Adding Real-World Evidence to a Totality of Evidence Approach for Evaluating Marketed Product Effectiveness

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Duke | MARGOLIS CENTER *for* Health Policy

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Disclosures

Mark B. McClellan, MD, PhD, is an independent board member on the boards of Johnson & Johnson, Cigna, Alignment Healthcare, and Seer; co-chairs the Accountable Care Learning Collaborative and the Guiding Committee for the Health Care Payment Learning and Action Network; and receives fees for serving as an advisor for Cota and MITRE.

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WHITE PAPER

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EXECUTIVE SUMMARY

This paper responds to growing interest in using real-world data (RWD) and real-world evidence (RWE) in regulatory decision-making. In comparison with randomized controlled trials (RCTs), RWD has the potential to provide more representative information on a therapy's impact in a broader patient population, capture the evolving standard of care, and better reflect routine clinical care. With the increased curation of relevant and reliable RWD, and with the development of advanced analytical methods to make valid causal inference, RWE has the potential to complement the evidence generated from RCTs and to fill evidentiary gaps for healthcare decision-making. Because of this potential, the 2018 Framework for FDA's Real-World Evidence Program called for exploration of the use of RWE and RWD for regulatory decision-making regarding the effectiveness of marketed products.

When seeking an original approval by the U.S. Food and Drug Administration (FDA) for a product, an evidence package generally contains three types of studies: clinical pharmacology, non-clinical toxicology, and clinical studies. During subsequent effectiveness labeling changes (for example, use in a new population or adding or modifying an indication), the evidence package includes the prior submitted evidence and new evidence, which often consists of clinical studies only. **Traditionally, these clinical studies were in the form of RCTs; however, this paper explores how RWE studies may contribute to an evidence package.**

Regardless of study type, setting, or design, FDA does not evaluate one study only when making regulatory decisions. Instead, FDA uses a totality of evidence approach, examining all available evidence in the package including the quality of the studies and the clinical and regulatory contexts. Multiple factors inform the weighting that is assigned or degree to which each piece of evidence contributes to the regulatory decision. **Therefore, this paper discusses how an evidence package including RWE can contribute to substantial evidence within a totality of evidence approach to inform an effectiveness labeling change.** To illustrate how RWE can fill evidentiary gaps and contribute to the evidence package, case studies for existing marketed products and hypothetical case studies were reviewed through the lenses of the clinical and regulatory contexts.

How This Paper Was Developed

This paper is informed by a literature review, a full-day private workshop on "Improving RWE Study Credibility and its Role in Totality of Evidence" (June 20, 2019), and the expert opinion of the Duke-Margolis RWE Collaborative Methods Working Group. During the workshop, stakeholder experts representing sponsors, academic research groups, data vendors, providers, and patient networks provided input for key considerations for real-world study designs and methods. This paper focuses on the role of RWE in an evidence package, as evaluated through a totality of evidence approach. The companion methods paper Understanding the Need for Non-Interventional Studies Using Secondary Data to Generate Real-World Evidence for Regulatory Decision Making, and Demonstrating Their Credibility (Duke-Margolis, 2019) focuses on the quality and credibility of individual studies. This work builds on prior Duke-Margolis work, including the white papers Determining Real-World Data's Fitness for Use and the Role of Reliability (2019), Characterizing RWD Quality and Relevancy for Regulatory Purposes (2018), and A Framework for Regulatory Use of Real-World Evidence (2017).

Background

Stakeholders are eager to increase the use of RWD—"data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources"—throughout the life-cycle of drug development, approval, and access.[1] In particular, stakeholders want to analyze RWD to generate RWE about the use, benefits, and risks of medical products and then make that RWE actionable by a wide array of health care decision makers.[1] FDA is exploring the use of RWD and RWE within regulatory decision-making, per Congressional mandates in the 21st Century Cures Act and 6th Prescription Drug User Fee Act (PDUFA). FDA's December 2018 Framework for its Real-World Evidence Program outlines core considerations for using RWD and RWE for regulatory decisions about effectiveness for marketed drugs and biologics. The Framework includes a three-pronged approach that considers "whether: 1) RWD are fit for use; 2) studies that use RWD can provide adequate scientific evidence to answer regulatory questions; and 3) study conduct meets regulatory requirements."[1] This paper focuses on the second prong of the Framework.*

The Value of Real-World Data and Real-World Evidence

RWE studies can complement evidence from randomized controlled trials (RCTs) and contribute to a robust evidence package to support regulatory decision-making related to effectiveness. There is a well-established history of the FDA using RWE to support labeling changes related to safety; however, RWE studies might also be useful in labeling changes related to effectiveness.

