): 1325-1326.

<sup>5</sup> 2016 US Government Publishing Office, 2016, Part 312.8 <<https://www.gpo.gov/>>

<sup>6</sup> Bateman-House, Alison et al. "Right-to-Try Laws: Hope, Hype, and Unintended Consequences." *Annals of internal medicine* 163.10 (2015): 796-797.

In an attempt to raise the status of Right to Try laws and create confusion around alternative approaches to accessing pre-approved drugs, the Goldwater Institute falsely claims that paperwork to apply for Expanded Access through the FDA takes almost 100 hours. These claims continue to appear in Goldwater publications, testimonies, and in the media, yet are categorically untrue. Debunking this myth has been difficult, mostly because this incorrect statistic has been repeated ad nauseam by Right to Try proponents. The fact of the matter is that the 100 hours required to complete paperwork for the FDA includes work done by the company long before the initiation of a Clinical Trial for any given drug.<sup>7</sup> In truth, the time to complete an application to the FDA for Expanded Access is quick, a decision rendered in emergency cases is often made in a matter of hours.<sup>8</sup> To make things even smoother, the FDA has recently amended its application and states that it should take no longer than 45 minutes to complete. As well, they have committed to providing a “conciierge service” to help physicians complete the form quickly and accurately.<sup>9</sup>

So is the FDA truly the barrier they have been made out to be by Right to Try advocates? The data says No. FDA documents provide data on Expanded Access applications and approvals from 2009–2015. In successive years beginning in 2009, the FDA granted approval to 98.4%, 99.9%, 99.7%, 99.6%, 99.7%, and 99.5% of applications received.<sup>10</sup> While, as Right to Try proponents rightly point out, these approximately 1200 applications received per year do not account for those that were never submitted to the FDA in the first place, what is clear is that the FDA grants access to the vast majority of patients who request it. Rather than demonizing the FDA, a more fruitful approach would be to investigate why some patient requests for access to investigational drugs are never submitted to the FDA.

Where then does the discrepancy lie between the many Americans needing access to life-saving drugs and the few approvals being granted? Many would say the fault lies with the pharmaceutical companies directly.<sup>11</sup> Companies often feel that allowing access outside of the clinical setting could negatively impact the approval process for drugs under development. The fear that negative adverse events that take place could lead to a slowing or complete halt of a clinical trial is real and widespread throughout the industry.

<sup>7</sup> “How a Physician Can Work With a Not Yet Approved Drug Through ...” 2016. 15 Sep. 2016  
<<http://thehealthcareblog.com/blog/2016/04/17/far-from-evidence-based-prescribing-the-world-of-compassionate-use/>>

<sup>8</sup> “How a Physician Can Work With a Not Yet Approved Drug Through ...” 2016. 17 Sep. 2016  
<<http://thehealthcareblog.com/blog/2016/04/17/far-from-evidence-based-prescribing-the-world-of-compassionate-use/>>

<sup>9</sup> Martin, Caitlyn. “Questioning the Right in State Right to Try Laws: Assessing the Legality and Effectiveness of These Laws.” *Ohio St. LJ* 77 (2016): 159.

<sup>10</sup> “Expanded Access (Compassionate Use) > Expanded Access ... - FDA.” 2015. 16 Sep. 2016  
<<http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm443572.htm>>

<sup>11</sup> Rubin, Rita. “Experts critical of America’s right-to-try drug laws.” *The Lancet* 386.10001 (2015): 1325-1326.

The FDA, for its part, publicly states that negative adverse events in patients receiving investigational drugs via Expanded Access should not or will not impact the approval of medications under consideration. In an email directed to my organization in early 2014 while we were trying to gain access to an experimental therapy for a young boy suffering from a rare and progressive disease, Janet Woodcock, Director at the Centre for Drug Evaluation and Research (CDER), stated categorically, “As far as I know, and in our collective knowledge here at CDER, adverse events occurring during the development program have not delayed the programs. In one case, we know the drug development was actually accelerated.” Additionally, she stated that “In one case, long ago, an investigational product was given to a patient before any human studies were done. The individual, unfortunately, died immediately because of the toxicity of the dose given. This was a rare kind of case we try to avoid...”

In addition, the FDA updated their guidance for industry in June 2016 to address concerns from companies about adverse effects and their impact on the approval process. Their guidance states that “there are a small number of cases in which FDA has used adverse event information from expanded access in the safety assessment of a drug. However, FDA reviewers of these adverse event data understand the context in which the expanded access use was permitted (e.g., use in patients with serious or immediately life-threatening diseases)... and will evaluate any adverse event data obtained from an expanded access submission within that context.”<sup>12</sup>

As far as I know, and in our collective knowledge here at CDER, adverse events occurring during the development program have not delayed the programs. In one case, we know the drug development was actually accelerated

Janet Woodcock, FDA

Still, in my conversations with many companies that develop, test, and market rare disease treatments, the worry persists, and any proposed Right to Try legislation does nothing to alleviate those concerns. Although pharmaceutical companies will not have to report adverse events to the FDA under Right to Try, this doesn't remove the fear that an adverse event will derail the approval process for drugs. Any adverse event that takes place under Right to Try has a good chance of being reported in the media, whether local or national. Indeed, for companies that sell stock equity, the U.S Securities and Exchanges Commission requires the reporting of incidents that may have bearing on the success or failure of

development of the investigational drug. Such communications frequently find their way from shareholders to the general public. Thus, companies' fears of bad news becoming public are as real under proposed Right to Try legislation as they are under the Expanded Access program at the FDA.

<sup>12</sup> “Expanded Access to Investigational Drugs for Treatment Use - FDA.” 2014. 16 Sep. 2016 <<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351261.pdf>>

Where then, do the solutions lie? First, passing the complete 21st Centuries Cure Act into law would go a long way to alleviate concerns about the length of time it takes to have drugs approved in the United States. Shortening the length of time it takes to approve drugs can only benefit patients in the long run, and it's vital this gets passed into law in short order to help patients in need. Ensuring the Andrea Sloan CURE Act is taken up will increase transparency within the pharmaceutical sector and ensure companies publicly state their policy on expanded access to unapproved drugs. It will also ensure patients denied access are given proper rationale for such a decision.<sup>13</sup>

Additionally, we should be promoting enhancements to the FDA's existing Expanded Access Program that is showing promise for its high approval rates, transparent data collection, and focus on patient safety. While companies are hesitant to have such information collected, such data collected by the FDA during Expanded Access can only serve to inform good evidence-based practice and help expand our knowledge in a broader and more representative patient population. To alleviate these concerns, it is paramount that the FDA work with the pharmaceutical industry to clearly address how adverse events outside of the clinical trial setting will impact their path toward approval.

Work can also be done on an industry level in the short term to ensure access immediately, and there is evidence that companies are taking steps to ensure broader access for patients outside the clinical setting.

