Real-World Evidence (RWE) holds out the promise of reducing time and costs of product approvals, identifying new uses for existing products, increasing our ability to treat rare diseases, and improving clinical practices for using drugs and medical devices. The 21st Century Cures Act, enacted in 2016, requires FDA to evaluate the use of RWE in approving new drug indications. FDA in 2017 issued a final guidance document regarding RWE in regulatory decisions involving medical devices. The private sector is also focusing on RWE: more than half the pharmaceutical companies in a recent survey say they are significantly expanding their involvement in RWE. Nonetheless, misunderstandings and uncertainties remain, both about what constitutes RWE and its potential role in regulatory and other aspects of precision medicine.

What is Real World Evidence?
Regulatory approvals of new drugs have traditionally relied on randomized clinical trials (RCT’s), conducted in controlled conditions with trial subjects who meet specific eligibility criteria. RCT’s, though, have many limitations and deficiencies. Clinical trials are lengthy and expensive, typically representing about 60% of the cost of new drug products. Furthermore RCT’s are inefficient: only about 12% of new drug candidates which enter clinical studies ultimately receive marketing approval. While RCT’s might answer baseline questions of whether a product is safe and effective under the controlled conditions of the study, RCT’s may not reflect conditions in real-life patient use. The eligibility criteria for inclusion in clinical studies may not reflect the actual patient population which could use a product. For example, because of the need to minimize variables, RCT’s may not include patients who suffer from comorbidities (i.e., patients with multiple, unrelated, pathologic or disease processes). The inherently limited number of study subjects and the time limits of RCT’s mean that infrequent or long-term side effects may remain undetected at the time of product approval. RCT’s may not be practical for developing treatments for rare diseases, due to difficulties in recruiting adequate numbers of study subjects.
RWE represents both a potential alternative and complement to traditional RCT’s. RWE relies on evidence from actual clinical use of products to evaluate new applications of products and inform clinical decisions for using products.

As an initial matter, it is important to differentiate between RWE and “real world data” (RWD). FDA considers RWD to be the kinds of data relating to patient health status or the delivery of health care which are routinely collected from various sources. Examples of RWD include data from such sources as electronic health records (EHR’s), hospital or insurance company administrative and claims, data obtained directly from providers or patients during an observational study, patient-generated data from in-home monitoring devices or fitness trackers, and data obtained from registries which collect information on various aspects of health care or research. RWD may also include data on environmental exposures and socio-economic factors.

As is evident from the list above, many sources of RWD are developed for non-regulatory purposes, i.e., to document patient care or for submission of insurance claims. As such, not all RWD is suitable for regulatory purposes such as product approvals.

FDA defines RWE as “clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD”. The Duke-Margolis Center for Health Policy, in a 2017 white paper prepared with FDA funding, stated that RWE is “evidence derived from RWD through the application of research methods”. In other words, RWE is not merely passively collected or anecdotal data. Rather, RWE results from careful study designs to assess the treatment effects on patient outcomes. FDA’s recent guidance document, discussed below, provides information on how the Agency determines what constitutes RWE.

Used appropriately, RWE could advance medical and regulatory science in many respects, both in pre-approval and post-approval contexts. Pre-approval RWE could supplement RCT’s, reducing the time and costs of drug and device development. RWE could help to generate research hypotheses in clinical trials, and help select more appropriate clinical trial subjects. RWE could make development of treatments for rare diseases more feasible, particularly when it is not practical to recruit enough clinical subjects to support traditional RCT’s. RWE can also be used to evaluate prospective treatments when ethical considerations preclude RCT’s. Post-approval RWE of patient uses of a drug or device could help to identify and approve new indications, and identify factors in safety, effectiveness and clinical treatment practices which may not be apparent in traditional clinical trials. While it is highly unlikely that RWE will completely replace RCT’s in the foreseeable future, RWE can become an important complementary source of information where RCT’s are appropriate and a valuable alternative where they are not. The remainder of this article discusses recent U.S. legislative and FDA efforts to address use of RWE. It also includes some case studies involving the use of RWE for regulatory purposes where FDA has accepted, or indicated it can accept, RWE. While the focus of this article is on U.S. regulation, some of the case studies and other information may have broader applicability.

The 21st Century Cures Act

The 21st Century Cures Act, enacted in 2016, recognized the growing importance of RWE. Section 3022 of the Act directed the Secretary of HHS, who will act through FDA, to develop a program to evaluate the potential use of RWE. Section 3022 defines RWE as “data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.”