RWD is often collected by providers as part of clinical practice throughout the health system. Therefore, RWD can support analyses that better represent the broader impact of a medical product, including routine clinical care and self-care. RWD can also continuously capture the evolving standard of care, whereas RCTs capture information during a specified timeline. Drawing from RWD, RWE studies often have broader inclusion criteria than traditional RCTs, which might provide insight into the impact of a drug on patients who were not represented in the RCT. RWE studies might also capture outcomes that are more relevant to prescribers and patients. RWE might be generated more efficiently and with fewer resources, increasing the availability of information that might not otherwise be generated.

High-quality RWD and RWE can be used in different ways to support regulatory decisions related to both safety and effectiveness of medical products.[1] For example, FDA uses RWD and RWE to investigate the safety of medical products in the postmarket setting through the Sentinel Initiative.[2] To support original approval of medical products, RWD could also be used in the development of external control groups (Appendix C). RWD can also be used to contribute confirmatory evidence to support full approval after accelerated approval is granted.[2] However, great interest lies in the ability for RWE to support labeling changes for marketed products related to effectiveness (e.g., new indication).

This paper discusses considerations for how RWE can support effectiveness labeling changes for marketed products when evaluated through a totality of evidence approach. First, the totality of evidence approach is explained. Next, this paper outlines the components that make up an evidence package and the role of clinical and regulatory contexts for assessing the benefits and risks of a marketed product. Subsequently, this paper examines the weighting of each successive piece of evidence in an evidence package to contribute to substantial evidence through a totality of evidence approach. Last, this paper explores remaining barriers to RWE use for regulatory decision-making and suggests a potential pathway forward.

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* Previous Duke-Margolis work on RWD and RWE includes four white papers: 1) "Understanding the Need for Non-Interventional Studies Using Secondary Data to Generate Real-World Evidence for Regulatory Decision Making, and Demonstrating Their Credibility," 2) "Determining Real-World Data's Fitness for Use and the Role of Reliability," 3) "Characterizing RWD Quality and Relevancy for Regulatory Purposes," 4) "A Framework for Regulatory Use of Real-World Evidence." For more information, see Appendix B.

Using a Totality of Evidence Approach

A totality of evidence approach can be used to evaluate whether an evidence package supports an effectiveness labeling change. A labeling change occurs when a medical product's label is altered to include new information or modify existing information.

A review of the literature shows that FDA can and does use a totality of evidence approach. For example, Sherman et al. states, "The FDA considers the totality of evidence when evaluating the safety and effectiveness of new drugs. This phrase reflects the nature of drug development, with each successive piece of data building on prior data to provide the quantity and quality of evidence needed to adequately assess risks and benefits. Data from a study are always assessed within the context of other available data, never in isolation, and data from different studies are considered based on the reliability of a given study result."[3] Furthermore, in the *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* Guidance, FDA comments, "In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use. In these cases, although there is only one study of the exact new use, **there are, in fact, multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness.**"[4] Using a totality of evidence approach to evaluate the evidence package involves assessing a combination of factors, including each study's data within the context of all the other previously completed studies as well as the clinical and regulatory contexts surrounding a research question (Figure 1). These factors are explored further below.

