Robin Robinson

21st Century Cures Act Holds Promise for Patients

If the 21st Century Cures Act becomes law, the future will be bright for both patients and the pharmaceutical industry.

The 21st Century Cure Act, if passed, promises to promote the development and hasten the approval of new drugs and devices, especially treatments for cancer and rare diseases. It puts the view of the patient in the center of drug discovery, development, and delivery, balanced by insights derived from data analytics, clinical science, and a more flexible approval process. Clinical research provisions minimize unnecessary and duplicative administrative requirements, and to promote the broad availability of clinical research data, with adequate security and privacy measures, to advance medical product innovation. The bill also contains a provision to facilitate and encourage investigating treatments for rare diseases in clinical research.

The incentives that are part of the 21st Century Cures will create a money slide from big medicine into little medicine, and into rare disease medicine.

STEVE SMITH
Medidata

The House overwhelmingly passed its version of the bill in July of this year and the Senate is reviewing its draft — called the Innovation for Healthier Americans — and plans to make it public for review in early fall. (For summaries of the House's bill provisions, see bonus digital copy.)

Naysayers of the initiative raise concerns regarding patient safety, saying the act goes too far in pushing the FDA to speed up the drug approval process, and that the existing protocol is adequate and presents less of a risk to consumers.

According to reports from Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, those who say that the 21st Century Cures legislation lowers the standard of safety "are completely wrong." Steve Smith, chief patient advocate, Medidata, quotes her directly from her presentation at the DIA annual meeting in Washingon, D.C., in June, where he asked her to clarify her remarks.

"Dr. Woodcock, who has taken the lead for the FDA in discussing the bill, said the FDA would be the first to protest if the act did compromise safety; she has said unequivocally that the 21st Century Cures bill is a good bill," Mr. Smith says. "Dr. Woodcock clearly said it does not compromise safety and it does not lower the standard of efficacy that the FDA must uphold."

According to Max Bronstein, senior director, advocacy and science policy, EveryLife Foundation for Rare Diseases, the bark from safety watchdogs is not new, and has been clearly addressed by the FDA.

"We've heard concerns like this before," Mr. Bronstein says. "Detractors should listen to Dr. Woodcock, to Acting FDA Commissioner Dr. Stephen Ostroff, and to two former FDA Commissioners, Dr. Mark McClellan and Dr. von Eschenbach. They've all gone on record saying the 21st Century Cures Act will not affect the safety standards that the FDA has put in place in its mandate for safety; it will not have any impact on safety whatsoever."

FAST FACT

IN A RARE DISPLAY OF BIPARTISANSHIP IN POLITICALLY POLARIZED WASHINGTON, 344 MEMBERS OF THE HOUSE OF REPRESENTATIVES VOTED IN JULY TO PASS THE 21ST CENTURY CURES ACT.

Source: Peter Pitts

The EveryLife Foundation for Rare Diseases, a nonprofit organization dedicated to accelerating biotech innovation for rare disease treatments, has initiated efforts to nullify such fears, but opponents to the bill seem to be getting more press than the advocates.

"The media has featured dissenting voices, and while they are in the small minority, they tend to get quite a bit of airtime on the issue, so it's not as balanced a debate as it could or should be," Mr. Bronstein says.

With 7,000 untreated rare diseases and only 400 treatments for rare diseases, the need for such a bill is apparent to its advocates. Advances in science and technology, such as personalized medicine, are creating new opportunities to improve and expand research into rare diseases and the development of new treatments.

The act expedites research and development for a wide variety of debilitating illnesses, and makes it easier to get new treatments to patients who need them.

The 21st Century Cures Act would address the ambiguities around FDAMA 114 that limit the ability of pharmaceutical companies to effectively collect and share information with the payer community.

JIM ROBINSON
Astellas Pharma US

"The 21st Century Cure Act is one of several developments that I envision will usher in a more collaborative, patient-centric approach to develop new and innovative therapeutics, particularly in rare diseases," says Gene Kinney, Ph.D., chief scientific officer and head of research and development, Prothena.

"In these settings, where the successful regulatory and clinical approaches are typically undefined, it can be challenging," Dr. Kinney says. "As such, it's more important than ever to integrate patient insights into the earliest stages of drug development."

Advocacy groups — such as EveryLife Foundation for Rare Diseases — are an effective driver of engagement between patients, researchers, clinicians, and industry, enabling better design of clinical programs, sharing of scientific research, and the creation of educational disease awareness. Such collaboration should result in new treatments that demonstrably improve health outcomes, a win for both the patient and the health system as a whole, Dr. Kinney says.

This type of stakeholder collaboration has already been forged through the passing of the act through the House.

"The 21st Century Cures Act has been a remarkably galvanizing process," says Jim Robinson, president, Astellas Pharma US. "The collaborative spirit forged by Chairman Upton and Congresswomen DeGette, coupled with the parallel efforts being shepherded in the Senate by HELP Committee Chairman Alexander, is an admirable rallying cry that evidences bi-partisan support for the need to advance the discovery and development of innovative new therapies and treatments into the 21st century and one that the industry hopes will extend beyond this singular initiative."

Proponents are waiting impatiently for the Senate to publish its version, because time is of the essence with the upcoming election year bearing down on the bill's shelf life.

"One of our big concerns about the Senate initiative is that we haven't seen any draft legislation yet, and the Senate has a lot of distractions coming up," Mr. Bronstein says. "There's a presidential election that's starting to heat up, so if the Senate doesn't act on this bill this year, all the good work that was done by the House and all of the stakeholders and patients who were engaged in the process might be for nothing if the Senate doesn't make this a priority."

