BioCentury
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PATCHING COMPASSIONATE ACCESS

BY STEVE USDIN, WASHINGTON EDITOR

Six months after a viral media campaign saved seven-year-old Josh Hardy's life by persuading **Chimerix Inc.** to work with **FDA** to provide access to an investigational therapy, new compassionate access policies are being debated in the halls of Congress, corporate boardrooms and academic think tanks. So far, the legislative provisions under consideration represent only incremental changes to the system.

While cable television and Twitter have long since moved on, last week Rep. Michael McCaul (R-Texas), co-chair of the congressional childhood cancer caucus, told BioCentury he is drafting compassionate access legislation that he plans to introduce in 2015.

Co-Chair Rep. Chris Van Hollen (D-Md.) also said action is needed by Congress, companies or FDA to improve compassionate access. And members of the House Energy & Commerce Committee have expressed interest in including compassionate access reforms in legislation stemming from the Path to 21st Century Cures initiative.

Proposals under consideration on Capitol Hill include requiring that companies report compassionate access requests to FDA and respond to requests for access to unapproved drugs; creating incentives for companies that apply for breakthrough designation and Priority Review to implement expanded access programs; and giving FDA a larger role in adjudicating requests.

In parallel to legislative efforts, **BIO** and **PhRMA** have established working groups on compassionate access. In addition, the **New York University Langone Medical Center** has established a working group on compassionate use.

It is too early to predict precisely what kinds of policies will emerge from these efforts, but the early signs suggest they do not yet contemplate wholesale changes that would reform the system, such as removing

From left: Rep. Chris Van Hollen (D-Md.); Rep. Michael McCaul (R-Texas); and Nancy Goodman, executive director of Kids v Cancer.
SOURCE: BIOCENTURY AND THINKSTOCK

compassionate access decisions from drug companies and giving them to independent review boards; providing public funding when needed for compassionate access; creating appeals processes; and making the entire system more transparent and open.

In the meantime, debates over access to unapproved Ebola therapies show the issue goes far beyond children, and extends past national borders.

LEGISLATION IN 2015

McCaul told BioCentury he is working with stakeholders on legislation to reform and enhance the expanded access program at FDA.

Details are scarce. So far the lawmaker has indicated that he plans to require increased disclosure requirements for companies, and measures to encourage companies that received breakthrough and Priority Review designations to have expanded access policies in place.

"I expect this legislation will, at a minimum, incentivize companies applying for breakthrough and Priority Review designations to have public expanded access policies." It will also require greater disclosure regarding expanded access requests and the outcome of such requests, he said.

McCaul added: "It's important to have input from all sides to ensure this legislation balances the needs of terminal patients without jeopardizing the testing or approval of the treatments."

In addition to hearing from parents who are desperate to gain access to investigational drugs through his work on the childhood cancer caucus, McCaul has a personal connection to the issue. Andrea Sloan, an attorney from Austin, Texas, who failed in attempts to gain access to **BioMarin Pharmaceutical Inc.**'s BMN 673 investigational PARP inhibitor and eventually died from ovarian cancer, was McCaul's friend and constituent.

"We've heard stories about children who are denied access to clinical trials, that hear about a life-saving treatment, but they can't get access to it," McCaul said in introductory remarks at the fifth annual childhood cancer caucus summit on Sept. 19. "We hear those stories too often. We want to look at this legislatively."

In an interview with *BioCentury This Week* television, Van Hollen said the compassionate access "process is way too *ad hoc;* there's no clear path that parents know about to make the request, know what the status of the request is, understand the approval process. I think there is a lot we can do, either legislatively or working with the companies and FDA, to make it clear exactly how you navigate that path."

Van Hollen added: "Maybe we need legislation, maybe it is a question of working with FDA and others, but I do think we need to bring clarity and more certainty into this issue."

Also speaking on *BioCentury This Week,* Nancy Goodman, executive director of **Kids v Cancer**, said, "The reason kids need access to drugs through compassionate use is there are no pediatric clinical trials available with unapproved drugs."

Goodman and other pediatric cancer advocates are pushing Congress and FDA to modify the Pediatric Research Equity Act (PREA) to require drug developers to test more new cancer therapies in children (see "Targeting PREA," page 5).