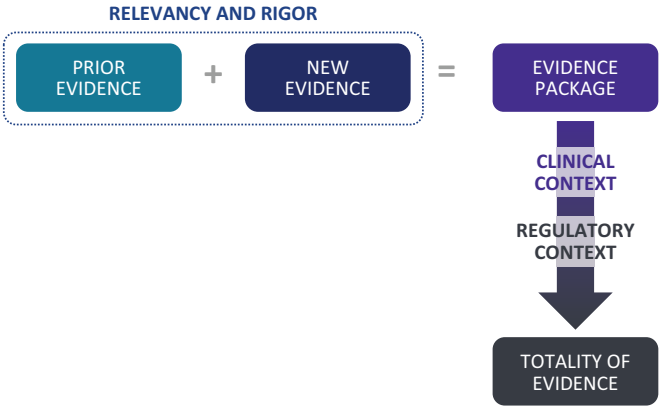

Figure 1. The totality of evidence approach for evaluating the risks and benefits of a medical product

Building the Evidence Package Using RWE

A sponsor submits an evidence package to FDA to support the approval of a new medical product or a labeling change for a marketed medical product. An evidence package for a new drug can contain three types of evidence: clinical pharmacology,* non-clinical toxicology,† and clinical studies (Figure 2).[5] In contrast, the evidence package for a labeling change of a marketed product includes not only the newly generated evidence to support the change but also the prior evidence generated for the original approval (Figure 3). In this scenario, the new evidence consists of additional studies to answer the regulatory research question. Typically, these additional studies are clinical studies.

* Clinical pharmacology studies include mechanism of action, pharmacodynamics, pharmacokinetics, microbiology, and pharmacogenomics.

† Non-clinical toxicology studies include carcinogenesis, mutagenesis, impairment of fertility, and animal toxicology and/or pharmacology.

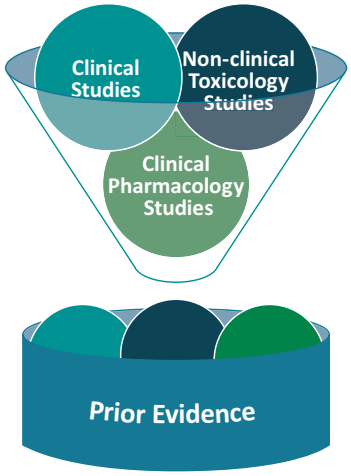

Figure 2. Components of an evidence package that is submitted to support a product approval

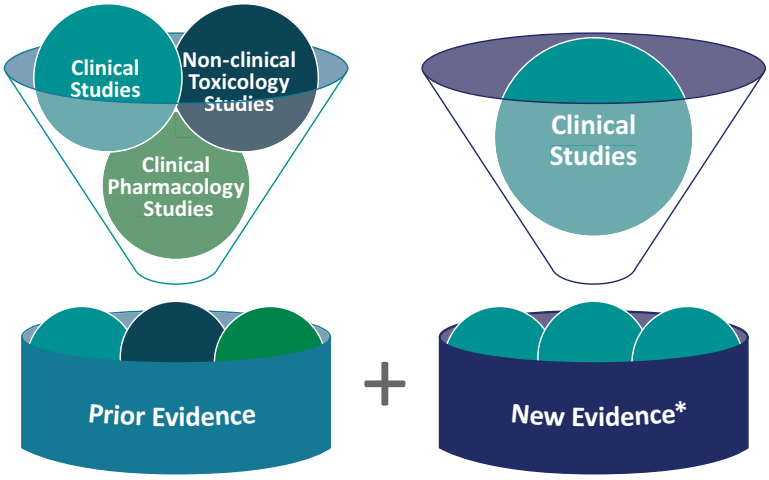

Figure 3. Components of the prior and new evidence packages submitted to support an effectiveness labeling change

*Typically, additional clinical pharmacology and non-clinical toxicology studies are not needed in future labeling changes; however, there are circumstances in which they would be included.

Clinical studies, or clinical investigations, seek to evaluate how a drug operates in humans, both from a safety and efficacy (or in the real-world setting, effectiveness*) perspective.[4] Clinical studies can occur in a controlled setting where care and data collection are prespecified (as with clinical trials) or a real-world setting where data reflects routine care (Figure 4).†[1] Clinical studies can have interventional or non-interventional treatment assignment and can include primary or secondary data.[6] Historically, clinical studies *generally* consist of RCTs. However, other types of clinical studies, including single-arm trials, open-label trials, and meta-analyses have been used (these study designs are defined in Appendix D). For example, single-arm trials have been used for original approvals in oncology and hematology, as well as for a number of rare diseases. (For a list of studies that used clinical study designs other than RCTs for an approval or labeling change, please reference Appendix C.) The use of clinical studies other than RCTs suggests that RWE studies can augment or replace RCTs to support effectiveness labeling changes. Of course, the specific type of RWE included in the evidence package depends on the research question, prior evidence, and the clinical and regulatory contexts.