If the bill does not reach or is not approved by this administration, the initiative would have to start all over, which would be a shame, Mr. Smith says, as there has been so much time and effort put into the bill so far.

"There has been such a thorough listening and information gathering process starting in House of Representatives that we're not going to get to this point again easily if the bill doesn't make it all the way through by the end of 2016," he says.

To help nudge the process along, the EveryLife Foundation for Rare Diseases took advantage of the captive audience at the Global Genes Conference and asked everyone in attendance to contact their senators. The group provided phone numbers and e-mails and a script and many attendees took action right then and there.

"We let all the folks know that when it comes to issues like funding for the NIH and FDA, the Senate needs to move on because quite frankly, a delay in legislation is going to delay treatment for patients," Mr. Bronstein says. "And if you're a patient who has a rare disease or any life-threatening disease, you do not have the luxury of time. The Senate has to take action, otherwise, we could miss this great window of opportunity."

Provisions in the Bill

The 21st Century Cures Act is large and complex — even though it has been cut in half by 200 pages from its original incarnation earlier this year — and its passing will have wide ranging implications across all healthcare stakeholders, not the least of whom are patients.

In addition to increasing medical research funding and expediting the process of making breakthrough therapies available to patients, if enacted into law, the bill would impose significant new requirements related to the regulation of health information technology. The bill includes several provisions related to federal oversight of clinical research, as well as provisions for Medicare and Medicaid, and several FDA-related changes.

The complexity of the legislature makes it difficult for all to agree, which is adding to the anxiety of those who believe that the

Don't Forget the Physician in 21st Century Cures Act

ERIK DALTON
Executive VP, Healthcasts

Most people are discussing the impact on R&D strategies, adaptive clinical trials, and how new breakthrough medications will help patients. Many people are also discussing the potential of the FDA bringing drugs to market faster, maybe with lower standards for providing drug safety and efficacy information. But, few people are discussing what this actually means to physicians. As more drugs are approved more quickly, HCPs will need to look at the clinical data more closely to make judgments on whether they consider a drug safe and effective for each individual patient. Their discretion and experience will play an even more important role in patient care.

Physicians will need to be able to quickly acquire new data that are published after a drug is launched so their assessment can evolve in real time. Adoption rates of new drugs may slow as physicians grapple with how to obtain the information they need. For these drugs to help patients most effectively, pharma will need to improve how they educate physicians and provide up-to-date clinical trial data and prescribing information. The FDA might consider publishing data being collected by physicians and making that information widely available.

act is paramount to better healthcare in this country and needs to be made into law as soon as possible.

The two predominant sections propose to change the processes by which U.S. regulators approve new medicines and spend public funds for research. Not many can argue with the need for more funding to further research by the NIH, but not everyone is onboard with changing the FDA drug approval process.

According to Seth Lederman, M.D., co-founder, CEO, and chairman of Tonix Pharmaceuticals, the two processes are not equally in need of fixing. Dr. Lederman believes the U.S. approval process of new medicines is appropriate, but that the NIH could use the boost of funds for further investigative trials for cancer research.

"In my opinion, the relative health of FDA and the relative dysfunction of NIH/NCI should be strongly considered in selecting the potency and potential risks of any intervention," he says. "The FDA's independence from political pressure is of paramount importance. In contrast, the NIH/NCI appears to need new systems of oversight, hopefully involving patients. I believe that a rededication of NIH/NCI to the unique mission of funding investigator-initiated basic research makes economic sense given the restricted funds currently available."

In contrast to the FDA, the health of the NIH/NCI system for providing funding for biomedical research is strained and there is widespread dissatisfaction among most of the participants, Dr. Lederman adds.

He adds that the funding constraints of "sequestration" have strangled the initiative to transform NIH/NCI from a basic research funding organization into a platform to discover and develop new drugs and compete with the private sector biopharmaceutical companies.

"Given the financial constraints, I would favor a rededication of the NIH/NCI back to funding basic research, with an emphasis on investigator-initiated research," Dr. Lederman says.

Despite his concerns, Dr. Lederman believes there is always a need to review new ways of doing things, and to discourage innovation through legislation does not bode well for the industry or the nation's healthcare.

"Given the U.S.'s global leadership in de-

The 21st Century Cure Act

Thought leaders respond to the relevant ways the 21st Century Cure Act is going to impact the industry: R&D strategies, clinical trials, and rare disease treatments.

MATT GROSS
Director of Health Care and Life Sciences, Global Practice, SAS

R&D STRATEGIES: Medical needs are often unmet because the research population is small and difficult to access. R&D will no longer depend solely on data they generate but will need to access external data to both identify patients and evaluate treatments. Data will be accessed from a variety of sources, including from other research sponsors through efforts such as trial data transparency, real-world data collected from healthcare providers, as well as self-reported health outcomes that can be captured from a variety of locations, including websites. In silico trials will likely play a more important role in the long-term R&D strategy.

CLINICAL TRIALS: This act will likely accelerate the use of in silico clinical trials as well as the introduction of new types of data from the real world, from sensors and devices. In addition, due to the limited potential patient population, the research process will adapt to address a more fluid or adaptive trial approach in order to reduce the number of participants needed as well as leverage real-world evidence to either supplement or support the findings.

RARE DISEASE TREATMENTS: This act fully supports the efforts around rare diseases and, in principle, precision medicine. The idea behind the act is that all medical needs, regardless of how small or how relatively low-value from a business perspective, still deserve focused attention. In essence, rare diseases are in the same category. The idea of how to reduce the difficulty in getting the data, evaluating the outcomes for conditions with small or hard to find patient populations and proving safety and efficacy will be completely applicable to research done for rare diseases.

