21ST Century Cures Act
Innovation, Breakthroughs, and Research in Under-Represented Populations

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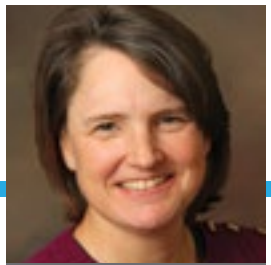
Background

On December 13, 2016, the 21ST Century Cures Act (H.R. 34) (the Act) was signed into law by President Obama.[1] Provisions in the Act were negotiated between the House and the Senate over a two-year period. The first version of the Act, the "21ST Century Cures Initiative," was introduced by the Energy and Commerce Committee in April 2014.[2] The Act is a bipartisan agreement to fund and accelerate cancer research and overall medical product discovery, development, and delivery (Division A, the 21ST Century Cures Act); to help families in mental health crisis (Division B); and, to increase the choice, access, and quality in healthcare for Americans (Division C).

The 21ST Century Cures Act Division A

Division A of the 21ST Century Cures Act provides funding for innovation projects and state responses to opioid abuse, precision medicine, and new drug discovery and development initiatives, and the overhaul of healthcare product regulations by the U.S. Food and Drug Administration (FDA). The regulatory affairs sections support product research and innovation, encourage acceptance of patient and real-world experience data, and call for streamlined marketing approvals for innovative medicines and devices, as well as for supporting the participation of certain less-represented population groups in clinical investigations.

Division A is divided into subparts to address: a) funding for various program initiatives for research and innovation; b) the overhaul of medical product regulations; and, c) the need for mental health initiatives. The funding details for various programs and mental health initiatives are not subjects of this article. Of greater interest from the regulatory and market access perspective are the regulatory-related provisions to allow the inclusion of patient experience and real-world data in marketing applications; the inclusion of pregnant and lactating women, as well as children, in clinical trials; the acceleration of medicinal product development and approval by implementation of expedited pathways; and, the creation of one or more intercenter institutes within the FDA to develop and coordinate activities on major disease areas.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Initiatives Specific to Women and Pediatric Patients

A long-standing problem area in clinical trials has been restrictions on the enrollment of pregnant and lactating women, children, and the elderly due to their respective vulnerability and special protections in place for these study populations. The enrollment of women and particularly those who are pregnant or lactating has historically been lacking or inconsistent.[3-6] Most clinical trials require use of contraception by women of childbearing age, therefore knowledge gaps as to treatment benefits for this "scientifically complex" population remain.[3] The "Task Force on Research Specific to Pregnant Women and Lactating Women," established by the National Institute of Child Health and Human Development, has scheduled several meetings throughout 2017 and into 2018 to identify and develop guidance to address gaps in knowledge required for the development of safe and effective medicines for pregnant and lactating women.[7]

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Clinical research in children is necessary to assure safety and efficacy of any drug under development because of physiologic and metabolic differences to the adult population for which most drugs are approved. Additional safeguards for children to be involved in research studies are necessary, which make clinical trial designs more complex. Recognizing the difficulties of conducting research in the pediatric population, Section 2072 of the Act mandates the establishment of a global pediatric clinical study network to provide grants, contracts, or cooperative agreements to support new and early stage investigators.[1] The participation of international authorities outside of the Unites States will be actively supported and maintained in the operating network.

Development of Regenerative Medicines

The opinion that the FDA does not approve new innovative medicines fast enough and prevents patient access to these medicines is addressed in the Act through the implementation of a host of provisions for accelerated approval pathways for regenerative advanced therapies as well as innovative devices. Most notably, the Regenerative Medicine Advanced Therapy (RMAT) Designation, which was originally labeled as "Regenerative Advanced Therapy or RAT," introduced in Section 3033 of the Act, builds on the existing four expedited development and review programs offered by the FDA.[1] A few RMAT designations have already been granted *(Table 1)*.

