L

ast July, Mallinckrodt announced that its regenerative skin
tissue product StrataGraft had received a regenerative
medicine advanced therapy (RMAT) designation from the
Food and Drug Administration (FDA). The RMAT designation
was established in the 21st Century Cures Act, the
bill passed by an overwhelming vote in Congress
in December 2016 and signed by President Barack
Obama amid praise from industry and patient
advocacy groups. The bill opened the door to a grab bag
of FDA regulatory initiatives, including the new RMAT
designation, aimed at making it easier, faster, and
cheaper for drug manufacturers to introduce new
products, such as StrataGraft, a cell-based tissue
graft that would provide a treatment for burn victims
that does not exist today. By bestowing the RMAT
designation, the FDA put Mallinckrodt on a path to earn priority
review and/or accelerated approval of the product.

The establishment of the RMAT designation was one of about
60 initiatives the Cures Act authorized the FDA to take. The
key provisions in the law are found in Title III, Part II, which
contains Subtitles B–G, each of them containing multiple
requirements. Subtitle B is “Advancing New Drug Therapies,”
Subtitle C is “Modern Trial Design and Evidence Development,”
and Subtitle D is “Patient Access to Therapies and Information.”
Each contains provisions concerning items such as qualifica-
tion of drug development tools, real-world evidence (RWE),
standards for regenerative medicine, and grants for continu-
ous manufacturing. Subtitle F contains provisions on medical
device innovation.

A year into implementation, the FDA has already chalked
up some accomplishments, such as launching the RMAT
designation. But implementation of the nearly 60 “to-do” items in
critical Title III appears to be moving slowly in some areas and
faster in others, in some cases because of the long lead times
Congress allowed for FDA action and in other cases because of
personnel limitations.

Where implementation has been minimal may have some-
ting to do with the multiplicity of open jobs at the FDA. “It
is hard for me to argue that if we are down hundreds of slots

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The 21st Century Cures Act:
FDA Implementation One Year Later
Some Action, Some Results, Some Questions
Stephen Barlas
Oncology Center for Excellence: A Marquee Provision

At the House hearings at the end of November, Dr. Gottlieb highlighted the FDA’s “standing up” of its new Oncology Center for Excellence (OCE) as “one of our first achievements” related to the Cures Act.1 Actually, former FDA Commissioner Robert M. Califf, MD, announced the establishment of the OCE six months before Congress passed the Cures Act, in good part to support the National Cancer Moonshot Initiative established by President Obama in 2016 and spearheaded by Vice President Joe Biden. What the Cures bill did was require the FDA to create additional centers of excellence patterned after the OCE. That has not happened. Dr. Gottlieb noted the FDA is “contemplating” similar centers for immunology and neurosciences.3

The Cures Act did not provide the FDA with money for the OCE; however, the National Institutes of Health (NIH) was tasked with sharing some of its $1.8 billion Moonshot money (over 10 years) with the OCE. The NIH received $4.8 billion over 10 years for four programs, including the Cancer Moonshot (see related coverage on page 131 of this issue).2 At the House hearings, Dr. Gottlieb explained, under questioning from U.S. Representative Diana DeGette (D-Colorado), “There have been some challenges associated with transferring those funds to FDA, some legal challenges.” He was referring to the transfer of Moonshot money to the OCE. The implication was that the OCE has been hamstrung, its small budget of $3.6 million in FY 2017 undoubtedly less than the FDA hoped for when it expected an infusion of Moonshot funds.

Reflecting its underfunded status, the OCE has nine employees to date in a full-time but “acting” capacity. Richard Pazdur, MD, was named the permanent Director on January 19, 2017, but he also serves as Acting Director of the Office of Hematology and Oncology Products at CDER. So his time is split between the two offices.

The OCE appears to be a promising model. It apparently made a major contribution when the FDA approved tisagenlecleucel (Kymriah, Novartis) in late August for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia. At the time, the FDA called the approval “historic,” making it the first gene therapy available in the United States, ushering in a new approach to the treatment of cancer and other serious and life-threatening diseases.