MIKE HODGSON
Partner and Chief Operating Officer, Cambridge BioMarketing Group

RARE DISEASE TREATMENTS: The bipartisan 21st Century Cure Act holds great promise for individuals affected by rare and other less studied diseases. By encouraging the potential for nontraditional sources of data, promoting adaptive trial designs, creating greater acceptance of biomarkers, and facilitating innovative approaches, this transformative legislation will continue to drive the breadth and depth of medical innovation in the rare disease space. Furthermore, it provides the biopharmaceutical industry with necessary information and tools to help accelerate the development of life-saving rare disease therapies by reducing time to market. Together with increasingly active patient communities and growing interdisciplinary cooperation across the healthcare system, the 21st Century Cure Act will help drive the next generation of life-saving advances across devastating orphan conditions, such as muscular dystrophy, cystic fibrosis, and even rare cancers.

KEN HORNE
CEO, Symic Biomedical

R&D STRATEGIES: It is clear that new therapies require a huge effort after an interesting discovery in a laboratory. One of the biggest challenges that the biotech industry faces is balancing the risks and timelines necessary to deliver a novel therapy to the market. By streamlining the process, particularly for therapies that address unmet medical needs, the regulators are fostering an environment where R&D strategies will likely shift toward more novel therapies, ultimately benefiting patients in need.

CLINICAL TRIALS: By removing some redundant administrative barriers, the regulators have identified hurdles that have made clinical trials increasingly complex, time consuming, and expensive over time.

veloping new medicines, no reasonable person can disagree with the idea that we should periodically review and improve our processes for approving new drugs and for providing public funding for biomedical research," Dr. Lederman says.

Increased funding for the NIH and the FDA is crucial to the discovery of new treatments and is an important part of the bill, Mr. Smith says.

"The new law would direct funding to the NIH and the FDA, which has been declining since 2000," he says. "This law calls for additional funding for the NIH, which provides very critical medical research. Funding for the FDA means that the agency is going to be able to do a better job stepping up to the mandates that this legislation actually requires of regulators and some recent past legislations, such as 2012 PDUFA V, which is also called the FDA Safety and Innovation Act."

Communications

Another provision would also allow the FDA to communicate with necessary parties to learn more about a drug's effectiveness, without being called out for being influenced by those discussions.

"A lot of good discussions, which need to happen, are being blocked by old-fashioned rules," Mr. Smith says. "We will start to see some of these behaviors change in the next few years. The FDA staff needs to be able to interact and be able to attend conferences and talk to whoever they need to talk to — people at pharmaceutical companies, physicians, and patients."

Mr. Robinson from Astellas Pharma is focused on the provisions that increase responsible communications of scientific and medical information by the industry to healthcare professionals and payers. For example, one provision in the bill would enable pharmaceutical companies to share pharmacoeconomic data with payers responsible for making coverage or reimbursement decisions.

Section 114 of the FDA Modernization Act of 1997 was intended to establish a pathway that allowed pharmaceutical companies to provide healthcare economic information to a formulary committee or other similar entity.

"However, the FDA has not provided formal guidance on its interpretation of the law and litigation on this provision has not resulted in any greater clarity," Mr. Robinson says.

"Payers want to know more about the value of the pharmaceutical products that they are allowing access to — not just the cost — and they are seeking such data," he says. "These lingering ambiguities around FDAMA 114 have limited the ability of pharmaceutical companies to effectively collect and share such information with the payer community."

The 21st Century Cures Act would address this situation, allowing payers access to information that could help them make more informed, efficient judgments, ultimately leading to better value overall for the healthcare system, improved quality of care provided, and improved patient outcomes.

Another provision would address communication between industry and physicians. The FDA would be required to issue draft guidance on pharmaceutical companies' ability to communicate accurate, non-misleading, scientific information on approved medications. According to Mr. Robinson, better clarity in this regard could enable companies to provide physicians with much-needed information on certain medically accepted alternative uses of medicines.

"These provisions represent encouraging steps forward, and I hope the Senate, in its parallel efforts to craft companion legislation to the 21st Century Cures Act, continues to focus on ways to facilitate the development and delivery of important data and information that has the potential to improve the quality of care provided and patient outcomes through a more and better informed healthcare delivery system, which includes payers, providers and patients," Mr. Robinson says.

Clinical Trials

The act will also directly impact clinical

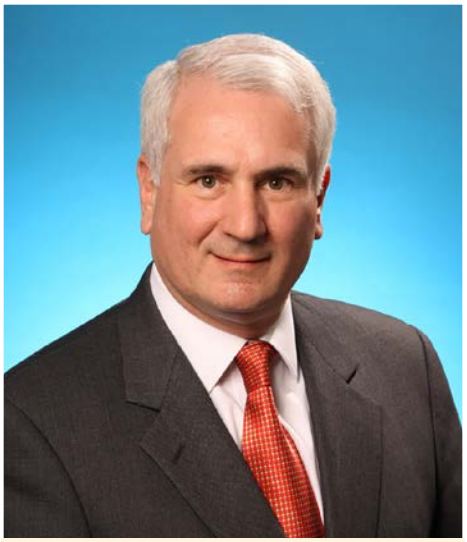
Further, inviting dialogue regarding different approaches to clinical development will allow industry to work alongside the FDA to ensure solutions to unmet clinical needs are brought to patients as safely and rapidly as possible.

RARE DISEASE TREATMENTS: One of the biggest challenges we face is how to assess the benefits of a potential new therapy in diseases that have few patients available for clinical studies. The increased focus on biomarkers and surrogate outcomes is very welcome. In addition, personalized medicine will have a huge impact in diseases with small number of people affected.