Case in point - Janssen Pharmaceuticals, in partnership with the NYU Langone Medical centre, recently introduced a "transparent, fair, beneficent, evidence based, and patient-focused" program to review compassionate use requests for one of their drugs currently being investigated in a clinical trial (Daratumumab).<sup>14</sup> An independent review committee (CompAC) was created to review such requests in a fair and equitable manner, free from bias based on income, sex, race, nationality, or celebrity status.<sup>15</sup> In addition, the committee would render decisions in an expeditious fashion, no more than 5 days after an application was received.

Data for the last half of 2015 suggest the program is working, and that patients are receiving access to the drug they need in an expeditious manner. Of 160 applications received, 62 resulted in compassionate use being approved for Expanded Access, with 43 applicants having a non-favourable benefit-risk profile and 28 requests deemed ineligible due to not having exhausted all alternative therapies.<sup>16</sup>

<sup>13</sup> "H.R.6 - 114th Congress (2015-2016): 21st Century ... - Congress.gov." 2015. 16 Sep. 2016  
<<https://www.congress.gov/bills/114th-congress/house-bill/6>>

<sup>14</sup> Caplan, Arthur L, and Amrit Ray. "The Ethical Challenges of Compassionate Use." *JAMA* 315.10 (2016): 979-980.

<sup>15</sup> Caplan, Arthur L, and Amrit Ray. "The Ethical Challenges of Compassionate Use." *JAMA* 315.10 (2016): 979-980.

<sup>16</sup> Caplan, Arthur L, and Amrit Ray. "The Ethical Challenges of Compassionate Use." *JAMA* 315.10 (2016): 979-980.

Taken in context, the 62 patients approved for use under the CompAC program during 6 months in 2015 made up roughly 5% of all Expanded Access cases approved through the FDA program last year alone. Under Janssen/NYU's CompAC model for Expanded Access, patients most in need are gaining access quickly and fairly.

Additionally, BioMarin Pharmaceutical recently implemented an ambitious Early Access Program for patients suffering from a fatal and debilitating, heritable condition, CLN2, which is a form of Batten disease. The company has implemented this program under the existing FDA regulations governing expanded access and the will provide many patients with prompt access to the drug outside the clinical trial setting.

In this case, consistent with its own compassionate use policy and current FDA regulations, BioMarin sought and received the treatment protocol because CLN2 is a fatal condition, there are no other available treatments, initiation of early access for patients who were not enrolled in the clinical trial will not interfere with the clinical investigation of the drug. Enrollment decisions for this treatment protocol are being made independent of BioMarin.<sup>17</sup>

Biomarin's program underscores not only that a pathway to early access already exists for both individuals and larger patient populations under current Federal law, but also that every disease, investigational therapy, clinical trial design, and individual patient are different so benefit-risk should be evaluated on a case by case basis. All patients with such conditions deserve hope, but it should be balanced on the ability for a company to obtain enough safety and efficacy data that will allow the larger patient populations to benefit from a drug through FDA approval.

The current FDA Expanded Access Program does just that, rendering these Right to Try laws ineffectual. Moreover, the unintended consequence of clinical trial attrition in instances when a patient knows they are receiving placebo, which is the case when therapy is delivered through a device, is a very real risk of these right to try laws because of the false hope they provide patients.

These examples show that it's possible to adapt the current system we have in place through the FDA to help patients and families gain access to pharmaceutical products outside the clinical trial setting. These examples show that it is possible to bridge the gap between patients, patient organizations, the FDA, and the pharmaceutical industry. It's examples like these that will provide our patients with the Hope they thought was lost, not Right to Try legislation, and we must continue to promote and strengthen these programs throughout the United States if we want to see a pivotal shift toward broader access to pharmaceutical products for our patients.

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<sup>17</sup> "BioMarin Announces Positive Data From Cerliponase Alfa Program for ..." 2016. 16 Sep. 2016  
<<http://investors.bmrn.com/releasedetail.cfm?releaseid=958565>>



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration  
Silver Spring, MD 20993

**STATEMENT  
OF  
PETER LURIE, MD, MPH  
ASSOCIATE COMMISSIONER FOR PUBLIC HEALTH STRATEGY AND ANALYSIS  
OFFICE OF POLICY, PLANNING, LEGISLATION, AND ANALYSIS  
U.S. FOOD AND DRUG ADMINISTRATION  
DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**BEFORE THE  
COMMITTEE ON HOMELAND SECURITY AND GOVERNMENT AFFAIRS  
U.S. SENATE**

*"Exploring a Right to Try for Terminally Ill Patients"*

**SEPTEMBER 22, 2016**

**RELEASE ONLY UPON DELIVERY**

## INTRODUCTION

Mr. Chairman, Ranking Member Carper, and Members of the Committee, I am Dr. Peter Lurie, Associate Commissioner for Public Health Strategy and Analysis at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss expanded access to investigational products

As a physician, I have personally witnessed the suffering and the dilemmas facing patients and their families when they are confronted with serious or life-threatening conditions and limited treatment options. Having exhausted other treatments, they may wish to turn to investigational products. Prior to approval, Investigational new drugs undergo clinical trials to assess whether they can be used safely and deliver efficacious results for a particular indication in humans. FDA recognizes that, in many instances, patients with life-threatening diseases are more willing to accept the risk associated with investigational products than other patients, especially if they have no other available options.

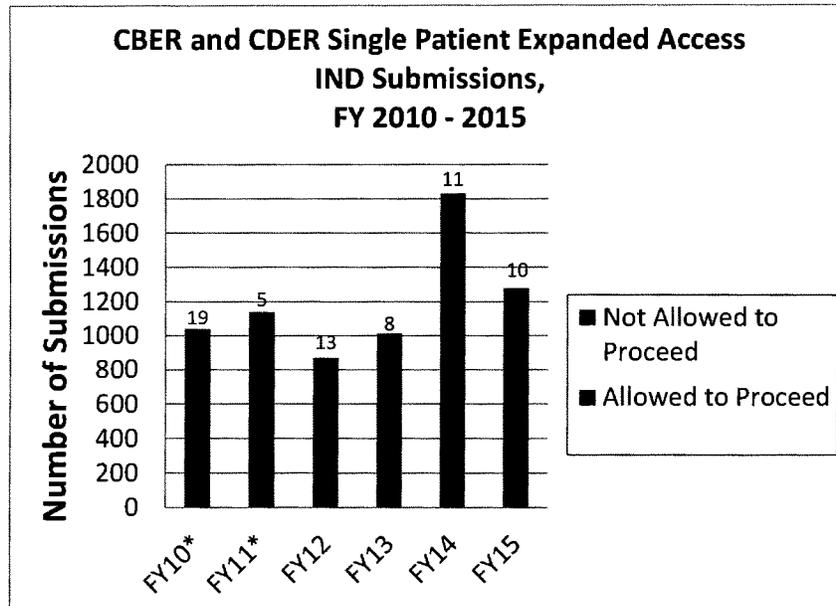
That is why, for over two decades, FDA has had in place a system to help patients gain access to investigational products, and FDA has authorized more than 99 percent of requests between 2010-2015.<sup>1</sup> To be clear: the best way to hasten access to safe and effective products for the largest number of patients is through the clinical trial process. Enrollment in clinical trials helps to ensure adequate protection for patients and leads to the collection of vital data that could eventually result in FDA approval of the investigational product. Once approval is secured, all patients with the condition may receive it, and much wider availability is almost certain to ensue.

