Chapter 36

Emergence of Real World Evidence in Precision Medicine

Neil A. Belson, MS, JD

Law Office of Neil A. Belson, LLC, Port Tobacco, Maryland, USA

Keywords: real world evidence, real world data, health economics, HEOR, drug development, drug approval, clinical evidence, drug regulation, US Food and Drug Administration, randomized clinical trials, natural history studies, rare diseases, precision medicine, personalized medicine, patient registries, disease registries, product registries, 21st Century America Cures Act, electronic health records, research and development, guidance documents, Expanded Access Program

36.1 Introduction

In June 2017, the US Food and Drug Administration (FDA) approved a new indication for a medical device without requiring the device manufacturer to conduct any new clinical trials. Instead, the Agency relied on the manufacturer's "Real World Evidence" (RWE) demonstrating safety and efficacy. Using RWE dramatically accelerated the time to FDA approval: Relying on traditional

The Road from Nanomedicine to Precision Medicine
Edited by Shaker A. Mousa, Raj Bawa, and Gerald F. Audette

ISBN 978-981-4800-59-4 (Hardcover), 978-0-429-29501-0 (eBook)
www.jennystanford.com

clinical trials the United States had been only the 42nd nation to approve the original use of the device, a transcatheter aortic valve replacement (TAVR). In contrast, using RWE in its regulatory decision-making process allowed the United States to *become* the first country to approve a new valve-in-valve procedure for the device [1, 2].

This device approval demonstrated the emergence of RWE as a potentially transformative new tool in personalized medical care and drug development and regulation. RWE can provide the information which informs precision medicine decisions. As one commentator has been stated [3]:

> *As the pharmaceutical industry shifts to value-based, personalized health care, RWE can help is answer the hard questions in health care, such as what works, for whom, why does it work, and in what context. All of these questions are at the heart of value-based personalized medicine…*
>
> *RWE is becoming essential to decisions across every aspect of the pharmaceutical value chain, from the early research and development stage.*

RWE could substantially reduce the time and cost of commercializing new drugs and medical devices. RWE is already impacting the life sciences industry: A Deloitte 2018 survey found that nearly 90% of biopharmaceutical companies surveyed that they have either already established or plan to invest in RWE capabilities [4].

RWE is also impacting the FDA. Former FDA Commissioner Dr. Scott Gottlieb stated in December 2018 that RWE and Real World Data (RWD, which is used to generate RWE) are "a top strategic priority for the FDA" [5]. The FDA centers responsible for drugs, biologics and medical devices have all issued guidance documents relating to the use of RWE for regulatory purposes. RWE could supplement or even replace traditional randomized clinical trials (RCTs) in many situations.

The need for new methods of drug and device regulation is clear. Director of the FDA's Center for Drug Evaluation (CDER), Dr. Janet Woodcock, has repeatedly referred to the FDA's traditional system for approving new drugs, using RCTs, as "broken" and not serving the interests of patients [6]. RCTs

represent approximately 60% of the approximately $2.6 billion to develop a new drug [7, 8].[1] Yet they are in many ways an inefficient and incomplete way of measuring drug and device safety and efficacy. Only about 12% of drug candidates which enter Phase I clinical studies ultimately receive FDA commercial marketing approval [9].

The deficiencies of traditional RCTs are well known. While RCTs are useful in evaluating the baseline effectiveness of a drug under controlled conditions, they often fail to accurately predict the effectiveness of a drug in real-life conditions. RCTs generally have strict inclusion and exclusion criteria, which may not accurately reflect the likely patient population. For example, RCTs are often limited to subjects between the ages of 18 to 65 years old, even though a substantial portion of the target population may be outside this age range. Similarly, RCTs often exclude patients with comorbidities (the presence of multiple chronic diseases), although many prospective patients suffer from multiple disease conditions. RCTs may not detect uncommon side effects due to inherent limitations in the number of patients who can participate in a study. Additionally, 80% of clinical trials fail to meet their initial subject enrollment projections [10]. RCTs are also generally unsuitable for studies involving rare diseases, due to the unavailability of adequate numbers of study subjects.

