Under 21st Century Cures legislation, stem cell advocates expect regulatory shortcuts

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**WEST PALM BEACH, FLORIDA—**As the 21st Century Cures Act [**cleared the U.S. Senate**](http://www.sciencemag.org/news/2016/12/senate-sends-massive-biomedical-innovation-bill-obama-signing) last week, many attendees of the annual World Stem Cell Summit (WSCS) here took a victory lap. The meeting assembled some of the lawyers, analysts, and activists who have long pushed for reform of how the U.S. Food and Drug Administration (FDA) handles regenerative medicine. And the [**behemoth biomedical bill**](http://www.sciencemag.org/news/2016/12/senate-sends-massive-biomedical-innovation-bill-obama-signing) predicted to get a presidential signature this week could allow some stem cell products a faster and more flexible premarket approval process.

“For the first time, I would submit to you, in the United States, regenerative medicine is taking its place,” said Bernard Siegel, executive director of the Regenerative Medicine Foundation, the nonprofit advocacy group that organizes the annual meeting, said of the bill in his 6 December welcome address.

The allure of stem cells—their ability to repair the body by multiplying and differentiating into more mature cells—has inspired researchers to try out hundreds of therapeutic applications, from [**grafting them onto damaged skin**](http://www.sciencemag.org/news/2014/11/stem-cells-show-potential-treating-rare-skin-disease) to [**infusing them into fetuses with bone disease**](http://www.sciencemag.org/news/2016/04/ailing-fetuses-be-treated-stem-cells). But because many of these therapies have yet to prove their clinical value and clinics around the world are selling untested treatments that may pose risks to patients, Congress’s push for faster approval of stem cell therapies is also causing anxiety. The Cures language on regenerative medicine, added during final negotiations last month between House of Representatives and Senate representatives, salvages certain aspects of a highly controversial Senate bill known as REGROW (Reliable and Effective Growth for Regenerative Health Options that Improve Wellness), first introduced in March by senators Mark Kirk (R–IL) and  Joe Manchin (D–WV). That bill outlined a “conditional approval” system for stem cell therapies that would have spared their sponsors the large, costly, and time-consuming phase III clinical trials designed to confirm efficacy. Instead, once safety was generally shown in smaller trials, sponsors would get marketing approval and then could collect such evidence through follow-up studies of customers—once they were also collecting revenue. The bill was meant to stimulate investment in the field and get potential treatments to desperate patients faster. But both academic societies and trade groups panned it, arguing that it would compromise FDA’s standards and allow useless or even dangerous drugs onto the market.

The relevant Cures language is undeniably gentler: It lets companies apply to FDA for a new designation, “regenerative advanced therapy” that makes them automatically eligible for several existing types of special treatment, provided that their product targets a serious disease and, based on preliminary clinical evidence, has the “potential to address unmet medical needs.” Among the most enticing of these existing FDA perks is a pathway called accelerated approval, which allows a drug to reach the market based on what are called intermediate or surrogate clinical trial endpoints—measures like imaging data or markers in blood that are predictive of longer term disease outcomes like survival. Compared with the standard approval pathway, that can mean fewer, shorter, or smaller trials.

That’s an exciting prospect for Joanne Kurtzberg, a pediatric transplant researcher at Duke University in Durham, North Carolina, who presented at the meeting, and who is preparing a clinical trial that gives young cerebral palsy patients infusions of umbilical cord blood containing stem cells. Kurtzberg is considering seeking accelerated approval for the therapy, but has worked with drug sponsors who sought that designation before and were denied. “In my view as a clinician, the data was strong enough and compelling enough, and the need was compelling enough,” she says of those cases. To date, no stem cell treatment has been granted accelerated approval—and none has yet been approved by FDA via any pathway. The new bill “at least opens the door for some conversations that have not been possible up to now,” Kurtzberg says.

Some regenerative medicine advocates hope the new law will make FDA more receptive to future submissions just by explicitly stating that the accelerated approval should apply to stem cell therapies. But if the new criteria for a regenerative advanced therapy overrule the existing ones for accelerated approval—as they appear to do—stem cell treatments would also face less restrictive criteria for entering that pathway, notes Michael Druckman, a lawyer at Hogan Lovells in Washington, D.C., who helped WSCS attendees dissect the bill at a 9 December session. For example, the criteria don’t specify that a proposed treatment must provide a benefit over existing therapy.

“That’s a pretty big deal,” says C. Randal Mills, president of the California Institute for Regenerative Medicine in Oakland, the state-sponsored stem cell research funding agency that has been a strong proponent of regulatory reform. The existence of some non–stem cell alternative currently gives FDA an easy route to reject an accelerated approval application, he says.

Because it backs away from the idea of conditional approval, the Cures language has the support of some groups who saw REGROW as too radical/aggressive, including the Alliance for Regenerative Medicine—[**a high-profile industry opponent**](http://alliancerm.org/sites/default/files/ARMSenatorKirk_REGROWActletter_March2016_.pdf) of the older bill. But suggesting special treatment to regenerative medicine also sends a troubling signal, says public health policy expert Aaron Kesselheim of Harvard University. “The FDA already has these tools that, if there is a new important regenerative medicine therapeutic, it would apply,” he says. “I just don’t know what this section of the bill does, other than push the FDA to apply these pathways to regenerative medicine therapeutics before there’s any kind of reasonable belief that that would be useful.”

And though Cures stops short of explicitly removing a requirement for phase III trials, winning accelerated approval can make them unnecessary. “Accelerated approval is conditional approval,” Mills says. (Like conditional approval, it comes with the requirement to collect postapproval evidence of efficacy. The Cures bill also specifies that such evidence can come from sources outside a clinical trial, such as electronic health records or patient registries.)

Drugs for rare diseases have long depended on the accelerated pathway to reach the market, Mills notes, and “they’re lucky if they get two trials.” In fact, [**an analysis**](http://www.permed2020.eu/_media/PHGJ_Available_Tools_to_Facilitate_Early_Patient_Access_to_Medicines_inEUandUSA.pdf) of the 20 drugs approved under FDA’s accelerated pathway between 2011 and 2015 found that only 20% relied on phase III data.

Under the new Cures act, FDA will still ultimately decide just how flexible to be with data requirements, says Marc Scheineson, a lawyer at Alston & Bird LLP and counsel to the Bipartisan Policy Institute, a Washington, D.C.–based think tank that suggested some of the bill’s provisions. FDA must report to Congress annually on how many regenerative advanced therapy applications it received and how many were granted. “We gave them statutory basis and tools to use. Can we force them to use those tools? No. They have a lot of authority, FDA. They’re an 800-pound gorilla in the trade,” he says. “But we can make them accountable, and we can make it transparent.”