Nonetheless, FDA recognizes that there are circumstances when patients with serious or life-threatening conditions and no comparable or satisfactory alternative therapy are not eligible for a clinical trial, either because of where they live, their age, or some other disqualifying factor. These patients may consider seeking access to investigational drugs, and FDA's expanded access program is intended to serve them.

To qualify for the program, the patient's treating physician must determine that the patient has a serious or life-threatening condition and no comparable or satisfactory alternative therapy. The physician then approaches the pharmaceutical company to ask for its agreement that it will provide the drug being sought. The company has the right to approve or disapprove the physician's request. If the company agrees to the physician's request, the physician can then apply to FDA for permission to proceed. Should they do so, they are highly likely to be allowed to proceed. As shown in the chart below, FDA has authorized more than 99 percent (7110/7176) of single patient expanded access Investigational New Drug (IND) requests received in Fiscal Years 2010-2015. Emergency requests are usually granted immediately over the phone and non-

<sup>1</sup> FDA has multiple expanded access programs for investigational drugs and devices: single patient INDs and protocols (including emergency applications), intermediate size INDs and protocols and treatment INDs and protocols for widespread use; and – for devices – emergency use, compassionate use, and treatment use (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm>). There are far more applications for single patient INDs and protocols, and they are the focus of this testimony.

emergencies are processed in a median of four days. The treating physician is then responsible for obtaining informed consent from the patient and approval from an ethics committee before administering the drug.



Data include emergency and non-emergency single patient IND submissions.  
 CBER = Center for Biologics Evaluation and Research; CDER = Center for Drug Evaluation and Research  
 \*For FY 10 and FY 11, the reporting period was October 13 through October 12 of the following year.  
 Source: <http://www.fda.gov/downloads/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/UCM471305.pdf>

Access to investigational products requires the active cooperation of the treating physician, industry and FDA in order to be successful. In particular, the company developing the investigational product must be willing to provide it – FDA cannot force a company to manufacture a product or to make a product available. Companies might have their own reasons to turn down requests for their investigational products, including their desire to maintain their clinical development program or simply because they have not produced enough of the product.

Based on information available, it appears that pharmaceutical companies turn down considerably more applications from physicians than does the Agency. For example, one

company indicated that it had turned down 98 of 160 applications for a single drug in a six-month period.<sup>2</sup> Another company reportedly turned down “hundreds” of applications for its drug over two years.<sup>3</sup> In contrast, over six years, FDA has put on clinical hold 66 applications from the thousands it has received.

With regard to investigational medical devices, FDA also has a process in place for responding to requests for expanded access to these products as. Since 2012, we have approved more than 98 percent of these requests. In 2015, FDA approved 99 percent<sup>4</sup> of expanded access requests received under an Investigational Device Exemption. Unlike drugs and biologics, emergency use of investigational devices does not require prior authorization from FDA, as long as certain criteria are met, such as submitting a report of the emergency use within five working days from the time the sponsor learns of the use.

Since the expanded access program began, FDA has worked to improve it. FDA established an expedited telephone process for daytime and after-hours emergency requests for expanded access, and revamped the regulations regarding expanded access to investigational drugs to make the process and responsibilities of physicians more clear and concise. More recently, in response to feedback from physicians that completing the two expanded access forms was time-consuming, in June 2016, FDA released a single new form (FDA form 3926) for individual patient expanded access. This form is estimated to take 45 minutes to complete and requires just one attachment (the previous one required up to eight). Along with the new form, we released step-by-step instructions on how to complete it. We also released a Questions and Answers guidance that explains what expanded access is, when and how to request expanded access, and the type of information that should be included in requests. At the same time, we released a third guidance that explains the regulations regarding when and how patients may be charged for investigational drugs, notably that the sponsor may recover only its direct costs associated with making the drug available to the patient. Simultaneously, FDA revamped its expanded access website and produced Fact Sheets for physicians and patients. Almost immediately, physicians began to take advantage of the new form. In addition to web pages directed specifically toward patients, physicians and industry, FDA has staff available to assist physicians and patients in understanding how to apply for expanded access.

However, even patients with serious or life-threatening diseases and conditions require protection from unnecessary risks, particularly as, in general, the products they are seeking through expanded access are unapproved – and may never be approved. Moreover, FDA is concerned about the ability of unscrupulous individuals to exploit such desperate patients. Thus, with every request, FDA must determine that the potential patient benefit from the

<sup>2</sup> Caplan AL, Ray A. The ethical challenges of compassionate use. *Journal of the American Medical Association* 2016;315:979-80.

<sup>3</sup> Usdin S. How Chimerix, FDA grappled with providing compassionate access to Josh Hardy. *BioCentury on BioBusiness*, March 31, 2014. Available at: <http://www.biocentury.com/biotech-pharma-news/regulation/2014-03-31/how-chimerix-fda-grappled-with-providing-compassionate-access-to-josh-hardy-a7> (accessed September 11, 2016).

<sup>4</sup> 99.04% of 208 evaluable submissions received. More information is available on this website: <http://www.fda.gov/MedicalDevice/s/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm>.

investigational drug justifies the potential risks and that the potential risks are not unreasonable in the context of the disease or condition to be treated. For this reason, even as it permits more than 99 percent of applications to proceed, FDA makes meaningful changes in 11 percent of expanded access IND applications to help ensure patient safety, including changes in dosing, safety monitoring, and informed consent.

While we welcome suggestions that might improve the expanded access process, we would caution against any changes that would reduce FDA's role in expanded access or that might undermine the crucial clinical trial development process. As noted, enrollment in clinical trials remains the best option for patients wishing to gain access to investigational medical products as it assures adequate protection for patients and leads to the collection of data that could eventually result in FDA approval of the investigational therapy and thus widespread availability. Criticism that effective therapies are being kept from Americans is unfounded; FDA is committed to new drug development. In 2014, consistent with a trend that has been in place for many years, 60 percent of new molecular entities were approved in the United States before any other country.<sup>5</sup> In calendar year 2015, FDA approved 45 new molecular entity drugs. About 47 percent of these drugs were approved to treat rare or "orphan" diseases that affect 200,000 or fewer Americans.

It is therefore critical that we maintain and not undermine the clinical trials process that has served Americans so well. Most fundamentally, the Agency is concerned that some legislative proposals could undermine FDA's ability to protect and promote the public health through science-based regulation of drugs and devices. FDA's expanded access process strikes a careful balance between helping to facilitate patient access to investigational therapies, while providing patients with appropriate human subject protections and preventing interference with the product's development program. Upsetting this balance has the potential to expose patients to unreasonable risks and stymie the development of medical products that could benefit us all. Notably, FDA often has safety information unavailable to the public that is an important consideration in these decisions.