MICHAEL MURPHY, M.D., PH.D.
Chief Medical and Scientific Officer, Worldwide Clinical Trials

CLINICAL TRIALS: The 21st Century Cures act highlights opportunities within patient-focused drug development that are potentially transformative for pharmaceutical R&D. Qualification of drug development tools, including disease-related and pharmacodynamic biomarkers, patient-specific outcomes, and identification of patient subsets using genetic or phenotypic information codifies the importance of ongoing approaches toward personalized medicine. Novel trial methodology additionally creates a phase of discovery in development standing apart from traditional phase nomenclature, enhancing the importance of translational research methods. Addressing impacts on healthcare utilization and the economics of product access acknowledges data requirements of diverse stakeholders and helps create a value proposition influencing formulary placement, reimbursement mechanisms, and patient access in tandem with requirements for registration.

RARE DISEASE TREATMENTS: For repurposed products, novel chemical entities, or biologically based therapies, an ability to deduce evidence of target engagement, and possibly efficacy and registration (under subpart H guidance) is essential with limited populations for prospective interventional research. In addition to encouraging identification of disease subsets, the use of clinical experience obtained outside of clinical trials, for example, concurrent observational research, affords information regarding disease burden and transitions in care for orphaned states directly relevant to protocol and program design. Additionally, observational data gain emphasis as an additional substrate for considering approval of new drugs or shaping postapproval surveillance, enabling accelerated approval, and expedited access while assuring population safety.



No reasonable person can disagree with the idea that we should periodically review and improve our processes for approving new drugs and for providing public funding for biomedical research.

DR. SETH LEDERMAN
Tonix Pharmaceuticals

trials, modernizing them by allowing the use of technology throughout the process.

"The act will speed clinical trials, make them safer, and make them more effective," Mr. Smith says. "It's going to enable us to use more of our modern technology. It's going to enable us to use more patient data — such as patient experience data, patient's descriptions of their risk versus benefit tolerance — in ways we have not been able to do before. It's going to enable us to use unstructured data more. It's going to reduce the uncertainty in the use of applications and new kinds of devices such as mHealth devices. It's going to increase the use of software and other technologies, which there's a lot of hesitation to use today, especially the mHealth devices and apps. The legislation will remove all the fear and uncertainty and obstacles around these devices and apps. Even if the bill doesn't pass in 2016, the fact that it was born out of such a strong desire from all stakeholders means it will happen someday."

To prepare for the possibility of the legislation becoming law in 2016, drug makers will want to implement cutting-edge systems and technology to design and run clinical trials and collect data in new ways. Adaption to these types of systems has already begun, spurred on by the 2012 FDA Safety and Innovation Act but the 21st Century Cures Act strengthens these provisions, such as the breakthrough therapy designation: the FDA will grant breakthrough therapy designation to a product as long as ongoing data can be captured, updated, analyzed, and communicated with the FDA during ongoing clinical trials. Companies will want to have these abilities in place in order to streamline the drug approval process.

Organizations will also want to be up to date with data collection procedures, as the FDA will be putting more pressure on the value and efficiency of the data collected, looking for high-quality and efficient data collection during the breakthrough therapy process.

"Efficiency and accuracy will become key, as companies won't want to make data mistakes if they are applying for a breakthrough therapy designation," Mr. Smith says.

OPEN Act and Incentives

Under the act, the FDA will be mandated through the legislation to develop processes for validating biomarkers. Right now biological evidence inside the human body is under-utilized as evidence in clinical trials. Within the bill, there is language that would require the FDA to release guidance around biomarker qualification. This would mean the end point for whether a treatment is working or not could be determined earlier in the trial, by using biomarkers as surrogate endpoints. Instead of using life expectancy as the only measurement, biological factors can be monitored in shorter time periods.

"This is really a game changer because suddenly we can greatly accelerate the pace of a clinical trial," Mr. Bronstein says. "This is huge for those patients with rare diseases, because trials can be conducted faster and much more cost-efficiently, and suddenly we're not talking about getting these patients a treatment in 20 to 30 years; we are talking about moving potential treatments forward in a much shorter time period."

Another provision in the act that would benefit the rare disease patient population is the Orphaned Product Extensions Now Accelerating Cures & Treatment or OPEN Act within the 21st Century Cures Act.

In short, the OPEN Act creates an incentive for industry to repurpose existing drugs for a rare disease indication. It's modeled on the Best Pharmaceuticals for Children Act, and that law provides incentives to study the impact of drugs in children. This law is widely seen as very successful and very effective in terms of creating labeling changes for children's medications.

"So right now there are about 400 treatments for rare diseases and we think the OPEN Act, if it becomes law, could actually double the number of treatments that are available for rare disease patients," Mr. Bronstein says. "We see this as hugely important for patients and obviously this has implications for industry as well because if companies are able to get that six-month exclusivity extension, this will have big implications for the bottom line."

The incentive could make repurposing for orphan drugs a very common occurrence, which is a win-win for patients and the industry.

"The reason these incentives are good is that they make the money slide from big medicine into little medicine into rare disease medicine," Mr. Smith says. "The money that's moving from big drugs to rare disease drugs is coming from the private sector. There's no government spending at all. All we need the government to do is allow the incentive."

Overall, the act will directly impact the development of all medicines, but especially those for rare diseases.

"Medical science has made tremendous advances in many areas, but huge unmet needs still remain complex diseases such as Alzheimer's disease, Parkinson's and a multitude of rare diseases," Dr. Kinney of Prothena says. "Many companies have invested in the development of drugs for rare diseases in recent years to address the needs of patients, but also incentivized by the Orphan Drug Act and the 21st Century Cures Act. I believe that we will see more innovations that can address not only rare disease, but also new approaches that target remaining unmet needs for diseases with much larger indications."