Before the House committee, Dr. Gottlieb called the OCE’s role in the approval of tisagenlecleucel “instrumental” and stated, “I think the essential point is the center allows us to consolidate the clinical review and take a more multidisciplinary approach to how we look at the evaluation of efficacy and safety around these products. And we do think that this kind of center approach represents the future of how we want to approach other therapeutic spaces.”3

In December 2016, the American Society for Clinical Oncology (ASCO) issued a press release calling the Cures Act “historic.” Despite Dr. Gottlieb’s praise, ASCO spokeswoman Rachel Martin says, “Unfortunately we don’t have enough information to provide additional comments on the OCE.”

Biomarkers

Just as the existence of the OCE predated passage of the Cures Act, so did the FDA’s biomarker program, which has been in place since 2006 when a White Paper was issued. Biomarkers are seen as a means of telling drug developers earlier whether their drug may have toxicity or that it may not work at all, and to get that early read on what’s going to be successful. In the past, biomarkers have been developed by single companies conducting clinical trials and have been, for the most, proprietary. But rousing successes on biomarkers have been few and far between. At the House hearings, U.S. Representative Eliot Engel (D-New York) said, “My understanding is that a lack of taxonomy and evidentiary standards has made it difficult to develop workable biomarkers that can be replicated during the drug approval process.”3

The Cures Act anticipates consortiums applying for biomarker qualification, and once accepted and validated, those biomarkers would be publicly available, allowing any company to use them. Dr. Gottlieb said the FDA currently has eight biomarkers under consideration as part of the new three-step qualification process endorsed by the Cures Act. The sponsors of those eight applications have not been made public.

Besides establishing this new qualification process, it is not clear if the FDA is using standards different than it was using before. The minimal FDA biomarkers qualification website is silent on that. So it is hard to tell whether the 21st Century Cures bill has led to substantive changes in qualification or to bureaucratic changes only, given that there has been some “office shuffling” within the FDA to ostensibly ease the way for biomarker approval. What is known is that the FDA has progressed further with clinical outcomes assessment (COA) tools that are linked with biomarkers in the Cures Act provision on “drug development tools.” The first COA from the COA Drug Development Tool Qualification program has been accepted—the Symptoms of Major Depressive Disorder Scale—and the agency expects to act on that submission soon, according to Dr. Gottlieb.3

Dr. Gottlieb was a little defensive with regard to progress on drug development tools, both biomarkers and COAs. “So that might not sound like a big number,” he explained to the House committee, referring to the number of applications in the new qualification pipeline. “In our estimation, it is a profound number given the fact that these are still early days in the development of these new frameworks, and we are seeing this level of interest.”3

Real-World Evidence

While the promise of biomarkers is that they will shorten clinical trials, clinical trials will remain the sine qua non of drug development. Sections 3021 and 3022 of the Cures Act focus on novel clinical trial designs and RWE, respectively.2 These have been hot topics, especially RWE, considered to be post-market data from health insurance databases, disease registries, and other compendia that can be used by the FDA, instead of clinical trials, to approve new uses of existing drugs. The Cures Act gives the FDA two years to establish a draft framework for a program to evaluate the potential use of RWE.

The FDA has made more progress on RWE for medical device approval than for drug approval. There is final guidance on the former, but none on the latter. The FDA actually used RWE, in this case data from the Transcatheter Valve Therapy Registry, a partnership of the American College of Cardiology and the Society of Thoracic Surgeons, as part of the rationale...
for its approval last June of the Sapien 3 transcatheter heart valve (Edwards Lifesciences), which is implanted in high-risk patients whose surgically placed aortic or mitral bioprosthetic valves are old and worn out.

