Congressional Hearing Written Submission
Exploring a Right to Try for Terminally Ill Patients

Andrew McFadyen | The Isaac Foundation

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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.

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> 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."[1]

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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

[1] "About Right to Try - Give Terminal Patients the Right to Try." 2015. 15 Sep. 2016 <http://righttotry.org/about-right-to-try/>

[2] Bateman-House, Alison et al. "Right-to-Try Laws: Hope, Hype, and Unintended Consequences." *Annals of internal*

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."[2] 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."[3]

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.[4] 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.[5] 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.[6]

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[2] Bateman-House, Alison et al. "Right-to-Try Laws: Hope, Hype, and Unintended Consequences." *Annals of internal medicine* 163.10 (2015): 796-797.

[3] Bateman-House, Alison et al. "Right-to-Try Laws: Hope, Hype, and Unintended Consequences." *Annals of internal medicine* 163.10 (2015): 796-797.

[4] Rubin, Rita. "Experts critical of America's right-to-try drug laws." *The Lancet* 386.10001 (2015): 1325-1326.

[5] 2016 US Government Publishing Office, 2016, Part 312.8 <https://www.gpo.gov/>

[6] 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.[7] 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.[8] 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 "concierge service" to help physicians complete the form quickly and accurately.[9]

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.[10] 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.[11] 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.

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[7] "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/>

[8] "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/>

[9] 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.

[10] "Expanded Access (Compassionate Use) > Expanded Access ... - FDA." 2015. 16 Sep. 2016 <http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm443572.htm>

[11] 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."[12]

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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.

[12] "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.[13]

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).[14] 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.[15] 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.[16]

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[13] "H.R.6 - 114th Congress (2015-2016): 21st Century ... - Congress.gov." 2015. 16 Sep. 2016 <https://www.congress.gov/bill/114th-congress/house-bill/6>

[14] Caplan, Arthur L, and Amrit Ray. "The Ethical Challenges of Compassionate Use." *JAMA* 315.10 (2016): 979-980.

[15] Caplan, Arthur L, and Amrit Ray. "The Ethical Challenges of Compassionate Use." *JAMA* 315.10 (2016): 979-980.

[16] 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. [17]

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.

[17] "BioMarin Announces Positive Data From Cerliponase Alfa Program for ..." 2016. 16 Sep. 2016 <http://investors.bmrn.com/releasedetail.cfm?releaseid=958565>