Another incentive within the act would drive the development of antibiotics and antifungals.

"It's heartening that the act recognizes the need for further incentives for antibiotics and antifungals development, Mr. Robinson of Astellas Pharma says.

"For example, the legislation would incentivize new antimicrobial drug development through higher reimbursement rates in the Medicare in-patient payment setting for new qualifying drugs or indications," he says. "Such a policy would be a notable step toward encouraging investment in this extremely challenging therapeutic area."

"We know that incentives are a good idea," Mr. Smith says. "We know there are ways to get companies to change their behaviors and to collaborate. And the 21st Century Cures will drive that in a modern way with all the modern technologies in mind." PV

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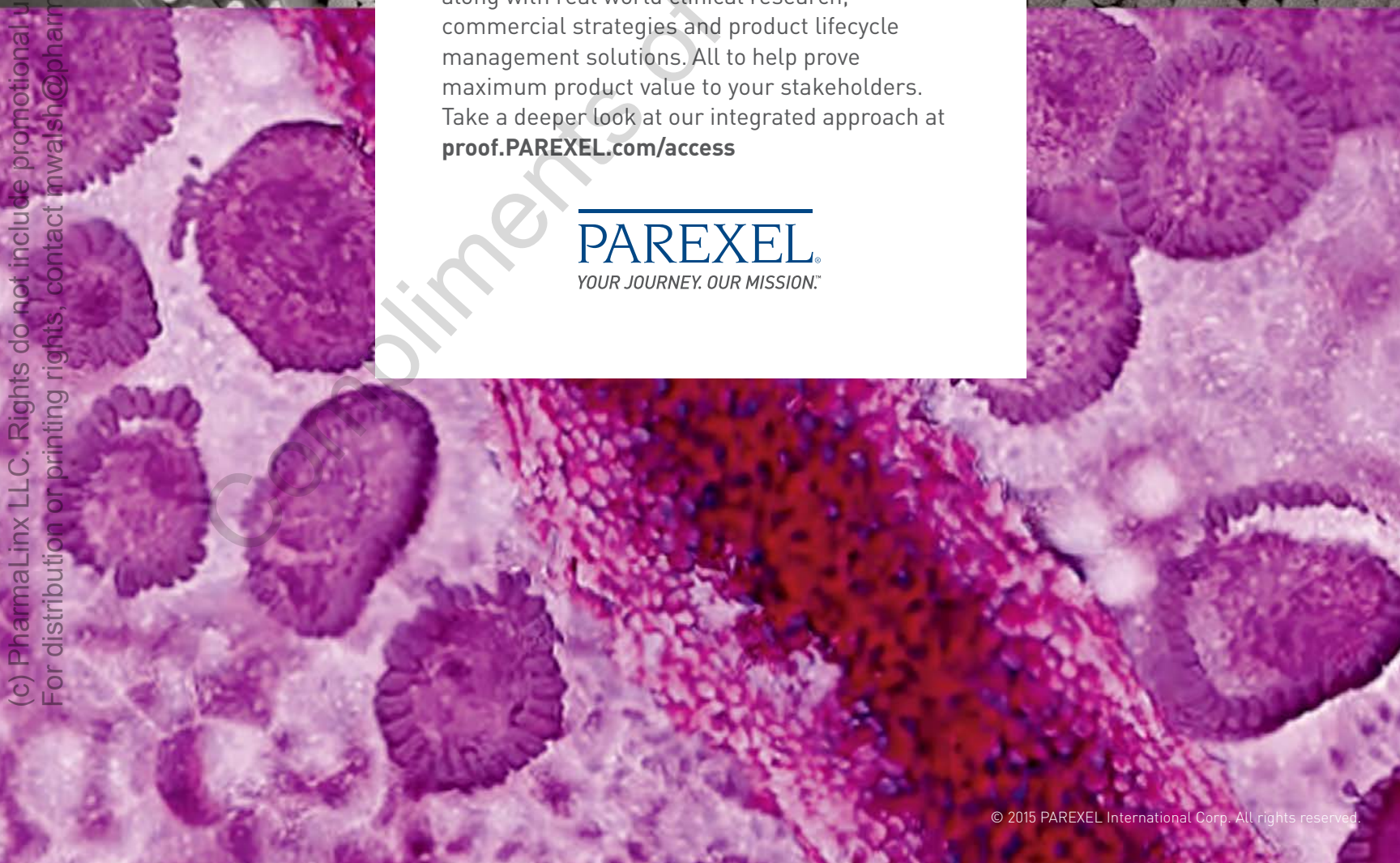

Robin Robinson

21ST Century CURES ACT Provisions

The 21st Century Cures Act is a complex piece of legislation with a number of subsections. Below is a summary of some of the areas that could have the most impact in the near future.

NIH Innovation and Other Funds

This is one of a few sections within the act that is devoted to funding for special projects and especially to rewarding excellence in research. These funds are designed to reward promising research and young researchers.

The programs contained within the act are for:

- Young and emerging scientists and direct funding of research, student loan forgiveness in exchange for service, and an increase in the maximum amount for other loan repayment tools (to $50,000 from $35,000)
- Capstone awards for more established scientists who the Institutes decide are worthy
- The promotion of increased clinical trials for children
- Researching high-risk approaches to important diseases and conditions that for-profit firms may not conduct but that have the potential for breakthrough therapies

Promoting Innovation

One of the most prominent themes underlying the 21st Century Cure Act is an acknowledgment that the U.S. desires to reward innovation in medicine where it is needed the most. It is clear the draft leans heavily toward new and innovative ways to reward organizations that develop much-needed medications.