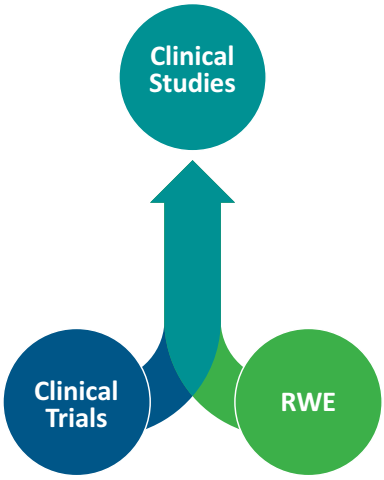

Figure 4. Clinical studies can consist of clinical trials or RWE

* In the *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* Guidance, FDA states "As used in this guidance, the term efficacy refers to the findings in an adequate and well-controlled trial or the intent of conducting such a trial and the term effectiveness refers to the regulatory determination that is made on the basis of clinical efficacy and other data." This distinction between efficacy and effectiveness is observed in this paper.

† Randomized controlled trials (exploratory trials) are an example of a clinical trial study design. Studies that are designed to generate RWE may include hybrid studies, randomized studies (e.g., pragmatic trials and large simple trials), observational studies, and use of RWD for the development of external controls.

The Role of Clinical and Regulatory Contexts in Assessing Benefits and Risks of a Medical Product

For an effectiveness labeling change, the evidence package is evaluated by considering the **clinical and regulatory contexts** of the research question through a totality of evidence approach. The clinical and regulatory contexts help to determine the acceptability of each piece of evidence in a submission. Therefore, the contexts influence the types of studies conducted to generate evidence for the targeted labeling change.

Regulatory Context

Regulatory context is dependent on a variety of factors including the selection of a regulatory pathway, degree of product use beyond the intended population or indication, and eventual regulatory decision. While different regulatory context considerations can impact evidence generation and approval decisions, this paper focuses on two additional regulatory factors: the labeling changes that RWE might support and the proximity of the proposed labeling change to the original labeling. It is important to remember that labeling changes can extend beyond modifying the indication or population (such as adding patient experience data or additional supportive clinical studies to the label). The various types of labeling changes, as outlined in FDA's RWE Framework and a subsequent draft guidance on document submissions, include the following:

- "Adding or modifying an indication
- Change in dose, dose regimen, or route of administration
- Use in a new population
- Adding comparative effectiveness information
- Adding safety information
- Other labeling changes."[7]

The ability to rely on prior evidence to support a labeling change depends on the degree to which the proposed label differs from the original label. During review, FDA might rely more on existing data in instances where labeling changes are within close proximity to original labeling and clinical and regulatory contexts are similar. However, as the departure from the original indication increases, the relevance of prior evidence to the proposed labeling change decreases (Figure 5). In this instance, the need for new evidence under a totality of evidence approach increases.

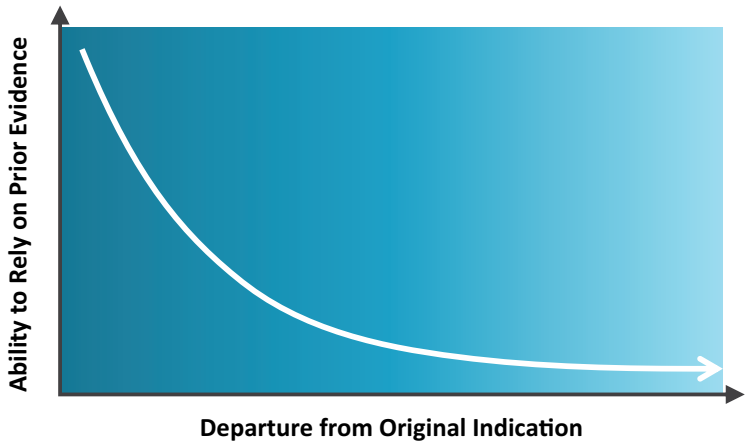

Figure 5. Weight of prior evidence is informed by the proximity of the labeling change to the original indication

