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21st Century Cures Act

A Rare (Overwhelmingly) Bi-Partisan Success; Bodes Well for Life Sciences Sector

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In an extraordinary show of bi-partisanship, particularly in light of the political polarization of the last several years, both the House and the Senate passed by overwhelming majority votes, 392-26 in the House and 94-5 in the Senate, the 21st Century Cures Act (Cures Act). The Bill was signed by President Obama last week and, in our view, is probably the most important legislation for the life sciences sector since ObamaCare and certainly far more favorable ultimately to the health of the sector. As such, we thought it useful to review some of the key components of the Bill that mandates additional funding for basic early stage research, targeted funding for intractable diseases, genetic diseases and CNS conditions as well as stepped up funding for the FDA. Specifically targeted funding, a mandated more "relaxed" regulatory environment and revisions in the use of patient information for research purposes hold important implications for the biopharma and medical device market sectors.

TOP LINE FUNDING

1. NIH: The current $33 billion NIH budget, funded by the Public Health Service Act, will be amended to reauthorize funding through fiscal year 2018 and at the same time, an additional $4.8 billion will be added to NIH funding over the next 10 years to support the establishment of a NIH Innovation Fund. NIH funding under Obama had been severely curtailed. Rep. Fred Upton, Chair of the chair of the Energy and Commerce Committee, succeeded in securing the new NIH funding from future sales from the Strategic Oil Reserve. In addition to specific funding, the NIH will be charged with facilitating research in pediatrics by promoting support of early stage investigators and high-risk, high reward research. The Bill charges NIH with management of the Pediatric Research Initiative (PRI), the establishment of guidelines for appropriate pediatric age groups for research and the establishment of a National Pediatric Research Network. The scope and activities of the PRI will likely approximate the Comparative Oncology and the Neurobiology Initiatives.

2. Targeted funding: The Bill sets forth specific targeted funding of research in several key indication areas. Precision Medicine (molecular diagnostics, patient-based therapies, et al) is targeted with an additional $1.4 billion of Federal funding, the Cancer Moonshot program will receive $1.8 billion and $1.8 billion is ear-marked for the Brain and CNS conditions. In addition, $1 billion also has been allocated to state programs for opioid addiction, substance abuse and mental health. The magnitude of this problem is highlighted in an article published in the *Wall Street Journal* on December 13, 2016, which reported that opioid-related issues among pregnant women and infants is not only rising in rural areas faster than in cities, but the number of infants exposed to heroin and other opioids rose **six-fold** in rural communities from 2004 to 2013 versus a three-fold increase in urban communities. The resultant infant syndrome, neonatal abstinence syndrome, grew from 1.2 to

7.5 cases per 1,000 births and opioid delivery complications rose to 1.3 to 8.1 cases per 1,000 rural area deliveries. The data was derived from a recently published JAMA Pediatrics study.

The primary area negatively impacted by the Cures Act was ObamaCare's preventive medicine initiatives. To gain passage of the Bill, $3.5 billion in funding for preventative medicine, funds set up under ObamaCare to study chronic conditions like Alzheimer's and diabetes and hospital-acquired infection were cut which amounts to about 30% of the total ACA allocation for preventive medicine. GOP leaders tried and failed to include a provision in the Cures Act that would have permitted the FDA to conditionally approve stem cell treatments without a large Phase III clinical trial. In addition, Democrats were able to block a provision in the Bill which would have extended market exclusivity for certain orphan-designated drugs.

FDA: CHANGES IN DRUG AND DEVICE APPROVAL PROCESSES

1. In addition to receiving $500 million in new funding for the FDA, the Bill directs several other significant changes aimed at improving drug or device approval processes and increasing innovative treatment availability. On the spending side, the FDA has been mandated to create a sister Innovation Fund to that being created at the NIH. This follows the establishment of an innovation initiative at CMS that, among other accomplishments, has resulted in the development of Alternative Payment Systems and the FDA/CMS Parallel Review program. In a nod to persistent industry complaints, the Cures Act mandates the FDA train all employees involved in the review of premarket submissions and to audit the effectiveness of the training no later than 18 months after the enactment of the Cures Act. Further, the FDA will establish a three year, $30 million "matching dollar" grant program targeting regenerative and stem cell therapies.

2. On the regulation side, provisions in the Act roll-back certain regulatory stances of the FDA that will now allow the FDA to take a more "relaxed" approach in the clinical review process. Ultimately, for some products, this may result in randomized clinical trials becoming less important for approval under certain circumstances. The Act directs the FDA to adopt a "real world evidence standard" and to accept anecdotal data, such as observations, patient or professional opinion, as well as non-validated or scientifically measured outcomes to support clinical validity. In addition the FDA will be able to approve drugs based on a drug's impact on biomarkers or other disease surrogates, rather than actual clinical trial data validating the efficacy of the drug.

3. The Act also addresses a number of patient record and information items, including the establishment of patient registries, allowing patient data to be used in research and facilitating the use of unique medical device identifiers in Electronic Medical Records for enhanced post-marketing surveillance. A noteworthy change is clinical testing of devices or drugs may no longer require informed consent of the subjects being tested, if the treatment poses no more than minimal risks and includes appropriate safeguards.

505(b)(2) Regulatory Path for Existing Approved Drugs Eased: Under the Act, the 505(b)(2) approval process will become more flexible with lowered standards. The FDA will be required to evaluate the use of real world evidence to help support the approval of a new indication for a previously approved drug and to help support or satisfy post-approval study requirement. Pharmaceutical companies may only be required to submit a "data summary" or statistical sampling for new indications their own existing approved products. This approach would allow the agency possibly to look at other sorts of data, such safety surveillance data, patient-reported outcomes and observational studies to support an approval.

