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21st Century Cures Act & Real World Evidence: Device Policy as Foundation

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The 21st Century Cures Act (the ''Cures Act'') (Pub. Law 114-255, § 3022), signed by President Obama on December 13, 2016, requires FDA to develop a framework and guidance for evaluating real world evidence (''RWE'') in the context of drug regulation to (1) support approvals of new indications for previously approved drugs and (2) support or fulfill post-approval study requirements. This directive to apply RWE in the drug sphere is a particularly interesting development since FDA has already issued a draft policy on the use of RWE in the context of medical devices, but has generally been silent about applying RWE to pharmaceutical and biologic regulatory considerations. We will briefly review the RWE policy for devices, FDA's recent public remarks on RWE, and then provide some predictions on how FDA will implement the RWE policy throughout the different program areas.

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FDA's Proposals on RWE Evaluation for Medical Devices

In July 2016, FDA released a draft guidance (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf) entitled *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices* (the ''Device RWE Draft Guidance''), which explains FDA's current thinking on possible, acceptable uses for RWE in the established medical device regulatory scheme. The Device RWE Draft Guidance defines two terms that attempt to capture the Agency's expectations on the scope of RWE:

1) Real-World Data (RWD) – ''Data collected from sources outside of traditional clinical trials''

2) Real-World Evidence (RWE) – ''Evidence derived from aggregation and analysis of RWD elements''

FDA lists many potential sources of device RWD, including ''large simple trials, or pragmatic clinical trials, prospective observational or registry studies, retrospective database studies, case reports, administrative and healthcare claims, electronic health records, data obtained as part of a public health investigation or routine public health surveillance, and registries,'' and states that data from these sources, if appropriately validated, can provide valuable insight into the performance of medical devices used in actual clinical settings and in routine medical practice. However, a major part of industry stakeholders' criticism of the Device RWE Draft Guidance was directed at FDA's focus on the use of registries as primary sources of reliable RWE.

Although FDA explicitly states in the Device RWE Draft Guidance that expanded use of RWE will not alter the existing evidentiary standards for medical device regulatory decision-making, the Agency allows that RWE could potentially be used to:

1) support expansion or modification of cleared or approved device indications;

2) supplement information necessary to support clearance or approval of a next-generation device;

3) provide ongoing device safety surveillance information as a postmarket control;

4) conduct post-approval studies which FDA may impose at the time of approval; and

5) replace individual Medical Device Reports, in certain circumstances.

To ensure that RWE is suitable for use in a regulatory context, FDA explained that it would apply threshold criteria to determine whether the collected RWE is (1) sufficiently relevant to the applicable regulatory question or requirement and (2) reliable enough to satisfy that regulatory question or requirement. By necessity, these criteria can only be evaluated on a case-by-case basis and entail significant Agency discretion, potentially leading to another type of premarket review to vet each proposed use of RWE.

The Device RWE Draft Guidance also alludes to FDA's National Evaluation System for Health Technology (''NEST'') program through which the Agency has already begun to leverage RWD. As part of MDUFA IV negotiations (http://www.fda.gov/ForIndustry/UserFees/MedicalDeviceUserFee/ucm454039.htm), FDA committed to fund and staff the NEST Coordination Center and to conduct pilot projects to determine how RWE can be applied in the regulatory process. Pilot programs include exploring RWE use for:

1) expanding indications for use of cleared or approved devices;

2) clearance or approval of new devices;

3) improving malfunction reporting.

FDA has suggested that using RWE as part of the NEST program will provide an opportunity to build out registries with clinical trial information and improve evidence generation, in general. These commitments certainly align with FDA's suggested uses for RWE in the Device RWE Draft Guidance and are consistent with the Agency's apparent trend toward placing more emphasis on postmarket data to provide evidence of device safety and effectiveness.

At the very least, the Device RWE Draft Guidance strongly encourages a sponsor to structure data collection and analysis methods according to a prospective analysis plan. This process requires the sponsor to develop a full rationale and plan to guide the collection and analysis of RWE to (1) ensure that the data will meet FDA's threshold criteria and (2) assess whether a more rigorous collection and analysis method, such as a randomized clinical trial, is necessary to generate the required data.

In addition to applying strict threshold criteria, FDA will potentially limit RWE use even further by applying an investigational device exemption (''IDE'') to RWE collection and analysis. The Device RWE Draft Guidance states that collection of RWE to support a determination of device safety and effectiveness ''may be considered a clinical investigation'' and, therefore, may require an IDE since a sponsor must obtain an IDE for any premarket clinical investigations of a device. FDA does not describe the circumstances in which a collection of RWE would be considered a clinical investigation and simply states that such determinations must be made on a case-by-case basis. This process introduces yet another premarket review to authorize the use of RWE, ultimately increasing sponsor frustration and reducing the likelihood that the medical device industry will make significant use of RWE for regulatory purposes.

FDA's Latest Public Statements on the Use of RWE in the Regulatory Process On December 8, 2016, FDA Commissioner Robert Califf, along with the Directors of relevant Centers and Offices, published a commentary (http://www.nejm.org/doi/full/10.1056/NEJMsb1609216) on RWE in The New England Journal of Medicine, titled *Real-World Evidence—What Is It and What Can It Tell Us?* The article sets forth a general theory of RWE and its potential uses that closely parallels the Device RWE Draft Guidance.

