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

December 19, 2019
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About the Duke-Margolis Center for Health Policy

The Robert J. Margolis, MD, Center for Health Policy at Duke University is directed by Mark McClellan, MD, PhD, and brings together expertise from the Washington, DC, policy community, Duke University, and Duke Health to address the most pressing issues in health policy. The mission of Duke-Margolis is to improve health and the value of health care through practical, innovative, and evidence-based policy solutions. Duke-Margolis catalyzes Duke University's leading capabilities, including interdisciplinary academic research and capacity for education and engagement, to inform policy making and implementation for better health and health care. For more information, visit healthpolicy.duke.edu.

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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. 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. 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.” This paper focuses on the second prong of the Framework.

High-quality RWD and RWE can be used in different ways to support regulatory decisions related to both safety and effectiveness of medical products. For example, FDA uses RWD and RWE to investigate the safety of medical products in the postmarket setting through the Sentinel Initiative. 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. 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.

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.

* 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.”

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.”

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.

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).* 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.

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* 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.
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. 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). Clinical studies can have interventional or non-interventional treatment assignment and can include primary or secondary data. 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.

* 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”

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.

Clinical Context

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

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

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

* 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.

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. 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
A 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.
APPENDIX A. WORKSHOP PARTICIPANTS

Improving RWE Study Credibility and its Role in Totality of Evidence
Duke-Robert J. Margolis, MD, Center for Health Policy
1201 Pennsylvania Ave, NW, Suite 500 • Washington, DC 20004
June 20, 2019

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APPENDIX B. PREVIOUS DUKE-MARGOLIS WORK ON RWD AND RWE

A Framework for Regulatory Use of Real-World Evidence
September 15, 2017

Characterizing RWD Quality and Relevancy for Regulatory Purposes
October 1, 2018

Determining Real-World Data’s Fitness for Use and the Role of Reliability
September 26, 2016

Understanding the Need for Non-Interventional Studies Using Secondary Data to Generate Real-World Evidence for Regulatory Decision Making, and Demonstrating Their Credibility
November 26, 2019

Adding Real-World Evidence to a Totality of Evidence Approach for Evaluating Marketed Product Effectiveness
December 20, 2019

Provides a framework for regulatory use of RWD, outlining considerations and high-priority opportunities to improve such development and use.

Provides an overview of the data curation process and identifies potential challenges for regulators in assessing the underlying appropriateness of the RWD source for the given regulatory question of interest.

Examines the key components of RWD fitness for use considerations and identifies principles for developing a minimum set of reliability checks.

Provides guidance on when conducting non-interventional RWE studies may not be possible and how to demonstrate credibility in the causal inference made by non-interventional studies using secondary data (observational studies).

Explores how RWE studies can support regulatory decision-making based on a totality of evidence approach.
## APPENDIX C. EXAMPLES OF DRUG APPROVALS AND LABELING CHANGES USING EVIDENCE GENERATED FROM NON-TRADITIONAL STUDY DESIGNS

### Table C1. RWE studies

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>SPONSOR</th>
<th>DISEASE</th>
<th>STUDY DESIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bavencio® (avelumab)</td>
<td>Pfizer and Merck KGaA</td>
<td>Metastatic merkel cell carcinoma</td>
<td>1. Open-label single-arm multicenter trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. RWE-generated historical control as benchmark</td>
</tr>
<tr>
<td>Blincyto® (blinatumomab)</td>
<td>Amgen</td>
<td>B-cell precursor acute lymphoblastic leukemia</td>
<td>1. Open-label single-arm multicenter trial</td>
</tr>
<tr>
<td>Brineura® (cerliponase alfa)</td>
<td>Biomarin</td>
<td>Infantile batten disease</td>
<td>1. Non-randomized single-arm dose-escalation study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Non-randomized comparison with natural history cohort</td>
</tr>
<tr>
<td>Carbaglu® (carglumic acid)</td>
<td>Recordati Rare Diseases Inc.</td>
<td>Hyperammonemia</td>
<td>Retrospective unblinded uncontrolled case series</td>
</tr>
<tr>
<td>Cordarone® (amiodarone hydrochloride) tablets</td>
<td>Sanofi</td>
<td>Arrhythmia</td>
<td>Retrospective open-label self-controlled study</td>
</tr>
<tr>
<td>Ibrance® (palbociclib)</td>
<td>Pfizer</td>
<td>Male breast cancer</td>
<td>Retrospective cohort study using EHR data, insurance billing data, and postmarketing studies</td>
</tr>
<tr>
<td>Intravenous ganciclovir</td>
<td>Exela Pharma Sciences</td>
<td>Acquired immunodeficiency virus syndrome (AIDS) and cytomegalovirus (CMV) retinitis</td>
<td>Retrospective non-randomized study</td>
</tr>
<tr>
<td>Luthathera® (lutetium Lu 177 dotatate)</td>
<td>Advanced Accelerator Applications, a Novartis company</td>
<td>Somatostatin receptor (SSTR) positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs)</td>
<td>1. Randomized open-label, active-controlled multicenter trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Retrospective study</td>
</tr>
<tr>
<td>Omegaven® (fish oil triglycerides)</td>
<td>Fresenius Kabi</td>
<td>Parenteral nutrition-associated cholestasis</td>
<td>1. Open-label single-center trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Open-label single-center trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Historical control</td>
</tr>
<tr>
<td>Tepadina® (thiotepa)</td>
<td>Adienne SA</td>
<td>Pediatric class 3 beta-thalassemia</td>
<td>Retrospective observational trial</td>
</tr>
<tr>
<td>Yescarta® (axicabtagene ciloleucel)</td>
<td>Kite, a Gilead company</td>
<td>Diffuse large B-cell lymphoma</td>
<td>1. Open-label single-arm multicenter trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Retrospective analysis of patients receiving standard of care as benchmark</td>
</tr>
<tr>
<td>Zostavax® (zoster vaccine live)</td>
<td>Merck</td>
<td>Herpes zoster (shingles)</td>
<td>1. Randomized double-blind placebo-controlled trial (ages 50–59)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Randomized double-blind placebo-controlled trial (age &gt;60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Prospective observational cohort study</td>
</tr>
</tbody>
</table>
Table C1. RWE studies (continued)