Clinical Context

Clinical context is a multifaceted, complex concept that can include any clinical information surrounding the research question. Clinical context informs the design

of new clinical studies and affects the addition of new populations or indications. For example, rare disease studies might not have enough patients to power a study when compared to a highly prevalent disease, such as heart disease, so the study sample size must be evaluated within the clinical contexts of prevalence and disease severity. Some of the most vital clinical context information includes the **understanding of the disease, treatment alternatives, therapy, patient perspective, and provider perspective.**[3] (Descriptions can be found in Appendix E.) Table 1 lists a few key factors that underpin various aspects of clinical context, but is not an exhaustive list of all possible considerations. Additional overarching clinical context considerations include social determinants of health, such as access to high-quality care and the impact of lifestyle disease-modifying factors on patients.

Table 1. Clinical context considerations that may contribute to the quantity and type of evidence required in an evidence package to support substantial evidence

DISEASE	TREATMENT ALTERNATIVES	THERAPY	PATIENT PERSPECTIVE	PROVIDER PERSPECTIVE
• Disease prevalence in target population • Characteristics of study population (e.g., vulnerable population) • Nature of disease (chronic or acute) • Disease severity • Predictability of disease progression rate	• Level of unmet need • Number of available therapies • Effectiveness • Safety profile • Type of regulatory approval (e.g., accelerated approval)	• Mechanism of action • Biological plausibility • Type of regulatory approval (e.g., accelerated approval)	• Preference for treatment • Benefit-risk • Quality of life • Sub-population considerations	• Patient-specific characteristics • Adoption of treatment alternatives

Weighting the Components of an Evidence Package through a Totality of Evidence Approach

Using a totality of evidence approach, each piece of the evidence package contributes a different "weight" to inform an effectiveness labeling change decision. The weight describes the degree to which each piece of evidence contributes to the regulatory decision. This weight is based on the quantity and quality of the studies. While multiple studies* that provide consistent evidence to answer a research question might be favorable, the study design must be of sufficient quality to carry weight in an evidence package.[8] For example, one high-quality randomized real-world study likely has more impact than multiple case studies. For RWE, study quality is contingent on the data's fitness for use and the ability of the methods to support valid causal inference.[9–12]

As previously mentioned, when evaluated through a totality of evidence approach, the weight of the new evidence depends on the relevancy of the prior evidence in addition to the clinical and regulatory contexts. The relevancy of the prior evidence, which might include the same patient populations, intended uses, and endpoints of interest, is determined by the regulatory research question. For example, prior evidence on a particular endpoint provides information on expected effect sizes in studies in new populations or for new uses of the drug. If the expected effect size is relatively large, more tolerance for "noise" in the new study might enable the use of different study designs. The weight of individual pieces of evidence can increase depending on the clinical context, such as instances with a high level of unmet need. The regulatory context can also affect the weight of evidence, such as a labeling change to include a new population that is highly similar to the population in which it was originally approved. If each piece of evidence is not weighted highly, additional studies are required to meet the threshold of substantial evidence.

Determining Product Effectiveness: Legislative and Regulatory History

An evidence package must meet "**substantial evidence**" to demonstrate product effectiveness.[13] According to the Federal Food, Drug, and Cosmetic Act, substantial evidence is "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly be concluded by such experts that **the drug will have the effect it purports** or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."[13] In the *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* Guidance, FDA interprets the statute to mean "that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness … Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing."[4] The regulations that define the characteristics of adequate and well-controlled studies are listed in Appendix F. Notably, in response to public comment on the regulation, FDA acknowledges that it "applies the regulation with judgment" and suggests that not every characteristic may be required for a study to be considered adequate and well-controlled.[14] In the *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* Guidance, FDA states that the adequate and well-controlled standard is intended to describe both "the quality of the required data" and the "quantum of required evidence."[4]

* There is precedent to support drug approval based on a single adequate and well-controlled trial or a single study supported by confirmatory evidence.

Figure 6 provides *hypothetical* examples of the types of studies that might generate new evidence for an original indication and effectiveness labeling change as well as various examples of weighting between new and prior evidence for an effectiveness labeling change. The area of each rectangle signifies the contribution weight of each piece of evidence.