Finally, prohibiting the Agency from reviewing adverse events that occur in expanded access use would be detrimental and raise significant ethical issues. Given that the Agency is charged with assessing the safety and effectiveness of medical products, the Agency cannot ignore valid scientific information. Of course, the Agency understands that adverse events that arise during expanded access use must be interpreted with caution. However, over the last decade, spanning almost 11,000 expanded access requests, there were only two instances in which a clinical hold was placed on commercial drug development due to adverse events occurring under expanded access INDs or protocols. In both instances, the development of the drugs continued after issues were addressed and the holds were lifted. FDA also recently published a guidance entitled *Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers*. This guidance makes clear that the Agency understands that expanded access is a very particular context (sicker patients, multiple illnesses, concurrent medications, etc.) and that FDA takes that context into account when interpreting adverse events.

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<sup>5</sup> Scrip Magazine (1982 -2006), Pharmaprojects/Citeline Pharma R&D Annual Review (2007 -2014).

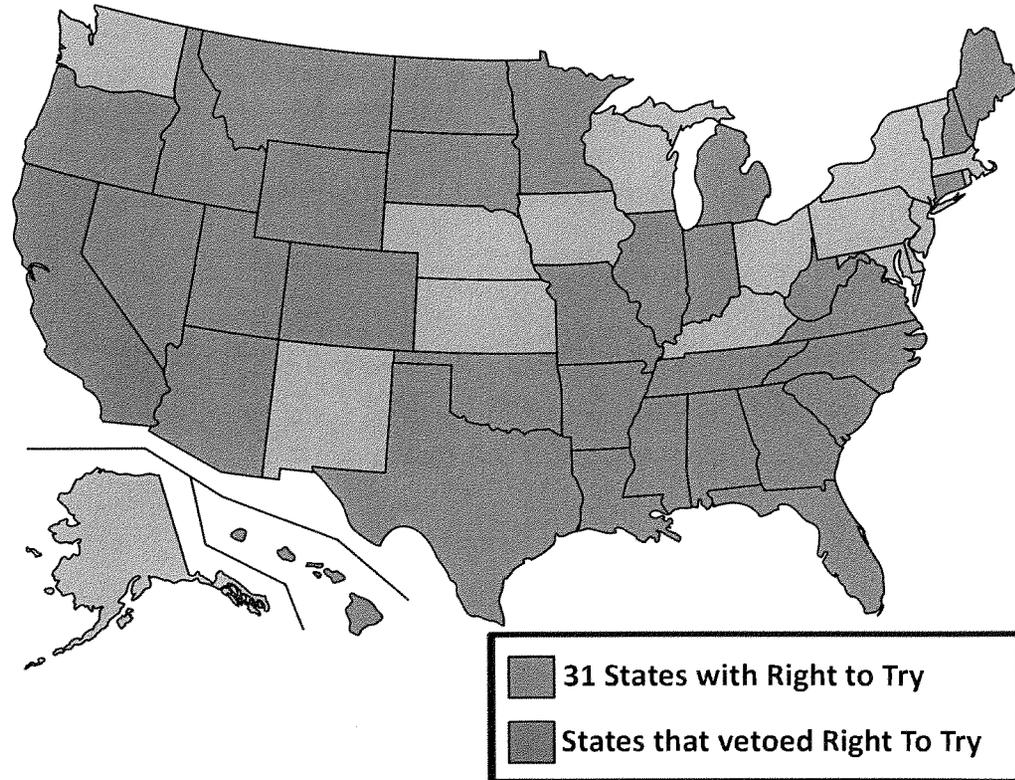
**CONCLUSION**

Clinical trials remain the best option for patients wishing to gain access to investigational products and bringing new, innovative products to market through the approval process remains the best way to assure the development of and access to safe and effective new medical products for all patients.

For those patients who cannot participate in trials, and are left in the difficult, heart-wrenching position of having no other therapeutic options, FDA is proud of its expanded access process for individual patients. It has stood the test of time and serves over 1,000 patients each year. FDA continues to work to improve the program and expects the new short form and the associated streamlined process to continue to help patients who cannot participate in clinical trials.

I am happy to answer any questions you may have.

## State-Level Right To Try Legislation



DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration <b>Individual Patient Expanded Access          Investigational New Drug Application (IND)</b> <i>(Title 21, Code of Federal Regulations (CFR) Part 312)</i>		Form Approved: OMB No. 0910-0814 Expiration Date: April 30, 2019 See PRA Statement on last page.
<b>1. Patient's Initials</b>		<b>2. Date of Submission (mm/dd/yyyy)</b>
<b>3.a. Initial Submission</b> <input type="checkbox"/> Select this box if this form is an initial submission for an individual patient expanded access IND, and complete only fields 4 through 8, and fields 10 and 11.	<b>3.b. Follow-Up Submission</b> <input type="checkbox"/> Select this box if this form accompanies a follow-up submission to an existing individual patient expanded access IND, and complete the items to the right in this section, and fields 8 through 11.	Investigational Drug Name  Physician's IND Number
<b>4. Clinical Information</b>		
Indication		
Brief Clinical History <i>(Patient's age, gender, weight, allergies, diagnosis, prior therapy, response to prior therapy, reason for request, including an explanation of why the patient lacks other therapeutic options)</i>		
<b>5. Treatment Information</b>		
Investigational Drug Name		
Name of the entity that will supply the drug <i>(generally the manufacturer)</i>		
FDA Review Division <i>(if known)</i>		
Treatment Plan <i>(Including the dose, route and schedule of administration, planned duration, and monitoring procedures. Also include modifications to the treatment plan in the event of toxicity.)</i>		
<b>6. Letter of Authorization (LOA), if applicable</b> <i>(generally obtained from the manufacturer of the drug)</i>		
<input type="checkbox"/> I have attached the LOA. <i>(Attach the LOA; if electronic, use normal PDF functions for file attachments.)</i> <b>Note:</b> If there is no LOA, consult the Form Instructions.		
<b>7. Physician's Qualification Statement</b> <i>(Including medical school attended, year of graduation, medical specialty, state medical license number, current employment, and job title. Alternatively, attach the first few pages of physician's curriculum vitae (CV), provided they contain this information. If attaching the CV electronically, use normal PDF functions for file attachments.)</i>		
<b>8. Physician Name, Address, and Contact Information</b>		
Physician Name <i>(Sponsor)</i>		Email Address of Physician
Address 1 <i>(Street address, No P.O. boxes)</i>		Telephone Number of Physician
Address 2 <i>(Apartment, suite, unit, building, floor, etc.)</i>		
City	State	Facsimile (FAX) Number of Physician
ZIP Code	Physician's IND number, if known	

**9. Contents of Submission**

*This submission contains the following materials, which are attached to this form (select all that apply). If none of the following apply to the follow-up communications, use Form FDA 1571 for your submission.*

- |   |  |
|---|--|
| <input type="checkbox"/> Initial Written IND Safety Report                    | <input type="checkbox"/> Change in Treatment Plan                |
| <input type="checkbox"/> Follow-up to a Written IND Safety Report             | <input type="checkbox"/> General Correspondence                  |
| <input type="checkbox"/> Annual Report  | <input type="checkbox"/> Response to FDA Request for Information |
| <input type="checkbox"/> Summary of Expanded Access Use (treatment completed) | <input type="checkbox"/> Response to Clinical Hold               |

**10. Request for Authorization to Use Form FDA 3926**

- I request authorization to submit this Form FDA 3926 to comply with FDA's requirements for an individual patient expanded access IND.