36.2 What Is "Real World Evidence"?

The FDA differentiates between "Real World Evidence" and "Real World Data." It considers RWD to consist of information relating to patient health status or patient health care treatment, including electronic health records (EHRs), insurance claims data, disease, or product registries, or home-use patient monitoring devices and mobile devices. RWD may also include data on socio-economic factors or environmental exposures. As is evident

[1]The authors of these publications [7, 8] estimated an average out-of-pocket cost per approved new compound was $1395 million in 2013 US dollars. This estimate linked costs of compounds discontinued prior to commercialization to the costs of compounds which received marketing approval. The authors calculated a total estimated cost of $2558 million by capitalizing the out-of-pocket amount at a real discount rate of 10.5%.

from this list, many sources of RWD are generated for non-regulatory purposes, such as documenting patient care or for submission of insurance claims. Not all RWD is therefore suitable for regulatory purposes such as product approvals.

Precision Medicine Committee, American Bar Association, Section of Science & Technology Law

The Precision Medicine Committee examines legal issues affecting the rapidly emerging field of precision medicine (previously known as "personalized medicine"). Precision medicine utilizes information on an individual's genetics and biomarkers, and environmental and lifestyle factors, to inform decisions on disease prevention and treatment. The PMC Committee's focus includes such diverse topics as drug and device development and regulation, payment and reimbursement, health IT, data privacy, ethical issues, intellectual property and business and investment, as they relate to precision medicine.

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In contrast, the FDA defines RWE as "*clinical* evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD" (emphasis in original text) [11]. The Duke-Margolis Center for Health Policy stated in a 2017 white paper prepared with FDA funding, that RWE is "evidence derived from RWD *through the application of research methods*" (italics added) [12]. RWE has also been described as "information that is generated in health care systems outside of a controlled trial" [13]. RWE is not merely passively collected or anecdotal data. Rather, RWE results from careful study designs for assessing treatment effects on patient outcomes [12].

Studies which generate RWE can be prospective, retrospective, or both—they can utilize pre-existing data, newly generated data, or a combination of both. In each case, though, RWE requires a careful clinical design to measure the effect of the study drug, device, or treatment on patient health. RWE-based studies must meet the same "substantial evidence" standards as RCTs for FDA regulatory purposes.

Used appropriately, RWE could advance medical and regulatory science in many respects, in both pre-approval and post-approval contexts. Pre-approval RWE could supplement RCTs, reducing the time and costs of drug and device development. RWE could help generate research hypotheses in clinical trials and help identify 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 RCTs. Post-approval RWE analyzing patient uses of a drug or device could help in identifying and approving new indications and in identifying factors in safety, effective clinical treatment practices, and personalized care, which may not be apparent in traditional clinical trials [14]. While RWE is unlikely to completely replace RCTs in the near future, RWE can become an important complementary source of information where RCTs are appropriate and a valuable alternative where they are not.

36.3 Emergence of Real World Evidence

21st Century Cures Act. The 21st Century Cures Act, enacted in December 2016 [15], marked a turning point in the emergence of RWE. Section 3022 of that Act directed the Secretary of Health and Human Services, through the FDA, to establish a program to evaluate potential uses of RWE for two purposes:

(i) helping to support approval of new indications for already approved drugs;
(ii) helping to satisfy post-approval study requirements [16].

In August 2017, the FDA's Center for Devices and Radiological Health (CDRH) and Center for Biologics Evaluation

and Research (CBER) published a final guidance document describing situations in which they could accept RWE in support of regulatory decisions involving medical devices. CDER and CBER have since followed with a series of draft guidances and other publications relating to RWE. They also published a framework for evaluating RWE in relation to drugs and biologics in December 2018 [11].

36.3.1 Use of RWE for Medical Devices

Although the 21st Century Cures Act focused on drugs, the Agency's first major final guidance on RWE following the Act addressed medical devices. On August 31, 2017, CDRH and CBER issued a guidance document entitled "Use of real-world evidence to support regulatory decision-making for medical devices" [17].

The FDA noted that there often exists no system for systematically characterizing aggregating and analyzing data from all uses of a medical device. The Agency hoped to create incentives for systematically collecting and organizing information from routine use of devices in medical care by expressing a willingness to consider RWE in its regulatory decisions.