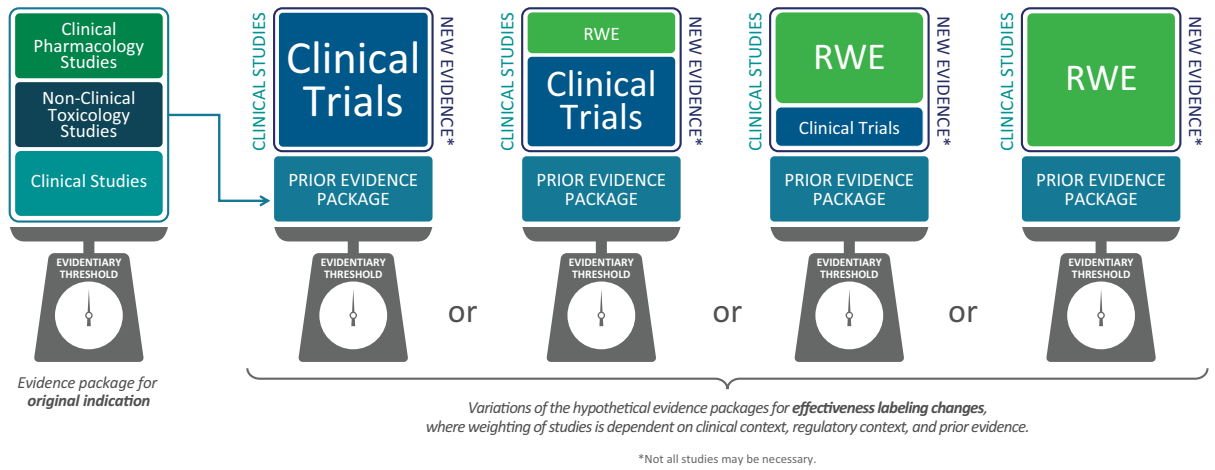

Figure 6. Hypothetical weighting of prior evidence and new evidence in various evidence packages evaluated through a totality of evidence approach for an original approval and an effectiveness labeling change. The size of the boxes corresponds to the relative amount of weight provided by each piece of evidence.

The first scale shows the types of studies that make up an evidence package for an original submission. When submitting new evidence for a labeling change, the evidence submitted to support the original indication becomes the prior evidence. As discussed previously, the new evidence typically consists of clinical studies. The second scale demonstrates a scenario in which the additional clinical studies are clinical trials in the form of RCTs. The third and fourth scales demonstrate the potential role of RWE studies in supporting an effectiveness claim by representing two hypothetical examples for the weight that the RWE studies, clinical trials, and prior evidence can contribute to the evidence package. The final scale demonstrates the potential for an evidence package that comprises prior evidence and new evidence, which consists of RWE only. The clinical and regulatory contexts are essential for determining which hypothetical weighting of evidence may be possible, given the unique complexity of each research question.

The use of RWE for labeling changes regarding effectiveness has been limited—examples include oncology, rare diseases, and diseases disproportionately affecting pediatric populations (Appendix C). This paper explores two examples of the use of RWE in case studies for effectiveness labeling changes: Ibrance® (Pfizer) and Invega Sustenna® (Janssen). The case studies can be found in Appendices G and H, respectively.

RWE can also be used in other diseases, including common or chronic diseases. To explore this potential and elucidate gaps for further research, hypothetical case studies have been developed: on a new indication for a Crohn's disease drug to include ulcerative colitis, and on the use of a patient-centered endpoint to assess a long-acting bronchodilator for treatment of chronic obstructive pulmonary disease

(COPD) (Appendices I and J, respectively). All evidence listed in the hypothetical case studies has been fabricated specifically for this paper.

Each case study takes a totality of evidence approach and considers the prior evidence and new evidence, with a focus on the RWE, evaluated in terms of the clinical and regulatory contexts. For these case studies, the regulatory context includes the labeling change and proximity to the original indication, and the clinical context includes understanding of the disease, treatment alternatives, therapy, patient perspective, and provider perspective. These case studies seek to demonstrate how the pieces of evidence, which each have differing weights, are evaluated through a totality of evidence approach to determine if the evidence package supports an effectiveness claim.