First, the article gives a definition of RWE that is equivalent to the Cures Act and the Device RWE Draft Guidance: ''information on health care that is derived from multiple sources outside typical clinical research settings, including [EHR], claims and billing data, product and disease registries, and data gathered through personal devices and health applications.'' Second, FDA identifies that, unlike clinical trials which impose strict eligibility criteria and controlled procedures, RWE can provide useful data about actual use in a clinical setting. However, FDA emphasizes in the article that clinical trial methodologies, such as randomization and planned intervention, are not inconsistent with methods for collection and analysis of RWE. In a way, FDA appears to acknowledge that RWE is useful and is different from the randomized clinical trial but also to lay the groundwork to support an RWE framework that uses controls that are similar to clinical trials to produce relevant and reliable data. Third, FDA repeats the warning that many RWE sources are not organized or optimized for supporting research or regulatory assessments. Finally, FDA's stated priority in developing an RWE framework is to make the best use of relevant RWE that are generated through reliable methods that limit the effect of bias and confounding factors as much as possible.

FDA also uses the article to differentiate the use of RWE in drug and device contexts by stating that since medical devices are developed in an iterative fashion, RWE is generated throughout the life-cycle of a device and relevant confounding factors are typically recognized and compensated for in the data analysis. However, in the context of accelerated approval of precision molecular treatments, RWE to confirm clinical benefit will need to be generated quickly and reliably to support the regulatory approval process.

On December 12, 2016, Bakul Patel, FDA's Associate Director for Digital Health, was part of a panel on real-world evidence at the Connected Health Conference in Washington D.C. While Mr. Patel's comments closely aligned with FDA's cautiously optimistic tone in the NEJM article, he stated that the primary challenge would not be in collecting the data but in connecting real-world data with appropriate contextual data to create comprehensible evidence that can advance regulatory decision making. These comments reveal that it may take some time for FDA to find the right formula for real-world evidence that can be used for any significant purpose and that the vetting processes alluded to in the Device RWE Draft Guidance may be necessary to flesh out that formula.

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New RWE Requirements in the Cures Act By enacting the Cures Act, Congress mandated that FDA create standards for broader use of RWE for regulatory decisions related to drug products and adhere to strict timelines for implementation. All requirements related to RWE appear in Section 3022 of the Cures Act, which creates Section 505f of the Federal Food, Drug, and Cosmetic Act (the ''FD&C Act''), or 21 U.S.C. § 355f. For the purposes of the Cures Act, ''real world evidence'' is defined as ''data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.'' The new provisions require FDA to establish a program to evaluate RWE for the following purposes:

1) To help to support the approval of a new indication for a drug approved under section 505(c); and

2) To help to support or satisfy post-approval study requirements.

FDA must establish a framework for the RWE program, which must be developed in collaboration with relevant stakeholders in the drug industry, and implement that framework within two years after the enactment date of the Cures Act. In addition, within five years of the enactment date, FDA must issue draft guidance describing (1) ''the circumstances under which sponsors of drugs may rely'' on RWE, and (2) acceptable standards and methodologies for collecting and analyzing RWE.

This provision explicitly states that the new RWE requirements stated in the Cures Act do not limit FDA's use of RWE for other purposes and do not change the standards of evidence required under sections 505(c) and (d) of the FD&C Act or section 351(a) of the Public Health Service Act.

The Future of RWE at FDA While FDA has historically clung to the controlled, randomized clinical trial as the gold standard for generating data to support all regulatory determinations, the Agency recently acknowledged that RWE meeting certain criteria could be used to support some regulatory decisions, at least in the medical device sphere. Now, the Cures Act requires that FDA meet an accelerated timeline for developing a regulatory framework for RWE that applies to drug applications, as well.

Comparing the Device RWE Draft Guidance and FDA's NEJM commentary reveal remarkable (and yet not so remarkable) similarities in the Agency's thinking on the use of RWE in both the device and drug regulatory schemes, as described above. Given the parallels in FDA's comments on controlling device and drug RWE, we expect that the RWE evaluation program framework required by the Cures Act will be based largely on the Device RWE Draft Guidance, applying similar criteria of relevant and reliability to RWE collection and analysis methodologies for drug products. Although the clinical use contexts of drugs differ greatly from those of devices, the real-world data sources for both drug and device use are essentially equivalent and the criteria FDA can impose upon collection and analytical methodologies (e.g., accounting for confounding factors, establishing consistent definitions, and controlling data capture) can be applied to all sources and RWE study types. However, since the Device RWE Draft Guidance was only released five months ago, there is little feedback from stakeholders and Agency officials about the effectiveness of the criteria described in the guidance and FDA has little experience applying the use of RWE in regulatory processes.

Even though FDA's development of the RWE framework and guidance for drugs may affect the content of the Device RWE Draft Guidance and its schedule for release, we do not expect FDA to alter the draft guidance significantly. In the NEJM article, FDA explained its rationale for applying RWE differently in the drug and device regulatory schemes, and it is unlikely to change. It is more likely that FDA's experience with RWE submitted by medical device study sponsors will lead to significant revisions of the Device RWE Draft Guidance.

Presumably, FDA will seek to coordinate efforts on RWE in the device and drug Centers, thus the Device RWE Draft Guidance may not be finalized as quickly as many would like. And perhaps FDA's process in developing an RWE framework for drugs will help to clarify what FDA considers ''relevant'' and ''reliable'' for application of RWE to device regulatory decisions.