While the previous draft of the act had multiple options for extending exclusivity for therapies, and therefore the incentives to perform the underlying research, the latest version is silent on exclusivity.

Instead, it focuses on reducing time to market by reducing the overhead of working through the regulatory hurdles.

The careful debate in Congress balances the need for faster approvals with the safety of the American population and crafted a set of changes to the NIH and FDA that will help organizations do their jobs in the right way at the right time for the right products.

One of the most prominent themes underlying the 21st Century Cure Act is an acknowledgment that the U.S. desires to reward innovation in medicine where it is needed the most.

Device Regulatory Process Improvements

Most of the proposed act that relates to breakthrough devices is for traditional products rather than software-based mobile medical apps. Subtitle L - Medical Device Regulatory Process Improvements open up the process to more sources of standards from outside "recognized" groups for Class I and Class II devices. This would allow a group to propose a third-party standard, perhaps one from the ISO or IEEE, to the FDA, and it gives the FDA 60 days to either adopt the standard or reject it, at its discretion.

The 60-day timeframe is almost certainly set short to provide the industry with the ability to iterate standards, if necessary, to create concrete rules by which manufacturers can play and get devices to market more efficiently.

The other process improvement mandated in the Act is education on "least burdensome means" training for FDA staff to ensure they act consistently and with the minimum valid requirements.

There has been some concern in the industry about variability among reviewers and this will help to alleviate it and improve the review process.

Mobile Medical Apps

Another directive of interest in this bill surrounds the definition of a Mobile Medical App. Subtitle M, which includes this information, titled "Sensible Oversight for Technology Which Advances Regulatory Efficiency." The wording here implies that perhaps the current regulatory environment isn't considered "sensible."

Current FDA guidance documents claim that they are bestowing some app categories with "regulatory discretion" and not regulating them. It is clear that the FDA's position is that all apps could fall within its purview and it gets to choose which ones it will, and won't, regulate. The bill, on the other hand, looks to draw a clear line between what the FDA does, and does not, regulate and remove the possibility of the FDA interfering with any categories outside its mandate.

The bill strives to achieve three categories:

- Medical Software: regulated by the FDA
- Health Software: not regulated by the FDA under the act
- Accessory or Component: could fit into one of the two above categories, depending on the master device

No More One-Click Protection

As this bill has progressed through Congress, half of it has been removed along with a significant amount of substance. The items that were removed and would appeal to and have impact on healthcare marketers include the "one click" rule, extended marketing exclusivity, and the ability to sell drug exclusivity. PV

Source: Excerpted from Klick.com special report: 21st Century Cures Act What the New Bill May Mean for Digital Health Care Marketing.

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Robin Robinson

POTENTIAL IMPACT of 21ST Century Cures Act ON Clinical Research

The act could have a ripple effect on all areas of clinical research.

The clinical research provisions of the House-passed version of the 21st Century Cures Act signal a trend by Congress to minimize unnecessary and duplicative administrative (including federal and institutional) requirements, and to promote the broad availability of clinical research data, with adequate security and privacy measures, to advance medical product innovation. The bill also contains a provision to facilitate and encourage the inclusion of underrepresented subpopulations in clinical research.

Provisions Relevant to Clinical Research

- Streamlining Clinical Trials [Section 2261]. This provision would simplify and facilitate researcher compliance by harmonizing differences, to the extent possible and consistent with statute, between the HHS Human Subject Regulations (45 CFR Part 46) and FDA Human Subject Regulations (21 CFR Parts 50, 56, 312, and 812). The agencies would be instructed to modify regulations and relevant guidance documents to reduce regulatory duplication and unnecessary delays, facilitate multisite research, and incorporate local considerations, community values, and protections of vulnerable populations. The revised regulations and guidance would delineate IRB roles during multisite research, as well as clarify requirements and policies related to the regulatory and legal liability concerns of a sponsor when relying on local IRBs for multisite research.
- Central IRB Review [Section 2262]. This provision would delete the requirement that medical device studies be overseen by a "local" IRB. By striking "local," this provision would allow all clinical trials of FDA regulated medical products to be overseen by a central IRB. FDA previously allowed for central IRB review of drug and biological product studies. With this provision, medical device studies also would be eligible for central IRB oversight.
- Waiver of Informed Consent for Minimal Risk Research with Appropriate Safeguards [Section 2263]. This provision would modify the investigational drug and device requirements to allow for waiver of informed consent if the proposed clinical testing poses no more than minimal risk to human subjects and includes appropriate safeguards to protect subjects' rights, safety, and welfare. Currently, a significant difference between FDA and HHS Human Subject Regulations is the authority of an IRB in the Common Rule, which is absent in FDA regulations, to waive consent for certain minimal risk research. With this new provision, Congress would allow FDA to harmonize with the Common Rule by permitting an IRB to waive informed consent for FDA-regulated minimal risk research if the subjects are adequately protected. FDA rule-making would predictably reflect the safeguards contained in the Common Rule, such as the requirements that the waiver of consent will not adversely affect the rights and welfare of the subjects, that the research could not practicably be carried out without the waiver, and that, whenever appropriate, the subjects will be provided with additional pertinent information after the study ends.
- Standardization of Data in Clinical Trial Registry Data Bank on Eligibility for Clinical Trials [Section 1101]. This provision would amend the statute authorizing www.ClinicalTrials.gov, by requiring NIH to ensure that the registry and results databank is configured in a way easily used by the public and is in a standardized format that identifies the disease studied and each study's inclusion and exclusion criteria. Those process changes are intended to facilitate lay use as well as communication between the databank and electronic health records and other relevant health information technologies.
- Facilitating Collaborative Research with Greater Data-Sharing [Sections 1121 and 1122]. This subtitle would establish a pilot program to make available certain de-identified data from qualified clinical trials, with appropriate security measures in effect, for further study of such data by scientific and medical researchers. This subtitle also establishes a National Neurological Diseases Surveillance System to track and record scientific information related to the epidemiology, natural history, prevention, detection, management, and treatment of neurological diseases, such as multiple sclerosis and Parkinson's disease. The information in the System, with appropriate privacy and security protections, will be made available to the public, including researchers.
- Grants to Collect Data on Natural History of Diseases [Section 1123]. This provision would encourage FDA to enter into public-private partnerships and award grants to patient advocacy groups to establish and facilitate information collection and analysis regarding the natural history of diseases, with a particular focus on rare diseases. The partnerships' data relating to the natural history of diseases would be made available, as appropriate, to the public (including researchers and drug developers) to help facilitate and expedite medical product development programs.
- Accessing, Sharing, and Using Health Data for Research Purposes [Section 1124]. This provision would require HHS to amend the HIPAA Privacy Rule to: (1) allow the use and disclosure of protected health informa-