Door Opened on Off-label Marketing: A significant change under the new legislation addresses off-label marketing. Drug companies will now be able to promote off-label usage of their existing products to

payers (insurance companies). This effectively causes the FDA to do an "about-face" on the subject of off-label marketing, which has been a source of numerous FDA punitive actions in the recent past. The Act now enables drug companies to market their products outside previously approved indications, age groups, dosages or routes of administration of drugs currently on the market.

Other "Guidance" Mandates:

-- the FDA is charged with establishing processes under which patient experience data may be considered in the risk-benefit analysis for a new drug.

-- both the NIH and the FDA will be required to establish registry data.

-- the FDA must define "precision" drugs and the evidence needed to support their use in specific patient subpopulations, approvals may rely on data from an alternative approved drugs/indications.

-- allows sponsors of genetically targeted or variant protein targeted drugs to rely on data for the same or similar technology from previously approved applications by the same sponsor.

-- requires the FDA to hold a public meeting and issue guidance documents that would assist sponsors in incorporating adaptive designs and novel statistical modeling into new drug applications.

Several Provisions of the Act Benefit Device Manufacturers: The Cures Act calls upon the FDA to make several key changes with regard to medical devices. These focus on reducing the regulatory burden for certain classes of devices, more clearly defining "combination products" and enabling a quicker regulatory path for devices with "break-through" technologies for high-need indications or treatments. Overall, these changes seek to put a renewed focus on the "least burdensome" approach to the regulation of medical devices. The concept was introduced in legislation almost 20 years ago to stop the FDA from requesting more information than was absolutely necessary, but industry has long complained the FDA has not adhered to the "least burdensome" intent.

Device-specific Related Provisions:

-- the FDA must develop a program for priority review of "breakthrough" medical devices which builds on the existing priority review device pathway. The FDA will define new medical devices that are considered "breakthrough" with off-label use.

-- the FDA will define types of medical devices that do not require submission of a (clinical) report prior to commercial marketing. The Act requires the FDA to update lists regarding the appropriate regulation of Class I and Class II devices.

-- raises the patient cap from 4,000 to 8,000 patients the number of patients that can be treated by humanitarian-exempted devices that may be exempt from "effectiveness requirements".

-- includes amendments to the regulation of drug-device combination products. The Act requires regulators to assign a primary mode of regulatory action (drug or device) to each combination product and then send it to the appropriate part of the agency for premarket review. Sponsors that disagree with the decision can ask for "a substantive rationale" to support the ruling and propose to run studies to support the revaluation of the product.

Accelerated approval for regenerative medicine

-- defines "regenerative medicine and advanced therapies" which includes cell therapy, gene therapy, gene-modified cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products.

-- requires the FDA to update guidance and regulations with regard to regenerative therapeutic products, and hold a public meeting to encourage innovation.

-- allows FDA to grant accelerated approval for regenerative therapeutic products. Directs the FDA to consider the unique characteristics of regenerative therapeutic products and provide a rationale with a determination of whether or not to grant accelerated approval.

-- establishes that devices used with a regenerative therapeutic product will be considered moderate risk devices, unless the FDA determines that the device or intended use requires a higher risk classification.

-- permits the FDA to grant regenerative medicine products accelerated approval if they can show that surrogate endpoints might indicate the drug works, subject to further study.

Tick-bone Disease Initiative:

The HHS is directed to conduct or support research on Lyme disease and other tick-borne diseases. Further the HHS must create an Interagency Lyme and Tick-borne Disease Working Group and submit a plan for tick-borne disease research. (Sec. 4061). To our knowledge, there is only one public company developing new vaccines for tick-borne diseases, Valneva SE (Euronext Paris: VLA:€2.88/Not rated). The Company has recently received IND approval from the FDA and the EMA to begin Phase I clinical trials of its poly-valent vaccine. There are 8 different serotypes of tick-bone disease carried by various *Borrelia* ticks. While all eight are present in Europe, Lyme disease is predominately caused by the *Borrelia burgdorferi* serotype in the US. The trial will be conducted at both the US (Nebraska) and European sites and the vaccine is intended to be given on a prophylactic basis.

BOTTOM LINE SECTOR BENEFITS

Taken in its totality, we believe the Cures Act will particularly benefit nano and micro-cap biopharma and device companies as many of the provisions seek to ease the cost and time burden of clinical trials, thus perhaps leveling the playing field with companies of much greater resources. The now precise, but broad definition of regenerative medicine products coupled with the Act's substantial targeted resources in terms of funding and accelerated regulatory path is likely to spur renewed interest in stem cell companies as well as continue to drive rare disease company valuations. The lower burden of clinical data requirements for 505(b)(2) products will also likely enhance valuations for that group of companies. But the real winners, in our opinion, will be medical device companies. We see the creation of a near "perfect storm" for the group by way of 1) almost assured long-term (or permanent) suspension of the medical device excise tax, 2) back-tracking by the FDA on regulating all diagnostics as devices, 3) renewed opportunity under 510(k) filings 4) reduced clinical trial burden and finally 5) off-label marketing opportunities for "breakthrough" devices. This last point is worth highlighting particularly in the context that more devices are being developed to take the place of or augment drug therapy such as in the treatment for chronic pain. It may take some months for the positives in the Cures Act to filter down to nano and microcap early stage biopharma and device companies, but we believe the Cures Act provides a strong base for a sustainable rally in these sectors. *SG*

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