Section 3022 requires the Secretary to:

- Establish a draft framework within two years of the Act’s enactment describing:
  - Sources of RWE
  - Gaps in data collection activities
  - Standards and methodologies for collecting and analyzing RWE; and
  - Priority areas, remaining challenges and potential pilot opportunities

- Consult with stakeholders including regulated industry, academia, medical professional organizations, representatives of patient advocacy organizations, consumer organizations, and disease research foundations regarding the above-mentioned framework;

- Within two years of the Act’s enactment, implement the program for evaluating potential use of real world evidence in accordance with the above-mentioned framework;

- Prepare a draft guidance for industry within five years of the Act’s enactment on the circumstances under which drug sponsors may rely on RWE and the appropriate standards and methodologies for collecting and analyzing such RWE; and

- Issue a revised or final guidance for industry within 18 months following the close of the public comment period for the draft guidance described above.

Importantly, section 3022 does not alter the standards of evidence for approving new drug applications, including the “substantial evidence” standard. Similarly, the Act does not alter the Secretary’s authority to require post-approval studies or clinical trials.
FDA Guidance Document on Real World Evidence and Medical Devices

Although the 21st Century Cures Act focused on drugs, it was FDA’s Center for Devices and Radiological Health (Device Center) which on August 31, 2017, together with FDA’s Center for Biologics Evaluation and Research (CBER), issued a guidance document entitled “Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices”. The Agency had issued the draft guidance on this subject on July 27, 2016.

FDA stated that “Under the right conditions, data derived from real world sources can be used to support regulatory decisions.” The guidance clarifies circumstances in which RWD may be used to support FDA decisions. This guidance, like other Agency guidance documents, is not binding on either FDA or the public. It does, though, represent FDA’s current thinking on the applicable topic and should be viewed as containing recommendations. Alternative approaches are nonetheless acceptable if they satisfy the requirements of applicable statutes or regulations. The Agency notes that its guidance does not alter the evidentiary standards that FDA uses to make regulatory decisions; rather, it describes circumstances in which RWD may be used to support various FDA decisions under the existing evidentiary standards.

In establishing the guidance, FDA noted that at present, there is often no system for systematically characterizing, aggregating and analyzing data from all uses of a medical device in a manner that informs regulatory decisions. By expressing a willingness to consider RWE in regulatory decisions, FDA hopes to create incentives for the medical community to obtain greater information from use of devices in routine clinical care.

FDA will consider RWE for both pre-market and post-market regulatory purposes. In a pre-market context, RWE can support both clearance or approval of a new device, or addition of new indications for existing devices. RWE may also supplement other evidence used to support such clearances and approvals. Aggregation of RWD, such as from medical device registries, may also be useful in post-market device safety surveillance.

Use of RWD for regulatory purposes requires a careful study design for both RWD already collected (retrospective studies) or data to be collected in the future (prospective studies). The studies should analyze similar elements as would be included in a traditional RCT. FDA recommends using the Agency’s pre-submission process when developing an RWD study, just as when preparing to conduct an RCT.

FDA will consider RWE in making regulatory decisions when it believes the RWE was generated using data of sufficient quality to inform regulatory decisions. What constitutes sufficient quality may depend upon the RWE’s intended purpose. For example, a particular registry may be useful for post-market surveillance but inadequate to support a premarket determination of safety and effectiveness.

FDA will consider use of RWD for a number of purposes, including for the following:

- generating hypotheses to be tested in a prospective clinical study;
- as a historical control, a prior in a Bayesian trial, or as one source of data in a hierarchical model or a hybrid data synthesis;
- as a concurrent control group or as a mechanism for collecting data related to a clinical study to support device approval or clearance in a setting where a registry or some other systematic data collection mechanism exists;
- as evidence to identify, demonstrate, or support the clinical validity of a biomarker;
- as evidence to support approval or granting of a Humanitarian Device Exemption, Premarket Approval Application (PMA), or De Novo request;
- as support for a petition for reclassification of a medical device under section 513(e) or (f)(3) of the FD&C Act;
- as evidence for expanding the labeling of a device to include additional indications for use or to update the labeling to include new information on safety and effectiveness;
- for public health surveillance efforts, if signals suggest there may be a safety issue with a medical device;
- to conduct post-approval studies imposed as a condition of device approval or to potentially preclude the need for postmarket surveillance studies ordered under section 522 of the FD&C Act;
- in certain circumstances, for use in generating summary reports of Medical Device Reports; and
- to provide postmarket data in lieu of some premarket data.