**11. Certification Statement:** I will not begin treatment until 30 days after FDA's receipt of a completed application and all required materials unless I receive earlier notification from FDA that treatment may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I also certify that I will obtain informed consent, consistent with Federal requirements, and that an Institutional Review Board (IRB) that complies with the Federal IRB requirements will be responsible for initial and continuing review and approval of this treatment use. I understand that in the case of an emergency request, treatment may begin without prior IRB approval, provided the IRB is notified of the emergency treatment within 5 working days of treatment. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

**WARNING: A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).**

**Signature of Physician**

To enable the signature field, please fill out all prior required fields. For a list of required fields which have not yet been filled out, please click here.

**Date**

**For FDA Use Only**

Date of FDA Receipt	Is this an emergency individual patient IND? <input type="checkbox"/> Yes <input type="checkbox"/> No	Is this indication for a rare disease (prevalence < 200,000 in the U.S.)? <input type="checkbox"/> Yes <input type="checkbox"/> No
IND Number		

This section applies only to requirements of the Paperwork Reduction Act of 1995.

**\*DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.\***

The burden time for this collection of information is estimated to average 45 minutes per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services  
 Food and Drug Administration  
 Office of Operations  
 Paperwork Reduction Act (PRA) Staff  
 PRAStaff@fda.hhs.gov

*"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."*



## Patient Access to Investigational Therapies

Many states across the country are considering so-called "Right to Try" legislation to provide patients with access to investigational therapies before they are approved by FDA. However, for over two decades, FDA has had processes in place to do just that. Expanded access, which is sometimes called "compassionate use," supplements the clinical trials process. FDA believes enrollment in clinical trials remains the best option for patients wishing to gain access to investigational drugs—it assures adequate protection for patients and leads to the collection of data that could eventually result in FDA approval of the investigational therapy, which provides the broadest availability to patients. Patients who are not eligible for a clinical trial because of where they live, their age, or some other disqualifying factor have the option to seek expanded access if they have serious or life-threatening conditions and no comparable or satisfactory alternative is available.

FDA acts quickly in response to expanded access requests and allows almost all of them to proceed. In fact, FDA authorized more than 99 percent of individual patient expanded access requests received in Fiscal Years 2010-14. Emergency requests are often granted immediately over the phone. For non-emergencies, the Agency strives to respond promptly and, in general, does not take longer than 30 days. Moreover, FDA continues to improve its processes. In response to feedback from physicians that the expanded access form was challenging, in February 2015, FDA announced the development of a new draft form for individual patient expanded access that is estimated to take only about 45 minutes to complete.

Expanded access to investigational treatments requires the active involvement and cooperation of parties other than FDA, including drug companies and healthcare providers. FDA can encourage drug companies to offer expanded access to their investigational therapies, but companies may choose not to do so for various reasons, including lack of available drug or a desire to focus their attention on completing the clinical trials necessary to support FDA approval.

### Facts:

- FDA has a longstanding and well-established process for individual patients to obtain access to investigational therapies—expanded access, which is sometimes called compassionate use.
- FDA allows almost all expanded access requests to proceed: more than 99 percent of individual patient expanded access requests made from 2010-14 were granted.
- FDA responds to individual patient expanded access requests quickly; emergency requests are often granted immediately over the phone. For non-emergencies, the Agency strives to respond promptly and, in general, does not take longer than 30 days.
- FDA is improving expanded access to make it easier to apply; a new form for individual patient expanded access requests is estimated to take physicians only about 45 minutes to complete.

FDA is an important part of the process and helps to ensure patients are adequately protected from unnecessary risk. The independent scientific review provided by FDA is an essential component of patient protection, particularly because one is considering treatments for which safety and efficacy have not been demonstrated.

### Contact Us

For more information, please contact FDA's Office of Legislation at 301-796-8900, or see FDA's website: <http://www.fda.gov/ExpandedAccess>.

Updated: June 2016

**Post-Hearing Questions for the Record  
Submitted to the Honorable Ian Calderon  
From Senator Jon Tester**

**Homeland Security and Government Affairs Committee Hearing:  
“Exploring a Right to Try for Terminally Ill Patients”  
September 22, 2016**

1. How are patients protected from fraudulent practices under right to try laws that shield manufacturers, dispensers, and prescribers from liability regarding experimental treatments?

**Response:** Any treatment that is accessed under a state Right to Try law must be undergoing a current clinical trial or evaluation by the FDA. We heard concerns in California that people would be preyed upon but this is simply not possible. No one is going to spend hundreds of millions of dollars to get a drug to a stage 2 or 3 clinical trial in order to prey upon terminally ill people. The only drugs and devices available under right to try are those that are being actively and safely used in FDA-approved clinical trials.

Furthermore, federal law prevents any drug company from making a profit on a drug that is not yet commercially available. So patients are protected on the financial front as well.

2. In the absence of a federal right to try law, what steps do you recommend that the Food and Drug Administration take to improve patients’ ability to request access to experimental treatments?

**Response:** The FDA could adopt Right To Try as its policy without a federal law. The agency could model its compassionate use process on Australia’s, which allows doctors to administer investigational medications to their patients without federal permission in advance, but requires the doctor to inform the Australian equivalent to the FDA that a patient is being treated outside a clinical trial process. The change here is subtle; it’s eliminating the “must ask permission first” step and transforming it into an “information-sharing to advance science” process.

Terminal patients should have access to drugs that have been approved in other developed countries. Right now only the very wealthy can afford to travel to other countries to have access to treatments that are widely available, safe, and saving lives. We should not put middle-class and working-class Americans at a disadvantage because they don’t have the financial resources to travel abroad.

**Post-Hearing Questions for the Record  
Submitted to the Honorable Jim Neely  
From Senator Jon Tester**

**Homeland Security and Government Affairs Committee Hearing:  
“Exploring a Right to Try for Terminally Ill Patients”  
September 22, 2016**

1. How are patients protected from fraudulent practices under right to try laws that shield manufacturers, dispensers, and prescribers from liability regarding experimental treatments?

Patients' responsibility.

2. In the absence of a federal right to try law, what steps do you recommend that the Food and Drug Administration take to improve patients' ability to request access to experimental treatments?

Expand access.