On the drug side, with regard to RWE, the FDA has established a big data analytics initiative called Information Exchange and Data Transformation (INFORMED), which is being run out of the OCE. One aspect of that effort is a collaboration with Flatiron Health to examine how RWE can be used to gain insights into the safety and effectiveness of new cancer therapies. In addition, in June 2017, the FDA announced a partnership with CancerLinQ, ASCO’s big data initiative. The initial focus will be on immunotherapy agents approved for melanoma.

**RMAT Designation**

Moving from data to disease, the FDA established the RMAT designation program, as authorized in section 3033 of the Cures Act. The program covers therapeutic tissue engineering products, human cell and tissue products, and combination products, as well as gene therapies that lead to a durable modification of cells. To qualify, a product must be:

- Defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products;
- Intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and
- Preliminary clinical evidence indicates the product has the potential to address unmet medical needs for such a disease or condition.

The RMAT program is housed at CBER. Products granted designation are eligible for increased early interactions with the FDA, including all the benefits available to breakthrough therapies. Because these are considered investigational products, the FDA does not identify which products have gained RMAT designations unless the company makes an announcement itself, as Mallinckrodt did with StrataGraft.

In November 2017, the FDA released two draft guidance documents describing the expedited programs available to sponsors of regenerative medicine and describing how CBER will encourage flexibility in clinical trial design to facilitate the development of data to demonstrate the safety and effectiveness of regenerative medicine therapies. The first addresses how the FDA intends to simplify and streamline its application of the regulatory requirements for devices used in the recovery, isolation, and delivery of RMATs, including combination products.

The second draft document describes the expedited programs that may be available to sponsors of regenerative medicine therapies, including priority review and accelerated approval.

Michael Werner, of ARM, explains that the RMAT designation is significant for two reasons. First, it sends a signal to the regulated industry and patients waiting for therapy that there will be a specific pathway for new products. There wasn’t one before. That puts the U.S. on the same footing as countries such as Japan, which have been more aggressive. Second, the designation allows a company to have meetings early in the clinical trial process with the FDA, which are, according to Werner and many others, “a real factor in determining success.” Designees also acquire the ability to use RWE, which is particularly important where a chemical is seen as having an impact on a rare disease but where recruitment for large clinical trials is close to impossible. There is also access to expedited approval pathways.

Peter Marks, MD, Director of CBER, acknowledged to the FDA’s Science Advisory Board last May that the scientific challenges behind regenerative therapies are “significant.” One of the key challenges is trying to facilitate reproducibility in manufacturing. Dr. Marks said CBER was “in the process now of working toward getting these partnerships in place because we very much agree that having development in a collaborative manner of standards that help with the development of these products will facilitate reproducible manufacturing and will hopefully take some of the uncertainty out of product development.” With that challenge in mind, the FDA awarded a $2.3 million contract in November to Nexight Group LLC, which has one year to write a report on the standards landscape for regenerative medicine therapies.

While the Cures Act seeks to set the stage for manufacturing improvements for regenerative products via an initial framework of consensus standards, there is a Cures Act provision that jumps directly into manufacturing, in this case what is called continuous manufacturing. Continuous manufacturing—a technologically advanced and automated manufacturing method—provides a faster, more reliable way to make pharmaceuticals. This can help reduce drug shortages and recalls related to problems with product or facility quality. During FY 2017, CDER granted an award to the University of Connecticut to develop and build a continuous manufacturing platform with modular components for complex dosage forms, as well as to create a library based on graphical user interfaces. These activities support quality-based risk assessment and provide a roadmap to modernize technology and solve continuous manufacturing challenges for complex dosage forms. They can also help the agency with review processes and provide necessary information to guide policy development.

The FDA has made significant progress implementing some of the 60 provisions of the 21st Century Cures Act. To the extent that it could have been expected to make more progress in some areas, the fault lies partly with funding shortfalls, which is no fault of the agency’s. Those money problems may be remedied. That will be up to Congress.

**REFERENCES**

The 21st Century Cures Act

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