Since RWD is often developed for non-regulatory purposes, FDA must assess whether such data is useful for regulatory purposes. It is therefore important to have a pre-defined common set of data elements, a common definitional framework, and pre-specified time intervals for data element collection and analysis. FDA may also consider the ability to supplement the RWD with linkages to other data sources such as EHR’s or claims data.

In evaluating the suitability of RWD for regulatory purposes, FDA will evaluate its relevance and reliability. With regard to relevance, FDA will examine such factors as (i) whether the data contains adequate detail to evaluate use of the device, exposure, and relevant outcomes in the appropriate population; (ii) whether the data is amenable to sound clinical and statistical analysis; and (iii) whether the data and resulting RWE can be interpreted using informed clinical and scientific judgment. For reliability, the primary
factors FDA considers include how the data was collected and whether the processes and people used during data collection and analysis are adequate to minimize errors and to provide data of sufficient quality and integrity.

Case Studies of Real World Evidence for Regulatory Purposes

The examples below are generalized from situations where FDA has actually used or accepted RWE in regulatory decisions relating to medical devices (the TAVR example below is a specific instance of using RWE). The list below is not exhaustive, but does illustrate some instances where RWE may be appropriate.

Use of Registries to Support Expanded Indications.

- Registries typically collect information about persons with a specific disease or condition, or persons of varying health status who agree to participate in research on particular diseases. Registries may also collect RWD from routine clinical care on persons with approved or cleared devices, including treatment for off-label purposes. RWD from such a registry could be used to expand labeling of devices captured in the registry.

- Alternatively, FDA contemplates the use of registries in a situation in which a device which has experienced technological advances since its initial marketing approval is now used in clinical practice outside of its approved indications. However, data to support the safety and effectiveness of the new indications is lacking, and therefore participating medical societies establish a national registry to collect data on patients using the device at participating institutions. This registry also includes a validated algorithm to link to healthcare claims as a supplemental dataset. A study evaluating an off-label use and using the registry data and collection was initiated under an approved Investigational Device Exemption (IDE) application. If the RWD proves to be of sufficient quality to address safety issues, it may support labeling changes for the device.

- FDA reported in 2017 that it used RWE to expand the indications of a transcatheter aortic valve replacement (TAVR), the Sapien 3 produced by Edwards Lifesciences, to include valve-in-valve procedures. FDA utilized data from the Transcatheter Valve Therapy Registry, which contained records for over 100,000 TAVR procedures, 600 of which were for off-label valve-in-valve procedures. FDA relied on this data to evaluate the off-label procedure, including the valve function, improvement of patient symptoms and safety of the procedure, to approve the new indication.
FDA representatives noted that the U.S. had been only the 42nd country to approve the original TAVR device in 2011. However, through use of creative regulatory procedures, the U.S. became the first country to approve the new indication.

- Use of RWD to Conduct Post-Market Surveillance Studies. FDA issued a series of post-market surveillance orders under section 522 of the FD&C Act, to investigate patient safety information regarding multiple Class II devices with similar design and intended uses made by different manufacturers. Many manufacturers, in order to comply with the orders, established a patient registry in collaboration with a relevant clinical professional society and FDA to collect the required data.

- Post-Approval Device Surveillance as a Condition of Approval. FDA was able to provide an earlier device approval for a breakthrough Class III medical device, partly as the result of the manufacturer’s establishment of a registry which could meet FDA’s requirements early in the regulatory review process. Early construction of the registry permitted collection of data from all patients receiving the device upon approval. FDA granted early approval of the device conditioned upon continuing robust data collection and reporting following approval. FDA noted that the registry went on to be used for (i) collecting surveillance data on future devices with similar designs and uses; (ii) retrospectively analyzing data on all uses of the device to support expanded indications; and (iii) supporting prospective embedded clinical studies under IDE’s for new devices.

(Incidentally, FDA noted that the retrospective data collection activities of the registry which were used to support new indications did not require an IDE because treatment decisions were not influenced by the expectation of future analyses. However, an Institutional Review Board (IRB) did review the retrospective analyses for human subject protection purposes).

- Use as a Control Group. A medical device manufacturer seeking approval of a next generation device which contained substantial changes from previous versions of the device was able to use RWD from a registry which captures data on all uses of medical devices with a similar application as a clinical study control group. The manufacturer still had to perform clinical studies on the new device, but was able to use data from the registry for the control.