**Post-Hearing Questions for the Record  
Submitted to Richard Garr  
From Senator Jon Tester**

**Homeland Security and Government Affairs Committee Hearing:  
“Exploring a Right to Try for Terminally Ill Patients”  
September 22, 2016**

1. How are patients protected from fraudulent practices under right to try laws that shield manufacturers, dispensers, and prescribers from liability regarding experimental treatments?

There are several layers of "protection" built into the bill. First, any drug which can be prescribed under the bill has to have passed at least one FDA safety trial AND still be under FDA review. This insures that no "snake oil" is being sold. It is extremely expensive to conduct trials (remember this only applies to fatal diseases) like this and only serious scientific efforts make it that far; Second, it has to be requested by a licensed MD; another filter to screen out high pressure sales tactics by charlatans; finally, all of the safety and other information on any drug in an FDA trial is available on line, and both the patients and the doctors have easy, ready access to the information needed to calculate the risks involved with any experimental drug.

2. In the absence of a federal right to try law, what steps do you recommend that the Food and Drug Administration take to improve patients' ability to request access to experimental treatments?

It's hard to envision any drug owner (company) being enthused about easier access to their experimental drugs Without the Federal level protection. The 21st Century Cures act (if it passes this week in the senate) gives the FDA some additional flexibility to "grease the skids" so to speak, but none of the provisions address the potential liability issues that this act does. So from a practical point of view, I think it would be very hard to envision any steps that would be effective without passage of this bill.

**Post-Hearing Questions for the Record  
Submitted to Dr. Peter Lurie  
From Senator Ron Johnson**

**“Exploring a Right to Try for Terminally Ill Patients”  
September 22, 2016**

1. Does the FDA Commissioner believe terminal patients should be permitted to access Phase 1 approved treatments that are continuing toward final drug approval if: no other treatment options are available and enrollment in a clinical trial is not possible; the patient, his or her doctor, and the manufacturer consent; and if authorized by state law?
2. Why was the FDA’s streamlined application for expanded access, announced in February 2015, not finalized until June 2, 2016?
3. Will the FDA promulgate regulations or guidance advising pharmaceutical companies as to how, if at all, the FDA will use adverse events that occur outside of clinical trials conducted in accordance with FDA approved protocols (through FDA’s expanded access program, or otherwise) in the FDA’s decision-making process about whether a trial can continue and/or the drug can be approved?
4. How often does the FDA update the information made available to patients on [clinicaltrials.gov](http://clinicaltrials.gov)? Will the Commissioner commit to ensuring this information is up-to-date and accurate so that patients can learn about and pursue their options under clinical trials, expanded access, and right to try? What specific steps will the FDA take, and in what timeframe, to ensure this commitment?
5. Will the FDA provide the Committee with a list of each treatment and the number of patients treated for all compassionate use approvals over the past year?
6. If the FDA becomes aware that a physician or manufacturer is administering or making available to patients a treatment that has not received approval of a New Drug Application and remains in clinical study phase, pursuant to a state-passed right to try law, will the FDA attempt to enforce Federal laws against the physician or manufacturer? Has the FDA ever referred a physician or manufacturer to the Department of Justice, another law enforcement agency, or a state medical board for making treatments still in clinical trials available to patients under a state-passed right to try law? How does the FDA use information about a physician or manufacturer providing treatments pursuant to a state right to try law in its approval process for new drugs?

7. What policy changes would the FDA support to speed access to treatments for those with life-threatening illnesses (not including the FDA's expanded access program)? Does the FDA support reciprocal drug or device approval with international peer agencies? Does the FDA support personal importation of drugs or devices fully approved in other countries?
8. How are questions for advisory committee consideration developed? How does the FDA or a committee ensure they are presented with appropriate questions that do not unnecessarily hinder evaluation of a drug's effects? What is the public's role in developing the questions?
9. Who ensures the FDA is following the requirements of the Food and Drug Administration Safety and Innovation Act?
10. The FDA has finally made public a decision on the Priority Review of a NDA for a treatment of Duchenne muscular dystrophy. On February 8, 2016, the FDA delayed the Prescription Drug User Fee Act (PDUFA) date by three months to May 26, 2016? Why did the FDA miss this goal date by nearly four months? Has the FDA approved any expanded access applications for this treatment?
11. What influence or say does the FDA have over the exclusionary criteria employed in IND clinical study protocols?

*From FDA, February 2017:*

*The QFRs were with the Department when the Administration switched. Unfortunately that means they were closed. However, Senator Johnson's QFRs were identical to the questions he posed to Secretary Burwell in a letter. Attached is the response that I understand HHS sent to the Senator on January 18, 2017.*



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation  
Washington, DC 20201

The Honorable Ron Johnson  
Chairman  
Committee on Homeland Security and Governmental Affairs  
United States Senate  
Washington, DC 20510

JAN 18 2017

Dear Mr. Chairman:

Thank you for your letter of October 21, 2016, concerning actions by the Food and Drug Administration (FDA) regarding potential enforcement or disciplinary actions directed at parties acting pursuant to state "right to try" laws. Enclosed are responses to the questions you posed in your letter.

I hope this information is helpful to you. Thank you for your continued interest in the important work of FDA.

Sincerely,

A handwritten signature in black ink that reads "Jim R. Esquea".

Jim R. Esquea  
Assistant Secretary for Legislation

cc: The Honorable Claire McCaskill  
Ranking Member

Enclosure

**Enclosure**

- 1. Does the Department of Health & Human Services believe terminal patients should be permitted to access treatments that have completed Phase I testing and are continuing toward final drug approval if no other treatment options are available and enrollment in a clinical trial is not possible; the patient, his or her doctor, and the manufacturer consent and if authorized by state law?**

The Food and Drug Administration (FDA or the Agency) agrees that patients who cannot enroll in a clinical trial and who are in such a difficult situation should have a path to receiving medications that might help them, and that is precisely what the expanded access program seeks to do. It is important to acknowledge there is limited information available regarding the safety profile and effectiveness of an investigational drug during and at the conclusion of phase 1 studies. The purpose of phase 1 studies is to gain preliminary information about the safety profile of an investigational drug at various doses and phase 1 studies generally do not assess effectiveness. The population studied (healthy volunteers versus patients with the disease/condition) and the duration of exposure (single versus repeated dosing) depends on the nonclinical safety profile of the investigational drug and the disease/condition for which the investigational drug is being studied. More often than not, much more is learned about the safety profile of a drug after phase 1 studies, as greater numbers and more varied patient populations participate in studies of the investigational drug over a longer period of time during development of the drug and even after approval.

It is important that FDA is involved in expanded access efforts for both patient safety and the drug development approval process. This includes considerations such as safety signals that may have arisen during prior use of the drug, if the risks of the drug are likely to be outweighed by its benefits, if the person offering the drug has a history of fraudulent behavior, and if enrollment in clinical trials is threatened.