The **National Organization for Rare Disorders** (NORD) points to another stumbling block to compassionate access: institutional review boards. In a Sept. 10 statement, the Orphan disease advocacy group noted: "Even if the FDA and the sponsor agree that expanded access is appropriate for a patient, it may take several months for an IRB to review the proposal, as the FDA requires the approval of a convened IRB in which the majority of IRB members are present. Many full IRBs take months to deliver a decision. Access to IRBs is limited in many rural and underserved areas."

A BIGGER ROLE FOR FDA?

Goodman is pushing for FDA to have a bigger role in the compassionate access process, and to allow patients to make requests. Currently, the agency becomes involved only after a company has agreed to a physician's request to provide access to an investigational drug. FDA virtually always approves such requests.

Goodman has a track record when it comes to legislative advocacy. She persuaded Congress to enact the Creating Hope Act, which established incentives for drug companies to develop new drugs for rare pediatric indications.

"I would advocate for providing patients the right to start compassionate access requests through a point of contact at the FDA," Goodman told BioCentury. "The FDA would then send the company the request. In this way, companies would be on notice that a compassionate use request was made, treating doctors and patients would know whom to contact at the company, and the FDA would be able to follow compassionate use requests made for each drug."

Under this scheme, companies would retain the ultimate decision-making power. But Goodman wants to establish deadlines for companies to review compassionate access requests, and wants a requirement for written explanations if requests are denied.

She also wants to hold drug companies' feet to the fire for certain classes of drugs. "There is a subset of drugs for which the probability of benefit is very high, and the drug is life-saving. Examples that come to mind are HIV drugs and antivirals, such as in the case of Josh Hardy," she said.

The compound that saved Hardy's life was brincidofovir, which Chimerix had in Phase III testing to treat cytomegalovirus (CMV).

Hardy had contracted a potentially fatal adenovirus infection following bone marrow transplant and could not withstand the nephrotoxic effects of cidofovir, the marketed drug upon which brincidofovir is based.

"In Josh Hardy's case, his physicians had experience with this drug with patients like Josh. They knew there was a very high probability that with two weeks of treatment, Josh would live, and that without this drug, Josh would not live," Goodman noted.

She added: "For this special subset of drugs, we need a better system to ensure that companies are limited in their ability to deny access."

Brian Rosen, chief policy officer at **The Leukemia & Lymphoma Society**, also supports an expanded role for FDA in compassionate access. "We think there are ways FDA could help to ensure drug sponsors are open and that expanded access programs are available."

For example, Rosen argues the agency should provide more clarity to sponsors about the risks that compassionate access could derail drug development programs.

"Drug sponsors are sometimes in a difficult situation. They've expressed concern that, should they provide compassionate use to an individual patient, a potential adverse event or other data generated from that expanded use could have a negative impact on an existing review at the FDA," he said. "Given that concern, there is not only more clarity needed, but also guidance on how data collected from a particular compassionate use would or would not be utilized and considered by FDA reviewers."

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McCaul has not mentioned whether the legislation he is working on might include new responsibilities or authorities for FDA.

CLEAR PATHWAY

Many drug developers create expanded access programs (EAPs) following completion of pivotal trials and prior to an approval decision. Typically, EAPs are restricted to patients who would have qualified for a trial. The clinicaltrials.gov website lists about 70 available EAP protocols for drugs, the majority of which involve products that are in Phase III or later.

However, many compassionate access requests involve compounds that are earlier in the development process, and often the requests are made on behalf of children or adults who would not qualify for a trial.

At the childhood cancer caucus summit, McCaul singled out **Johnson & Johnson** for its engagement in compassionate access. "**Johnson & Johnson** has really been the leader among drug companies, stepping up to the plate to have this conversation," he said.

J&J's Janssen Research & Development LLC unit is one of a handful of companies that have posted instructions online for patients and physicians describing policies for EAPs and providing a single point of contact to make compassionate access requests.

"Generally we consider opening an EAP in the US when our clinical studies are done and we are waiting for approval of our investigational medicine from government health authorities," the website states.

It continues: "Janssen does not offer EAPs when investigational medicines are in early testing because there are still too many unknowns and we believe providing the medicine to patients at this point would put them at undue risk."

Amrit Ray, Janssen's CMO, told BioCentury the company also considers requests for access to unapproved drugs outside of an EAP.