Opportunities to Improve Submissions with RWE for Regulatory Decision-Making on Product Effectiveness

As previously discussed, opportunities exist for RWE studies to contribute to an evidence package in conjunction with prior evidence and other clinical studies. Building a new evidence package for a labeling change that contains several RWE studies, among other studies as necessary, allows for the triangulation of the treatment effect and the creation of a robust, informative evidence package derived from RWD.

Still, challenges prevent widespread use of RWE for regulatory decision-making, including ambiguity around the process for submitting and evaluating RWE for regulatory purposes. To start tracking RWE submissions, FDA has developed draft guidance for consistent sponsor reporting on RWE-relevant information in submissions to facilitate a tracking system.[7] The role and acceptability of RWE in situations in which RCTs have traditionally been used for regulatory decision-making also requires further examination. This might include discussion around whether or not RWE provides adequate evidence to support a labeling change to address a specific research question. For instances when the RWE is deemed inadequate to answer a research question, guidance on why the RWE was inadequate, as well as the types of studies that can be conducted to strengthen the evidence package, might be beneficial. Further discussion around the circumstances in which an RCT might be required as part of an evidence package in addition to RWE to support regulatory decision-making is also important to consider. As more RWE studies are included in evidence packages, increased familiarity with RWE among reviewers might be necessary to fill knowledge gaps. Additionally, dedicated resources within FDA for evaluating RWE might be beneficial to help inform the RWE evaluation process, which can potentially be supported by a collaborative pilot project.

Multi-stakeholder efforts can further support inclusion of RWE in evidence packages for effectiveness labeling changes. Use of RWE to support labeling changes is reliant on the quality of the study design, data, and methods. To contribute to this effort, sponsors can continue to ensure that evidence packages contain high-quality study designs used in real-world settings. Researchers can continue to develop and refine high-quality methodological approaches to demonstrate the ability to draw valid causal inference in RWE studies. Data organizations should continuously improve data curation processes and provide transparent data quality metrics so sponsors and researchers can determine if the data are fit for use to answer a research question. Linkage to other data sources may be needed in order to have a more

comprehensive collection of the key data elements needed for the research question. To further assist in demonstrating quality or introducing the use of new methods or data sources, pilot projects can be implemented. Pilot projects provide opportunity to test innovative ideas to bring about incremental change. For example, a pilot project could be used to test the validity, reliability, and potential acceptability of a novel outcome measurement tool. While the implementation of pilot projects can involve less risk than a clinical trial or RWE study, opportunity also exists to investigate innovative ideas as part of a clinical trial. For example, the novel measurement tool could be included as part of an exploratory endpoint within a clinical trial to more accurately assess the associated scientific and operational considerations. Extending this logic, including innovative data sources, methods, and study design components within a clinical trial in the form of an exploratory or secondary endpoint might be useful for assessing the acceptability within a regulatory submission and potentially lead to inclusion as part of a primary endpoint in a future study.

Clinical context plays a pivotal role in approvals and labeling changes for medical products. However, further elucidation on the types and quantity of clinical information that is most relevant for effectiveness labeling changes is necessary to understand how best to leverage RWE and the additional studies required to support submissions. With an increased quantity of RWE available for use, researchers will need to determine the RWE that is most relevant to include, raising questions in regard to the evidence not included. Standardized criteria for evaluating what evidence is and is not included is necessary.

Conclusion

RWE has great potential to contribute valuable information to the evidence package for an effectiveness labeling change through a totality of evidence approach. For a marketed product to be determined effective for a new indication or population, the evidence, in totality, must be substantial. A totality of evidence approach considers the full evidence package as well as the clinical and regulatory contexts. The evidence package may contain prior evidence from RCTs and new evidence generated by additional clinical studies, which can include RCTs and RWE studies or potentially RWE studies only. Additional clinical pharmacology and non-clinical toxicology studies might also contribute to the new evidence package.

Traditionally, two adequate and well-controlled RCTs have been considered the gold-standard for an evidence package to support an effectiveness claim. However, an evidence package can consist of clinical studies other than RCTs and still support an effectiveness claim when evaluated in the context of the additional evidence and research question. A totality of evidence approach demonstrates the opportunity to leverage RWD to generate RWE that is informative for not only regulators but also patients, providers, and payers.

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