The new RMAT designation provides the FDA with a program for expanding expedited review pathways for regenerative medicines without lowering safety of effectiveness standards. For example, a drug would be eligible for this designation if the drug is a regenerative medicine (cell therapy, therapeutic tissue engineered products, human cell and tissue products, and combination products except those solely regulated under PHS 361) intended to treat, modify, reverse, or cure a life-threatening disease/condition and preliminary clinical evidence indicates that it would meet an unmet medical need.[8] A drug designated as RMAT may be eligible for priority review and accelerated approval based on surrogate or intermediate endpoints likely to predict long-term benefit or on data from a meaningful number of clinical sites. Notably, products with RMAT designation can fulfill post-marketing requirements through channels additional to clinical trials, such as patient registries, real-world experience (e.g., electronic health records), collection of large confirmatory data sets, or post-approval monitoring data.

There has been controversy around the RMAT designation. An article in *Wired* states that under the 21ST Century Cures Act, "FDA would have the authority to grant accelerated approval for regenerative medicines, skipping straight from animal models and safety trials, over efficacy testing in humans, to post-marketing review."[9] It further states that it provides a direct path for acceptance of regenerative medicines by stem cell clinics – dubbed the "medicine's wild west" for an "inject and see" era.[9] Husten calls the provision repulsive.[10] Accelerated approval would only be granted based on surrogate or intermediate endpoints likely to predict a long-term clinical benefit or on data obtained from a meaningful number of sites, which is quite different from what the two critical articles suggest. Also, standards for approval of other expedited programs would remain.[11]

On the other hand, the REGROW Act[12] introduced by U.S. Sen. Mark Kirk early in 2016 would have allowed conditional approval of cell and tissue therapies based on preliminary clinical evidence of safety with reasonable expectation of efficacy, without the initiation of Phase III studies. Unlike the REGROW Act, the 21ST Century Cures Act does not eliminate the need for Phase III studies but allows reliance on surrogate endpoints and other intermediate endpoints.[13]

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Currently, seven companies have publicly announced that their product received RMAT designation. FDA does not publish this information and it is at the discretion of the company to publish the assignment of the designation.

The 21ST Century Cures Act mandates that the FDA track the applications for RMAT designation, the number of

Table 1: RMAT Designations under the 21ST Century Cures Act

Company	Product	Description	Indication	Date
Humacyte[14]	Humacyl®	Human acellular vessels	Kidney failure (vascular access for hemodialysis)	20 March 2017
Enzyvant[15]	RVT-802	Apply allogeneic thymus tissue to restore some immune function	DiGeorge syndrome	17 April 2017
jCyte[16]	jCell	Human retinal progenitor cells release neurotrophins to potentially rescue diseased retinal cells	Developmental retinitis pigmentosa	2 May 2017
Vericel[17]	Ixmyelocel-T	Autologous multicellular therapy of mesenchymal stromal cells and macrophages to repair damaged tissue	Serious cardiovascular disease	10 May 2017
Mallinckrodt[18]	Stratagraft®	Autologous skin tissue	Complex skin defects due to thermal burns	18 July 2017
Kiadis Pharma[19]	ATIR101™	Adjunctive immunotherapeutic of donor lymphocytes	Blood cancers	20 September 2017
Asterias Biotherapeutics[20]	AST-OPC1	Oligodendrocyte progenitor population derived from embryonic human stem cells	Spinal cord injury	2 October 2017

designations issued, and the ultimate disposition of the products involved per approval pathway, approvals, withdrawals, and authorization denials. The FDA is required to submit a report to Congress by March 1 of each calendar year of the applications and outcomes for the prior fiscal year. Furthermore, the FDA is required to develop guidance clarifying how devices used in the recovery, isolation, and delivery of regenerative advanced therapies will be evaluated (Section 3034).[1]