"When requests come in we weigh the evidence, look at the need, the data we have and what's in the best interest for the patients, and try to make a decision that is as helpful as possible for the patient, bearing in mind the need to conduct clinical trials," Ray said. "In cases where supplies are limited, we try to be thoughtful about prioritizing clinical trials."

He added: "The process and decision-making is transparent. Patients know that when physicians submit requests, they are evaluated in a thoughtful way and we get back to them as quickly as possible."

Ray said Janssen does not track the number of requests or the outcomes, and he has concerns about mandatory reporting requirements.

"It is important that we don't look at numbers that could be misleading in terms of just raw numbers of requests and approvals," he said.

For example, Ray noted several outcomes could result from a request for access to an investigational drug.

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"If a patient called and provided information that led us to believe they should go into a clinical trial; or they have a compelling need that is best met in an expanded access program that has already been launched; or the best [option] is to go into a clinical trial, but not for one of our products — would we report these?" he asked.

Ray envisions companies retaining power over compassionate access decision-making, and he rejected the idea of creating an independent appeals process. "Rather than an appeal, sometimes we look at trying to obtain additional data on individual cases," he said.

WORKING GROUPS

BIO and PhRMA have established working groups to consider new industry policies on compassionate access, but both trade associations told BioCentury they are not ready to make any public statements.

Meanwhile, the NYU working group on compassionate use has released some preliminary findings.

According to the group, compassionate access is "unregulated by federal authorities, subject to corporate policies that change mid-stream, and could potentially lead to adverse effects on clinical care in the future."

The academic group is particularly concerned about the ethics of access to unapproved therapies, which include the inequitable distribution of unapproved drugs.

"Those most capable of exploiting their social relationships (online or off-line) are more likely to gain access to unapproved treatments — and the possibility of medical benefit," the working group notes.

Arthur Caplan, director of the Division of Medical Ethics at NYU and leader of the working group, went further in an article posted on the *Health Affairs* blog, which was co-authored by former Chimerix CEO Kenneth Moch.

"A new system must be created to bring fairness, equality, and appropriate oversight to the availability of experimental treatments," the authors write.

Caplan and Moch call for consideration of a "national 'Expanded Access Institutional Review Board,' which would be able to weight factors including the proximate needs of the few versus the longer term needs of the many, the availability and cost of the experimental treatment, risks and benefits to the individuals, and equitable access."

They also argue that the "weight of such decisions should not and cannot rest solely on sponsoring companies."

Caplan and Moch call for regulators to address sponsors' concerns about compassionate access inappropriately hindering drug development, and suggest that mechanisms to pay for access to unapproved drugs should be considered.

Caplan and Moch conclude that if new policies are not implemented, "demands and threats will supersede science and logic, creating a system that promotes unfairness rather than equality and potentially destructive logjams rather than speedy development. If rescue is an important value of a humane society, then that society must insure that rescue is truly fair, transparent, and affordable by those in need." bc

BioCentury This Week's interview with McCaul, Van Hollen and Goodman will be broadcast at 8:30 a.m. on Sunday, Sept. 28, in Washington, D.C., on WUSA Channel 9, and at various times on select PBS stations. It will be available online at biocenturytv.com starting at 9:00 a.m.

COMPANIES AND INSTITUTIONS MENTIONED

BioMarin Pharmaceutical Inc. (NASDAQ:BMRN), Novato, Calif.
Biotechnology Industry Organization (BIO), Washington, D.C
Chimerix Inc. (NASDAQ:CMRX), Durham, N.C.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Kids v Cancer, Washington, D.C.
The Leukemia & Lymphoma Society, White Plains, N.Y.
National Organization for Rare Disorders (NORD), Danbury, Conn.
New York University Langone Medical Center, New York, N.Y.
Pharmaceutical Research and Manufacturers of America (PhRMA), Washington, D.C.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

REFERENCES

Caplan, A. and Moch, K. "Rescue me: The challenge of compassionate use in the social media era." *Health Affairs* blog (Aug. 27, 2014)
Unsigned commentary. "The equitable pathway." *BioCentury* 9-11 (March 31, 2014)
Usdin, S. "Viral crossroads." *BioCentury* 1-6 (March 31, 2014)
Usdin, S. "Josh Hardy chronicles." *BioCentury* 7-9 (Mach 31, 2014)