The FDA stated [17] that "under the right conditions, data derived from real world sources can be used to support regulatory decisions" in both premarket and postmarket regulatory contexts (Table 36.1). The Agency noted that use of RWD for regulatory purposes requires a careful study design. Such studies should analyze elements similar to those that would be included in a traditional RCT. The FDA recommended using the Agency's pre-submission process for prospective RWD studies, just as when preparing to conduct an RCT [17].

Since RWD is often developed for non-regulatory purposes, the FDA must determine whether such data is useful for regulatory purposes. When relying on RWD, it is important to have a predefined common set of data elements and a common definitional framework, together with prespecified time intervals for data element collection and analysis. The FDA may also consider the ability to supplement RWD with linkages to other data such as EHRs or claims data.

Table 36.1 Examples of purposes for which FDA will consider use of RWD relating to medical devices

• Generating hypotheses to be tested in a prospective clinical study
• A mechanism for collecting data related to a clinical study to support device approval or clearance where a registry or other means of systematic data collection exists
• Evidence to identify, demonstrate, or support clinical validity of a biomarker
• Evidence to support approval or granting of a Humanitarian Device Exemption, Premarket Approval Application (PMA), or *de novo* request
• Support for reclassification of a medical device
• 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
• Public health surveillance efforts, if signals suggest there may be a safety issue with a medical device
• Conducting post approval studies imposed as a condition of device approval or to potentially preclude the need for postmarket surveillance studies

36.3.2 Use of RWE for Drugs and Biologics

In December 2018, the FDA published a "Framework for FDA's Real World Evidence Program." The Framework covers use of RWE in relation to both drugs and biologics, although it does not cover medical devices. The purposes of the Framework are to

- evaluate potential use of RWE to help support FDA approval for new indications for which drugs which are already commercial;
- support or satisfy drug post-approval study requirements [11].

The RWE program will include demonstration projects, stakeholder engagement, and input from senior leadership and promote shared learning and consistent application, with issuance of guidance documents to assist drug developers.

Since RWE already has a significant history of use in evaluating product safety, the FDA will focus on use of RWE to demonstrate

product effectiveness. The FDA will evaluate the potential of RWE to support labeling changes, such as adding a new indication, changing a dosage regimen or route of administration, adding a new population, or adding safety information (Table 36.2).

Table 36.2 Factors that FDA will consider in evaluating use of RWE to demonstrate drug product effectiveness [11]

1. Whether the underlying RWD is fit for use
2. Whether the study design used to generate RWE provides adequate scientific evidence to help answer the regulatory question at issue
3. Whether the study conduct meets FDA requirements (e.g., for study monitoring and data collection)

Any RWD selected should be suitable for addressing specific regulatory questions. The strength of any RWE will depend on the clinical study methodology and the reliability and relevance of underlying data.

The FDA has considerable experience assessing electronic health care data (e.g., EHRs, medical claims data, registries) through experience with the Agency's Sentinel System, which is a national electronic system for monitoring the safety of drugs, devices, and other products on the market, as well as other data systems [11]. In fact, the FDA's use of the RWD and RWE, derived from the Sentinel System, has eliminated the need for postmarketing studies when potential safety issues arose involving five products [5]. The FDA plans to use this experience in assessing sources of RWD used to generate RWE for purposes of drug product effectiveness.

The Agency notes that the specific elements to consider in evaluating different sources of RWD may vary depending on the type of RWD used and its intended purpose. For example, the FDA considers the strengths and limitations of medical claims data as RWD to be well understood based on experience within government agencies, health care insurers, and medical researchers. Conversely, EHR data, which may provide more detailed patient data than medical claims, is at present not usually standardized or collected in structured fields which are readily extractable comparable across systems. Additionally, EHRs and medical claims data may not consistently capture certain co-variables (such as

obesity, smoking, or alcohol use) and outcomes (such as mortality or symptomatic changes).

Patient registries are another potentially significant source of RWD. A patient registry systemically collects uniform data from a population with a particular disease or condition, or who are receiving a particular drug or other medical treatment, in order to evaluate outcomes. The FDA considers that the fitness of patient registries for use in generating RWE depends on whether there are adequate processes for gathering follow-up information as needed, to minimize missing or incomplete data and ensure data quality.