tion by a covered entity for research purposes, including for studies whose purpose is to obtain generalizable knowledge, to be treated as the use and disclosure of such information for "health care operations"; (2) include research activities related to the quality, safety, or effectiveness of an FDA-regulated product as a public health activity to allow a covered entity to disclose protected health information under certain conditions; and (3) permit remote access to health information by a researcher if appropriate security and privacy safeguards are maintained and if the protected health information is not retained by the researcher.

- Reducing Administrative Burdens on Researchers [Section 1023]. This provision would require NIH to develop a policy to reduce administrative burdens on researchers who are funded by NIH, with input from the National Academy of Sciences and the Scientific Management Review Board. Within two years after enactment of the Act, NIH would be required to submit a report to Congress detailing how NIH has implemented the policy measures.
- Increasing Inclusion of Underrepresented Communities in Clinical Trials [Section 1029]. This provision would express the opinion of Congress that the National Institute on Minority Health and Health Disparities include within its strategic plan ways to increase representation of underrepresented communities in clinical research. This provision would be consistent with IRBs' mandate to ensure that the selection of subjects is equitable.
- Promoting Pediatric and Geriatric Research through NIH [Sections 1081, 1082, and 1083]. This section would recommend that NIH and FDA facilitate global pediatric clinical networks by increasing the salaries of new investigators participating in such studies, as well as by engaging the EMA and other regulatory entities to encourage their participation in such networks. These initiatives could be funded by the NIH and Cures Innovation Fund, to be established by the Act. Also, NIH would publish guidelines addressing under what justifications age should be an inclusion or exclusion criterion. NIH also would post on its website the number of children included in NIH-supported or conducted research, disaggregated by age group, race, and gender.

Provisions Related to Drugs and Biological Products

- Programs to Prevent Prescription Drug Abuse (Section 3141). The bill would permit Part D Prescription Drug Plan ("PDP") sponsors to establish drug management programs for at-risk beneficiaries under which the PDP sponsors may limit access to coverage for frequently abused drugs prescribed by one or more prescribers and dispensed by one or more pharmacies. Several due process protections for affected beneficiaries also are put in place, including strict notice requirements and a process for appeal and termination.
- Inclusion of Infused Biological Products in DME Payment Methodology (Section 4004). The bill would add infusion biological products to the payment methodology for infusion drugs furnished through durable medical equipment ("DME").
- Modification to Calculation of Average Manufacturer Price (Section 4002). The bill would exclude generic drugs from the calculation of the average manufacturer price ("AMP"), which manufacturers must report to CMS for all Medicaid-covered drugs on a quarterly basis as a requirement of the Medicaid drug rebate program. The AMP is used to calculate Medicaid rebates.

Provisions Related to Durable Medical Equipment and Disposable Medical Technologies

- Payment Reductions for Durable Medical Equipment (Section 4001). The bill would limit federal Medicaid reimbursement to states for DME to Medicare payment rates. In other words, the bill eliminates federal financial participation for state Medicaid DME fee schedule payments that in the aggregate exceed the amount Medicare would have paid, including in states that have launched competitive acquisition programs. Probably as a concession to industry concerns that competitive bidding will drive down quality and access, the bill also would require that a Medicare ombudsman monitor the effects of competitive acquisition programs on beneficiary health status and outcomes.
- Extension of Prior Authorization for Power Mobility Devices (Section 4005). The bill would exclude from Recovery Audit Contractor ("RAC") audits any claim for Power Mobility Devices ("PMDs") that has received a provisional affirmation under an advance determination. However, the bill specifies that such claims may be subject to audits for potential fraud in areas not covered by the advance determination, such as inappropriate utilization, changes in billing patterns, or information that could not have been considered during the advance determination such as proof of item delivery.
- New Medicare Payment for Disposable Medical Technologies Used in Home Health (Section 3061). The bill would establish separate payment to home health agencies for any disposable medical device used in Medicare home health delivery for which there is (1) a separate Healthcare Common Procedure Coding System ("HCPCS") code for which the description for a professional service includes the furnishing of such device; and (2) a separate Level I HCPCS code for a professional service that uses durable medical equipment instead of the device.