The 21ST Century Cures Act also mandates the development and implementation of a set of standards and consensus criteria to support the development and evaluation of regenerative therapy medicinal products or devices (Class III) used with a regenerative therapy product to ensure regulatory predictability. In August 2017, the FDA issued a call for proposals to complete this task and requires the interaction of a mixed group of stakeholders, with public involvement, to develop the standards, set criteria, and provide a process for implementation and oversight. *(Read more in "Leveraging Real-World Evidence for Regenerative Medicine and Advanced Therapy Success Beyond the Regulator" in this issue.)*

Medical Device Regulatory Changes

The 21ST Century Cures Act contains several provisions that support faster access to medical devices. Most notably Section 3051, inserting Section 515C into the FD&C Act (21 U.S.C. 351 et seq.), implements the new Breakthrough Device Designation to expedite the development of devices that represent breakthrough technology. Although, the Breakthrough Device Designation is like the 2015 Expanded Access Program (EAP) for devices,[21] there are some differences, for example:

- 510(k) devices are eligible for the Breakthrough Device Designation, whereas only devices requiring premarket approval or de novo applications were accepted for the EAP; and,
- The Data Development Plan is now optional rather than mandatory.

The designation can be obtained if the device:

a) provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating disease, and

b) 1. represents breakthrough technology,

2. no approved or cleared alternative exists,

3. shows significant advantage over existing alternatives, or

4. availability is in the best interest of patients.

Advantages of receiving the designation include assignment of a dedicated FDA staff team, interactive and timely communication with the FDA during the development and review process, agreement of a data development plan, ensuring clinical trial design is as efficient and flexible as practicable, and agreement on clinical protocols and priority review for market approval. This new program replaces the priority review previously noted in FD&C Act Section 515(d)(5). The FDA is expected to issue guidance for sponsors within a year. To date, two companies publicized receiving the Breakthrough Device Designation.

NeoTherma Oncology announced in April that its Vectron Thermal Treatment (TTx) system for treatment of pancreatic cancer was designated a Breakthrough Device. The Vectron

TTx system integrates electromagnetic field physics with thermographic imaging and computational imaging to modestly raise the temperature in the tumor environment. This adjuvant treatment was shown to significantly increase the effectiveness of radio-, chemo-, and immunotherapies.[22] Also in April 2017, N8 Medical, LLC received the breakthrough designation for their CeraShield Endotracheal Tubes. The endotracheal tubes, coated with a proprietary ceragenin compound, prevent bacterial and fungal growth while a patient is intubated for mechanical ventilation.[23]

Additional provisions of the 21ST Century Cures Act include Section 3052 that amends the Food Drug and Cosmetic Act to extend the Humanitarian Device Exemption from a previous maximum of 4,000 to the new maximum of 8,000 patients. More flexibility for the recognition of standards is introduced by Section 3053. Any person can submit the request for recognition of a standard established by a national or international standards organization. The Secretary will determine if the standard is recognized in part, full, or not at all and inform the requestor. The Act also provides for the establishment of new requirements for medical device classification panels, Clinical Laboratory Improvement Amendments (CLIA) waiver improvements, and a requirement that FDA staff are to determine the least burdensome pathway to demonstrate reasonable assurance of safety and effectiveness during review of 510(k) premarket notification and premarket approval applications.

Conclusion

The 21ST Century Cures Act brings about many regulatory changes. The implementation, and particularly the timeframe to achieve this, is very ambitious. The implementation of tools to allow for more efficient drug approval, e.g., regenerative medicine advanced therapy designation (Section 3033), breakthrough devices (Section 3051), and summary level review (Section 3031) have been met with criticism, citing lower standards for approval and the potential for ineffective or unsafe drugs or devices entering the U.S. market. However, it is important to consider the legislative text of the 21ST Century Cures Act that includes provisions to safeguard the current FDA approval standards. On the other hand, provisions such as the RMAT designation and the breakthrough device designation have been met with great enthusiasm from industry. Several applications have been approved since the Act was signed into law. Since the number of applications currently is not public information, the reports required from FDA on a yearly basis by March 1 for the preceding fiscal year will provide a better picture. Some of the task forces mandated by the Act have been formed already, but to see results from their work will take some time. ■

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