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>SPONSOR</th>
<th>DISEASE</th>
<th>STUDY DESIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savaysa® (edoxaban)</td>
<td>Daiichi Sankyo, Inc.</td>
<td>Atrial fibrillation</td>
<td>Randomized double-blind multinational non-inferiority study</td>
</tr>
<tr>
<td>Invega Sustenna® (paliperidone palmitate)</td>
<td>Janssen</td>
<td>Schizophrenia, schizoaffective disorder</td>
<td>Prospective randomized open-label active-controlled parallel-group trial</td>
</tr>
<tr>
<td>Inactivated polio vaccine</td>
<td>National Foundation for Infantile Paralysis (March of Dimes)</td>
<td>Polio</td>
<td>Randomized blinded placebo-controlled trial with additional observed controls</td>
</tr>
</tbody>
</table>

Table C2. Approvals based on <2 adequate and well-controlled studies

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>SPONSOR</th>
<th>DISEASE</th>
<th>STUDY DESIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altace® (ramapril)</td>
<td>King Pharmaceuticals, Inc.</td>
<td>Hypertension, heart failure</td>
<td>Randomized double-blind placebo-controlled multinational trial</td>
</tr>
<tr>
<td>Capoten® (captopril)</td>
<td>Bristol Myers Squibb</td>
<td>Hypertension, heart failure</td>
<td>Randomized double-blind placebo-controlled trial</td>
</tr>
</tbody>
</table>
| Darzalex® (daratumumab) | Janssen | Multiple myeloma | 1. Open-label single-arm trial (phase II)  
2. Open-label dose expansion dose-escalation trial |
| Keytruda® (pembrolizumab) | Merck | Metastatic melanoma | Randomized open-label dose-ranging multicenter cohort from a randomized open-label dose-finding activity-estimating safety and tolerability trial |
| Mavik® (trandolopril) | Roussel–Uclaf and Knoll Pharmaceuticals | Hypertension, heart failure | Randomized double-blind placebo-controlled trial |
| Vasotec® (enalapril) | Merck | Hypertension, heart failure | Randomized double-blind placebo-controlled trial |
| Zestril® (lisinopril) | Zeneca Pharmaceutical | Hypertension, heart failure | Randomized controlled multicenter open trial |
| Zykadia® (ceritinib) | Novartis | Metastatic non-small cell lung cancer | Open-label single-arm multicenter trial |
**APPENDIX D. STUDY DESIGN EXAMPLES**

Table D1. Examples of interventional study designs that historically have contributed to evidence packages for labeling changes

<table>
<thead>
<tr>
<th>STUDY DESIGN</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-arm</td>
<td>All trial participants received the experimental treatment(^{64})</td>
</tr>
<tr>
<td>Open-label</td>
<td>Trial participant and researcher knew which treatment was assigned to the participant(^{65})</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>A statistical analysis of combined results from multiple studies(^{66})</td>
</tr>
</tbody>
</table>
Understanding of the Disease
Understanding of the disease includes disease biology characteristics for the specific patient population that will be studied, among other factors.

Treatment Alternatives
Identifying challenges with current treatment alternatives and their status, inclusive of the effectiveness and safety profile, and opportunities for the new therapy to address these challenges may determine the degree of unmet need and value of studying the new therapy. When alternative therapies exist, considering if there is clinical equipoise, a requirement for conducting interventional studies, is important.

*Unmet need:* A condition in which the available therapies do not sufficiently address the diagnosis or treatment or when an available therapy does not exist. Unmet need can refer to an immediate need to treat a specific condition or population or a long-term societal need.67

Understanding of the Therapy
To compare the new therapy to existing treatment alternatives or to address an unmet need, a clear understanding of the intended therapeutic effect on the population of interest is necessary. The interplay between the therapy and the disease provides information on the impact on patients and likelihood of treatment success, including not only safety and effectiveness but also quality-of-life considerations.