Provisions Related to Pricing Process and Transparency

- Greater Transparency of Local Coverage Determinations (Section 3081). Effective six months after enactment, each Medicare administrative contractor that develops a local coverage determination would be required to publish the following information on the contractor's website and on the Medicare website: the determination in its entirety; where and when the proposed determination was first made public; hyperlinks to the proposed determination and responses to comments submitted; a summary of the evidence considered along with a list of the sources; and an explanation of the rationale supporting the determination.
- Medicare Site-of-Service Price Transparency (Section 3121). In order to facilitate price transparency of Medicare payment for hospital outpatient and ambulatory surgery center items and services, the bill would mandate that the Secretary make available via a public searchable website the Medicare estimated payment and beneficiary liability amounts for each item or service. The bill also provides a formula for calculating estimated beneficiary liability.

Provisions Related to Radiology

- Incentives to Transition to Digital Radiography (Section 4003). The bill would create incentives for the transition from traditional x-ray imaging to digital radiography. First, the bill would reduce the technical component of the payment amount for x-rays taken using film by 20%. Second, the bill would limit payment for computed radiography imaging services using an incremental approach: the technical component of the payment amount would be decreased by 7% for services furnished during 2018-2022 and by 10% for services furnished during or after 2023. Additionally, a multiple procedure payment reduction would not be applied to the professional component of apparently all imaging services unless the Secretary has published an empirical analysis demonstrating efficiencies.

Provisions Related to Federal Grants, Contracts, and Funding Agreements

- New Civil Monetary Payments for Grant and Contract Violations (Section 4006). The bill would add several new violations to the list for which penalties are available for imposition by the Office of Inspector General of the Department of Health and Human Services ("HHS OIG") under the Civil Monetary Penalties statute. Additionally, the bill would authorize the government to impose an "assessment" on the majority of these actions, which, depending on the nature of the violation, could require liable persons to pay an assessment of three times the amount claimed or three times the amount of HHS funds or property at issue. Among others, the newly added actions include: knowingly presenting or causing to be presented a false or fraudulent "specified claim" under an HHS contract or grant; knowingly making, using, or causing to be made or used a false statement, omission, or misrepresentation of material fact in a document required to be submitted to receive or retain funds under an HHS contract or grant; and failing to grant timely access to HHS OIG upon reasonable request for audits or to carry out other statutory functions in matters involving an HHS grant or contract.

Provisions related to FDA

- Communication of Truthful, Non-Misleading Off-Label Information: This provision would require that, within 18 months of enactment, FDA issue a draft guidance facilitating the dissemination of truthful and non misleading scientific information that is not in the approved labeling of drugs and devices. Notably, in June 2014, when the FDA granted a citizen petition submitted by the Medical Information Working Group (as Ropes & Gray previously reported), the FDA announced its own plans to issue guidance "by the end of the calendar year" (i.e., 2014) on distributing scientific and medical information on unapproved new uses and manufacturer discussions regarding scientific information. These guidance documents have yet to be issued. The Cures Act provision would impose a statutory deadline on the FDA's plans.
- Extended Exclusivity for Previously Approved Drugs and Biologics That Are Approved for a New Rare Disease Indication: This provision would provide an additional six months of exclusivity for already approved drugs and biologics that are approved for a new indication for a rare disease or condition. The additional six months of exclusivity would tack on to the end of any patent protection or exclusivity applicable to the drug or biologic.
- Reauthorization of Rare Pediatric Disease Priority Review Voucher Program: This provision would reauthorize the FDA's rare pediatric disease priority review voucher program, which encourages the development of drugs to treat rare diseases that primarily affect children by rewarding successful rare disease product applicants with a voucher that can be used to obtain priority review for a subsequent new drug application or biologics license application. Without congressional action, the program is scheduled to sunset in March 2016. This provision would extend eligibility in the program to all rare disease product applications submitted through December 31, 2018.
- Combination Products Review: This provision would require that, within 18 months of enactment, FDA issue a final guidance document describing the responsibilities of each Center regarding the review of combination products.
- User Fee Exemption From Sequestration: This provision would permanently exempt from sequestration various FDA user fees, including fees for medical devices, prescription drugs, generics drug, biosimilars, animal drugs, and generic animal drugs. The provision would ensure the agency's access to user fees and provide funding for drug and device review and other critical agency functions.
- Third-Party Quality System Assessment for Medical Devices: A placeholder in the April discussion draft has been replaced with a provision that would establish a program by which accredited third-parties could review and certify if a device manufacturer's quality system can reasonably assure the safety and effectiveness of devices subject to certain "device related changes." The provision provides that a device-related change covered by such a certification would not be subject to premarket notification, 30-day notice, or Special PMA supplement requirements that might otherwise apply.
- 510(k)-Exemptions for Certain Class I and II Medical Devices: A placeholder in the April discussion draft related to marketing notifications for class I devices has been replaced with a provision that would require FDA to publish rules identifying any class I and II devices that FDA determines no longer require a 510(k) notification.
- Expanded Access Programs for Investigational Drugs: A provision calling for drug manufacturers to disclose details on their expanded access programs for any investigational new drug within 60 days after initiating a phase 2 or phase 3 study has been modified to require publication of an expanded access policy at "the first initiation" of a phase 2 or 3 study. In addition, a provision has been added expressly permitting manufacturers to modify publicly available expanded access policies at any time.
- Reduction of Additional Incentive for Use of New Antimicrobial Drugs: This provision, part of a package of antibiotic-related reforms, decreases the additional payment incentive under Medicare for "DISARM drugs"—approved new antimicrobials intended to treat an infection for which there is an unmet medical need and which is associated with high mortality or patient morbidity—to a set percentage of total hospital payments per fiscal year.

Source: Ropes & Gray Global Law

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