- 2. Why was the FDA's streamlined application for expanded access, announced in February 2015, not finalized until June 2, 2016?**

In June 2016, FDA issued Form FDA 3926 and three final guidances. FDA adheres to good guidance practices.<sup>1</sup> This process includes FDA providing a draft guidance allowing for public comment and then FDA carefully reviewing and considering comments as the Agency works to finalize the guidance document. Clearing Form FDA 3926 involved a separate process, which included review and clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA). The final OMB approved form took into account comments received during the PRA notice and comment process and the guidance development process, as well as OMB review, and included modification of the form to include certain follow-up submissions.

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<sup>1</sup> 21 CFR 10.115

**3. Will HHS or the FDA promulgate regulations or guidance advising pharmaceutical companies as to how, if at all, the FDA will use adverse events that occur outside of clinical trials conducted in accordance with FDA approved protocols (through FDA's expanded access program, or otherwise) in the FDA's decision-making process about whether a trial can continue and/or the drug can be approved?**

As is the case for all Investigational New Drug Application (INDs), physicians submitting individual patient expanded access requests are required to report adverse reactions to the FDA.<sup>2</sup> The Agency must be made aware of adverse events, which raise legitimate scientific and public health concerns. Agency awareness of adverse events is critical for efforts to ensure that the approved labeling contains the essential scientific information needed for the safe and effective use of the drug. Reporting allows the FDA the opportunity to evaluate the events (in the proper context) and, if we find it appropriate to do so, require that prescribers be informed, via the drug's labeling, of these potential adverse events and/or of steps to take to try to prevent them.

As noted above, FDA interprets expanded access adverse events in their appropriate context. Agency officials consider the disease state of the patient, which may be further advanced than those of clinical trial participants. Patients receiving access to investigational products through expanded access are also often receiving other therapies for their disease or condition, and may be receiving therapies for comorbidities that disallow them from entering the clinical trial for the investigational product. There are a small number of cases for which FDA has included adverse event information from the expanded access program in the safety assessment of a drug, although in many cases, the information is considered anecdotal, outside the context of the trial data. This is explained in Question 25 of our Questions and Answers Guidance, one of the three released in June.<sup>3</sup> However, it is important to note that FDA is aware of at least two marketing

<sup>2</sup> See 21 CFR 312.32

**<sup>3</sup> Q25: What data and information must sponsors submit as follow-up for approved expanded access INDs or protocols?**

A25: As with any IND, in all cases of expanded access, sponsors are responsible for submitting IND safety reports and annual reports (when the IND or protocol continues for 1 year or longer) to FDA as required under 21 CFR 312.32 and 312.33 (see § 312.305(c)).

For individual patient expanded access, the regulations in § 312.310(c)(2) specify that, at the conclusion of treatment, the sponsor must provide to FDA a written summary of the results of the expanded access use, including adverse effects.

From a public health perspective, early identification of important adverse events is beneficial. For example, a relatively rare adverse event might be detected during expanded access use, or such use might contribute safety information for a population not exposed to the drug in clinical trials. There are a small number of cases in which FDA has used adverse event information from expanded access in the safety assessment of a drug. However, FDA reviewers of these adverse event data understand the context in which the expanded access use was permitted (e.g., use in patients with serious or immediately life-threatening diseases or administered in a clinical setting (not clinical trial) and will evaluate any adverse event data obtained from an expanded access submission within that context.

Expanded access INDs and protocols are generally not designed to determine the efficacy of a drug; however, the expanded access regulations do not prohibit the collection of such data. Because expanded access INDs or protocols typically involve uncontrolled exposures (with limited data collection), it is unlikely that an expanded access IND or protocol would yield efficacy information that would be useful to FDA in considering a drug's effectiveness.

applications for which clinical safety data from the expanded access program was used to establish a safety database large enough to adequately assess the risks versus benefits of the treatments: BLA 125327 for Voraxage (glucaridase) and BLA 125359 for Erwinaze (aspariginase *Erwinia chrysanthemi*).<sup>4</sup> The additional safety data generated from the expanded access program provided information needed to support the safety of these drugs for which patient exposure in the efficacy trials was limited.

We understand that sponsors are concerned that adverse events occurring in expanded access might endanger a clinical development program. To understand that issue better, FDA has reviewed the number of clinical holds placed on clinical development programs due to adverse events reported in the context of expanded access. Over a ten year period, of 1,033 unique Expanded Access INDs, only two were placed on clinical hold (0.2%). In both cases, the development of the drugs continued after the holds were lifted.

**4. How often does the FDA update the information made available to patients on [clinicaltrials.gov](http://clinicaltrials.gov)? Will you commit to ensuring this information is up-to-date and accurate so that patients can learn about and pursue their options under clinical trials, expanded access, and right to try? What specific steps will HHS take, and in what timeframe, to ensure this commitment?**

As you may be aware, [ClinicalTrials.gov](http://ClinicalTrials.gov) is a data bank maintained by the National Institutes of Health (NIH). On September 21, 2016, HHS issued a final rule on the submission of registration and results information for certain clinical trials involving FDA-regulated drug, biological, and device products. The final rule, which is effective January 18, 2017, with a compliance date of April 18, 2017, clarifies and furthers the implementation of Title VIII of the Food and Drug Administration Amendments Act of 2007. Under the final rule and the statute, responsible parties have regulatory and statutory obligations to update the information submitted to [ClinicalTrials.gov](http://ClinicalTrials.gov). The final rule includes a description of various potential legal consequences for not complying with the requirements. These include potential grant funding actions, civil monetary penalty actions, and civil and criminal court actions. FDA and NIH have already begun to provide information and training sessions (webinars, etc.) so that clinical trial sponsors and investigators understand their [ClinicalTrials.gov](http://ClinicalTrials.gov) responsibilities under the final rule, including those involving expanded access. FDA is making its [ClinicalTrials.gov](http://ClinicalTrials.gov) compliance program part of its bioresearch monitoring program, a robust compliance program which encompasses critically important responsibilities of those sponsoring and conducting clinical trials.

The final rule fully implements the statutory provision requiring the submission of information to [ClinicalTrials.gov](http://ClinicalTrials.gov) about the availability of expanded access for drugs being studied in applicable

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<sup>4</sup> Public information on expanded access program that supported approval of Voraxaze can be found in the medical review (page 23, Table 5.1) posted on our website at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/125327Orig1s000MedR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125327Orig1s000MedR.pdf) and the prescribing information for Erwinaze, which can be found at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/125359s088lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125359s088lbl.pdf) (1st paragraph under section 14 Clinical Studies).

drug clinical trials and how to obtain information about such access for persons who do not qualify to participate in the clinical trial listed in the ClinicalTrials.gov record. Those clinical trial sponsors who also manufacture the drug product and are submitting information to ClinicalTrials.gov must indicate in the registration record whether expanded access is available. If available, those sponsors must submit specific information to ClinicalTrials.gov that enables patients and health care providers to obtain further information about access to the product. Information on the availability of expanded access must be updated, according to the timelines specified in the final rule, when changes occur.