Filling gaps in information, which may be difficult to capture in the context of EHRs and medical claims data, will be part of the FDA's RWE evaluation program. Another component of the FDA's program will be addressing the lack of interoperability among different health care systems, and the difficulty of linking data sources for a single patient across different providers and health care systems, while maintaining patient privacy [11].

36.4 Case Studies Using RWE

Both the FDA and the private sector had used RWE and RWD even before enactment of the 21st Century Cures Act, in both regulatory and non-regulatory contexts. The discussion below provides case examples, both prior to and after the Act, in which parties used RWE and RWD in a regulatory context:

(i) *Postmarket Monitoring of a Drug*: The FDA has long used RWE for postmarket monitoring and evaluating the safety of drugs after they have been approved, through the Agency's "Sentinel System." The Agency's primary sources of information for such studies include electronic health data such as medical claims and pharmacy dispensing data. The Sentinel System had data on over 100 million individuals as of August 2018 [11].

(ii) *Natural History "Controls" in Studies of Treatments for Rare Diseases*: One of the most frequent uses of RWE in a drug approval context has been in natural history studies as a "control," particularly in cases of evaluating drugs to treat

rare diseases. A "natural history" study follows the progression of a disease or condition in the absence of a treatment from just before its onset until its final outcome (i.e., death, disability, or patient recovery).

In evaluating potential treatments for rare diseases, the FDA has often relied on "single-arm" studies of a drug, using a natural history study of the target disease as a non-treatment "control." Many of these cases have involved rare genetic disorders, where no FDA-approved treatment exists, and death or severe disability is imminent in the absence of treatment. In such instances, ethical considerations preclude the use of actual patient control subjects.

For example, the FDA approved Brineura (Cerliponase alfa) to treat a form of Batten disease based on single-arm study compared with a natural history control. No prior FDA-approved treatment existed for that form of disease, known as late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2), a rare genetic disorder which often causes children to lose walking ability and die in their teens. The FDA approved Brineura to treat CLN2 following an efficacy study involving 22 symptomatic pediatric patients, compared with a natural history cohort "control" or comparator consisting of 42 untreated patients. The study showed patients treated with Brineura suffered fewer declines in walking ability than the untreated patients in the natural history cohort [18].

The FDA plans to expand its use of natural history studies. Former FDA Commissioner Gottlieb stated that the Agency has "been working overtime to develop models that can simulate the behavior of placebo arms in the setting of rare diseases [19]. In conjunction with his comment, the FDA announced it would fund natural history studies relating, respectively, to Friedreich's ataxia, pregnancy and lactation-associated osteoporosis, sickle-cell anemia, Angelman syndrome, and myotonic muscular dystrophy type 1 [19].

(iii) *Utilization of the FDA's Expanded Access Program to generate RWE*: Most current discussion on the use of RWE in the context of regulatory approvals seems to focus new indications for existing products. Apart from its use in

natural history studies, there appear to be limited options for utilizing RWE to obtain an initial product approval—after all, how can a Sponsor obtain evidence from real-life drug usage regarding a product which is not approved for commercial use in "real-life?" One such option which may exist is the FDA's "Expanded Access Program" (EAP, also known as the "Compassionate Use" program), which grants patients access to investigational drugs when they have exhausted all approved treatments and cannot participate in clinical trials. The FDA has expressed openness to Sponsors' leveraging data from the EAP program to generate RWE [20].

One example where the FDA relied on RWE from an EAP study to support a drug approval involved Lutathera (lutetium Lu 177 dotatate), a radioactive drug (or "radiopharmaceutical") for treatment of somatostatin receptor-positive instances of a type of cancer known as gastroenteropancreatic neuroendocrine tumors (GEP-NETs) that affects the pancreas or gastrointestinal tract. GEP-NETs are a rare group of cancers for which there are limited treatment options if initial therapy is unsuccessful.