- Supplementary Data. Where RWD has been systematically collected, FDA has used RWD in combination with other sources of data, when safety issues arise with an approved device which were not detected in pre-approval studies. FDA cited an instance where it had been reviewing a class III device for a new indication, in which there was inadequate data from control groups. However, a pre-existing registry was collecting and reporting RWD on control treatments. FDA was able to use this pre-existing registry data to supplement and help interpret the clinical trial data, and reach a regulatory decision without requiring additional clinical trial data. In this case, the availability of RWE permitted FDA to reach a decision without having to expose additional study subjects to a device with questionable benefits.

National Evaluation System for Heath Technology (NEST)
In 2016 FDA awarded a grant to the Medical Devices Innovation Consortium, a non-profit public-private partnership, to establish the NEST Coordinating Center (NESTcc). The purpose of NEST is to “more efficiently generate better evidence for medical device evaluation and regulatory decision-making.” FDA envisions NEST as a voluntary network of data partners which will act as a national evaluation system to link and synthesize data from different sources of medical device information as clinical registries, EHR’s and medical billing claims in order to provide improved RWE that providers and patients can use in making treatment decisions.

NESTcc is intended to establish relationships between partners in a neutral, objective manner and seeks to “support the sustainable generation and use of timely, reliable, and cost-effective Real-World Evidence (RWE).” NESTcc has executed Memoranda of Understanding with nine organizations, representing approximately 108 million patients, to act as NESTcc’s initial data partners. NEST is expected to be fully operational by 2019.

In December 2017, NESTcc issued a request for “Concepts for Real-World Test-Cases.” NESTcc was seeking recommendations from medical device manufacturers for test cases using RWE which could be implemented with NESTcc’s data partners. Among the goals of the test cases are to explore the feasibility for industry to use the RWE sources available from NESTcc’s current partners and to identify areas where NESTcc could play a role in reducing transaction costs.

NESTcc listed eleven demonstration projects on its website as of the submission of this article. The purpose of these projects is to “provide proof of concept for scalable approaches to evidence generation across device types and across the total product life cycle.”

Future Challenges
RWE as a regulatory tool is in its early stages. Our knowledge of optimal uses of RWE, and the best methods for generating it, is still evolving. The list below, while not intended to be comprehensive, identifies some challenges in optimizing use of RWE for regulatory purposes:

- Lack of institutionalized methods of obtaining RWD. Many sources of RWD, particularly those generated by physicians or patients, are not collected for regulatory
or research purposes. Some sources of data are generated in formats (such as PDFs) which are not efficient for data analyses. FDA’s Device Center web site states that the “current fragmented health care ecosystem does not support the seamless, near real-time, cost-effective use of health data to generate high-quality evidence for medical devices needed for regulatory decision-making in both the pre- and post-market spaces.”

• Lack of Recognized Standards. Another challenge to broader use of RWE will be the development of useful standards for determining what data is useful or adequate to support regulatory decisions. Gregory Daniel, Deputy Director of the Duke-Margolis Center for Health Policy, which issued a white paper and hosted a workshop on RWE in September 2017 supported by funding and a cooperative agreement with FDA, commented that FDA will need to consider sources, methods used to generate evidence, regulatory and clinical context, and how the research community can standardize an understanding of useful RWE. Steve Miller, Chief Medical Officer at Express Scripts, commented that while pharmacy claims and laboratory results are reliable sources of RWE, subjective provider or patient-entered data are less so.

• Data Privacy Concerns. Recurring breaches of data privacy may discourage individuals from allowing their health data to be used for research purposes. Uncertainties also remain regarding use of patient data.

• Uneven Rules for Different Stakeholders. Pharmaceutical and device manufactures are largely prohibited from commenting on uses of their products that have not been approved by FDA. However third party payers and health care providers do not face such restrictions. It is hard to know how this uneven ability to use RWE and RWD will affect the development of RWE as a regulatory tool.

Conclusion

Use of RWE for regulatory purposes is in its early stage. Both the regulations and the technology affecting RWE are still evolving. Significant challenges exist regarding the proactive and systemic collection of RWD. Many questions remain regarding what constitutes adequate and appropriate RWE, what kind of RWD is useful RWE and what are the optimal uses of RWE.

Nonetheless, recognition of the limitations of traditional RCTs is widespread. Appropriately utilized, RWE could play an important role in reducing the time and cost of developing new drugs and medical devices, treating conditions which today have no effective treatments, and improving the quality and reducing the cost of health care.

References


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