**5. Will HHS provide the Committee with a list of each treatment and the number of patients treated for all expanded access approvals over the past year?**

Consistent with longstanding Agency practice, we do not discuss the substance of matters that may be pending before the Agency. This practice helps to ensure the integrity of the review process. However, generally speaking, in FY 2015, there were 1,278 individual patient expanded access IND submissions, of which 1,268 were allowed to proceed. This includes the FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). In calendar year 2015, there were 375 submissions requesting approval for compassionate use of a device, of which 371 were approved.

**6. If the FDA becomes aware that a physician or manufacturer is administering or making available to patients a treatment that has not received approval of a New Drug Application and remains in clinical study phase, pursuant to a state-passed right to try law, will the FDA attempt to enforce Federal laws against the physician or manufacturer? Has the FDA ever referred a physician or manufacturer to the Department of Justice, another law enforcement agency, or a state medical board for making treatments still in clinical trials available to patients under a state-passed right to try law? How does the FDA use information about a physician or manufacturer providing treatments pursuant to a state right to try law in its approval process for new drugs?**

FDA is not aware of any instances in which the Agency has made such referrals.

FDA would evaluate how to respond on a case-by-case basis.

**7. What policy changes would HHS support to speed access to treatments for those with life-threatening illnesses (not including the FDA's expanded access program)? Does HHS support reciprocal drug or device approval with international peer agencies? Does HHS support personal importation of drugs or devices fully approved in other countries?**

In May 2014, FDA issued final Guidance for Industry on *Expedited Programs for Serious Conditions – Drugs and Biologics*. The purpose of this guidance is to provide a single resource for information on FDA's policies and procedures for these four programs (fast track designation, breakthrough therapy designation, accelerated approval, and priority review

designation) as well as threshold criteria generally applicable to concluding that a drug is a candidate for these expedited development and review programs.

The Agency believes that any efforts to allow sponsors to gain approval of a drug or device in the United States must be accompanied by data demonstrating the safety and effectiveness of the product to our satisfaction.

The United States is the only country that reviews the raw clinical trial data provided by the companies seeking approval. Other countries base their approval decisions on the analyses and summaries of the data provided by the companies.

There have been a number of instances in which products were approved in other countries but not in the United States, and those products later proved to be problematic in various ways. Examples include:

- Lumiracoxib was a non-steroidal anti-inflammatory drug approved in the European Union, Canada, and many other countries for relief of various types of pain. The New Drug Application (NDA) for lumiracoxib was rejected by FDA because of a signal of liver toxicity. Ultimately, the drug was withdrawn from the market in all but a handful of countries because of serious liver toxicity.
- Rimonabant was an anti-obesity drug that was approved in the European Union and many other countries, but not given approval in the United States. Rimonabant was later withdrawn from the market because of serious psychiatric problems, including suicide.
- OvaCheck was indicated for the early identification of ovarian cancer and was self-certified in Europe. FDA's concerns with the product included lack of validation that it could predict or detect ovarian cancer and that the manufacturer inflated claims of accuracy. FDA did not allow marketing of this product and the company eventually left the European market.
- Venaxis' APPY1 test was CE marked (Europe's approval standard) in 2013. FDA subsequently denied Venaxis' U.S. marketing application.

FDA recognizes there are circumstances under which a United States citizen may wish to seek treatment with an unapproved drug/device that is not domestically available. Information regarding FDA's treatment of personal importation of such products, including when individuals with serious conditions wish to get treatments that are legally available in foreign countries but are not approved in the United States, can be found on FDA's website – see, e.g., Regulatory Procedures Manual, 9-2 - Coverage of Personal Importations (<http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm179266.htm>) and Import Basics – Personal Importation (<http://www.fda.gov/ForIndustry/ImportProgram/ImportBasics/ucm432661.htm>).

FDA also has a Personal Importation Policy (PIP) that describes FDA's approach to individual importation of such drugs for personal use (see Personal Importation Policy (PIP) Frequently Asked Questions (FAQs), <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/importsandexportscompliance/ucm297909.pdf>).

Under the PIP, several factors are considered in determining whether the Agency intends not to object to certain personal imports of drugs:

- The drug is for use for a serious condition for which effective treatment is **not** available in the United States;
- There is no commercialization or promotion of the drug to United States residents;
- The drug is considered not to represent an unreasonable risk;
- The individual importing the drug verifies in writing that it is for his or her own use, and provides contact information for the doctor providing treatment or shows the product is for the continuation of treatment begun in a foreign country; and
- Generally, not more than a three-month supply of the drug is imported.

It is important to remember that unapproved medical products from foreign sources do not have the same assurance of safety, effectiveness, and quality as medical products subject to FDA oversight. In many cases, such medical products have been found to be contaminated, counterfeit, contain varying amounts of active ingredients or none at all, or contain different ingredients altogether.

**8. How are questions for advisory committee consideration developed? How does the FDA or a committee ensure they are presented with appropriate questions that do not unnecessarily hinder evaluation of a drug's effects? What is the public's role in developing the questions?**

Questions that are posed to FDA Advisory Committees are generated by FDA subject matter experts. They are designed to elicit answers to the very questions FDA needs to answer in order to execute its statutory responsibilities.

As you know, the Food and Drug Administration Safety and Innovation Act (FDASIA) enacted in 2012 required FDA to engage with patient communities to solicit their views during the medical product development process. Accordingly, FDA provides the opportunity for externally led Patient-Focused Drug Development Meetings. In addition, FDA has conducted 18 disease-specific public meetings to gather a better understanding of patients' attitudes toward their condition and available therapies.

All of this information goes into FDA's assessment of a drug's development program and, implicitly, into how issues are presented to advisory committees. In addition, each advisory committee meeting has at least an hour devoted to an Open Public Hearing, during which patients and other members of the public may present their concerns.

9. **The FDA has finally made public a decision on the Priority Review of a NDA for a treatment of Duchenne muscular dystrophy. On February 8, 2016, the FDA delayed the Prescription Drug User Fee Act (PDUFA) date by three months to May 26, 2016? Why did the FDA miss this goal date by nearly four months? Has the FDA approved any expanded access applications for this treatment?**

Several factors contributed to the time needed to come to a final determination on this accelerated approval. For example, the sponsor submitted new data at two points during the review process, requiring more time to conduct review. In addition, it was important to have a robust scientific discussion and consider differing views on this complex topic, especially since the development program for eteplirsen included serious deficiencies in a number of respects that led to difficulties in regulatory review. Also, as seen in documents released by the Agency, there was an internal appeal regarding the approval, which required additional time for consideration and resolution.

An expanded access application is a type of an IND (or a submission to an existing IND). We do not approve INDs; they are either allowed to proceed or not allowed to proceed. In response to the question on whether an expanded access IND has been allowed to proceed for this treatment, we do not discuss the substance of an expanded access IND that may be pending before the Agency, consistent with longstanding Agency practice. This practice helps to ensure the integrity of the review process and the application.