Lutathera's approval was supported by two studies. One was an RCT with 229 patients. The second study was based on data from a single-arm, open-label study of 1,214 patients with somatostatin receptor-positive tumors, including GEP-NETS, who received Lutathera at a site in the Netherlands. Complete or partial tumor shrinkage was reported in 16 percent of a subset of 360 patients with GEP-NETs who were evaluated for response by the FDA. Patients initially enrolled in the study received Lutathera as part of an expanded access program [21, 22].

(iv) *Use of Patient Registries to Obtain Approvals for New Indications*: The manufacturer of the TAVR device described at the start of this article is an example of a company using a patient registry to avoid having to conduct RCTs for a new indication. The manufacturer obtained its initial marketing approval from the FDA in 2011. Upon obtaining this approval, the manufacturer then proactively established a product registry, which generated a database containing records of over 100,000 TAVR records. Among these records

were 600 records relating to the then off-label use of a new valve-in-valve procedure. Based on this registry data from these 600 records, the FDA approved the use of the new procedure without requiring any further RCTs [1, 2].

(v) *Private sector use of RWE* and *RWD*: Private sector drug development companies have used RWD as a tool in traditional RCTs to target their studies more precisely on patient groups and sub-groups that are most likely to show a positive response to drug candidates. RWD can be useful in generating study hypotheses for RCTs, identifying potential biomarkers, and identifying prognostic indicators or patient baseline characteristics to support clinical trial enrichment or stratification of clinical trial subjects. The FDA generally encourages such efforts and regards such uses of RWD as well established [11]. Some biopharma companies systemically collect data from their EAP programs, which they use as RWD in support of regulatory filings [23].

36.5 Future Challenges for the Use of RWE

RWE as a regulatory tool is in its early stages. Our understanding of prospective uses of RWE, and the methods for generating it, is still evolving. The list below identifies some challenges affecting the use of RWE for regulatory purposes:

- *Lack of institutionalized methods of obtaining RWD*: Many sources of RWD, such as those generated in EHRs and medical claims, are not collected for regulatory or research purposes. Some data is generated in formats (such as PDFs) which are not efficient for data analyses. The National Evaluation System for Health Technology Coordinating Center (NESTcc), an organization which evaluates use of RWE in relation of medical devices and which was established through a 2016 grant from the FDA to the Medical Device Innovation Consortium, has stated 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 postmarket spaces" [24].

- *Lack of Generally Accepted Standards*: The FDA and others are still in the process of evaluating which data is useful or adequate to support regulatory decisions.
- *Data Privacy Concerns*: Recurring breaches of data privacy may discourage individuals from allowing their health data to be used for research purposes.

36.6 Conclusions

The use of RWE for obtaining drug and device approvals is in its early stage, and our understanding of its prospective applications is still evolving. Many potentially useful sources of RWD, such as EHRs and medical claims, are not currently generated with a focus facilitating research. Additionally, there is not yet a common understanding as to what kind of RWE is necessary to adequately demonstrate product safety and efficacy. These factors, combined with lack of interoperability across different health care systems, makes the systemic collection, aggregation, and analysis of RWE a challenge.

Nonetheless, broad agreement exists regarding the limitations of traditional RCTs, and the need to develop new approaches for evaluating drug and device product safety. The biopharma industry is rapidly expanding its investment in RWE. Appropriately utilized, RWE could play an important role in reducing the time and cost of developing new drugs and medical devices and reducing the cost and improving the quality of health care.

Disclosures and Conflict of Interest

The author declares that he has no conflict of interest. The author received no payment for preparing this chapter. The author did not receive any assistance in preparing this chapter, apart from editorial assistance from Dr. Raj Bawa, the Series Editor.

The author is a Contract Attorney Consultant for Axovant Gene Therapies (New York, NY) and also the owner of the Law Office of Neil A. Belson, LLC (Port Tobacco, MD). The author is also a Manager and Membership Interest owner of Leafpro, LLC (Wilson, NC), a company that is developing naturally occurring leaf proteins from plants. The author is not aware of any affiliations,

memberships, or funding that might be perceived as affecting the objectivity of this chapter.

Corresponding Author

Neil A. Belson
Law Office of Neil A. Belson, LLC
6225 Hampstead Ct.
Port Tobacco, MD 20677, USA
Email: nabelsonlaw@hotmail.com

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