Patient Perspective
Considering the patient’s perspective is necessary because therapies can affect patients in unique ways. Considering outcomes, preferences, and treatment estimates that are most important among sub-populations is especially important for diseases that impact broad patient populations. Furthermore, different populations may be studied in RCTs compared to RWE studies, thereby potentially affecting the generalizability.

Provider Perspective
Because a provider will likely determine which drug to prescribe to each patient, provider perspective, including behavior and approach to clinical care, can also have a significant impact on the RWE study.
Subpart D — FDA Action on Applications and Abbreviated Applications

Sec. 314.126 Adequate and well-controlled studies.

(a) The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. The characteristics described in paragraph (b) of this section have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation. The Food and Drug Administration considers these characteristics in determining whether an investigation is adequate and well-controlled for purposes of section 505 of the act. Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is “substantial evidence” to support the claims of effectiveness for new drugs. Therefore, the study report should provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present.

(b) An adequate and well-controlled study has the following characteristics:

(1) There is a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results. In addition, the protocol should contain a description of the proposed methods of analysis, and the study report should contain a description of the methods of analysis ultimately used. If the protocol does not contain a description of the proposed methods of analysis, the study report should describe how the methods used were selected.

(2) The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. The protocol for the study and report of results should describe the study design precisely; for example, duration of treatment periods, whether treatments are parallel, sequential, or crossover, and whether the sample size is predetermined or based upon some interim analysis. Generally, the following types of control are recognized:

(i) Placebo concurrent control. The test drug is compared with an inactive preparation designed to resemble the test drug as far as possible. A placebo-controlled study may include additional treatment groups, such as an active treatment control or a dose-comparison control, and usually includes randomization and blinding of patients or investigators, or both.
(ii) Dose-comparison concurrent control. At least two doses of the drug are compared. A dose-comparison study may include additional treatment groups, such as placebo control or active control. Dose-comparison trials usually include randomization and blinding of patients or investigators, or both.

(iii) No treatment concurrent control. Where objective measurements of effectiveness are available and placebo effect is negligible, the test drug is compared with no treatment. No treatment concurrent control trials usually include randomization.

(iv) Active treatment concurrent control. The test drug is compared with known effective therapy; for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient. An active treatment study may include additional treatment groups, however, such as a placebo control or a dose-comparison control. Active treatment trials usually include randomization and blinding of patients or investigators, or both. If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

(v) Historical control. The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

(3) The method of selection of subjects provides adequate assurance that they have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed.

(4) The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease, and use of drugs or therapy other than the test drug. The protocol for the study and the report of its results should describe how subjects were assigned to groups. Ordinarily, in a concurrently controlled study, assignment is by randomization, with or without stratification.

(5) Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data. The protocol and report of the study should describe the procedures used to accomplish this, such as blinding.
(6) The methods of assessment of subjects’ response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response.

(7) There is an analysis of the results of the study adequate to assess the effects of the drug. The report of the study should describe the results and the analytic methods used to evaluate them, including any appropriate statistical methods. The analysis should assess, among other things, the comparability of test and control groups with respect to pertinent variables, and the effects of any interim data analyses performed.

(c) The Director of the Center for Drug Evaluation and Research may, on the Director’s own initiative or on the petition of an interested person, waive in whole or in part any of the criteria in paragraph (b) of this section with respect to a specific clinical investigation, either prior to the investigation or in the evaluation of a completed study. A petition for a waiver is required to set forth clearly and concisely the specific criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been employed, and what results have been obtained. The petition is also required to state why the clinical investigations so conducted will yield, or have yielded, substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(d) For an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(e) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

DISCLAIMER: The following evaluation of the Ibrance® approval process is an interpretation of the evidence conducted by this Center. This interpretation does not represent the opinions of the sponsors, manufacturers, or any third parties involved in the regulatory submission, nor does it represent the opinions of the FDA.

Ibrance® (Pfizer)

Regulatory Context
In 2019, Ibrance® (palbociclib) was approved to treat HR+ and HER2- advanced or metastatic breast cancer (BC) in combination with an aromatase inhibitor as an initial endocrine-based therapy in postmenopausal women or men, or with fulvestrant in patients with disease progression following endocrine therapy.29,30 Previously approved for women only (Figure G1), this labeling change for Ibrance® included men as a new population.

Clinical Context

Disease Background
Male breast cancer is extremely rare. Only 2,670 new cases of invasive breast cancer and 500 deaths from metastatic breast cancer in men are expected in 2019.69 Because the condition is so rare, a randomized trial is likely not possible, increasing the need to rely on RWE. Preclinical studies determined that the biology of the disease is similar in men and women; therefore, the proximity to the original indication was close. Additional clinical context information can be found in Table G1.
Current Therapies and Level of Unmet Need

There is a high unmet need for additional research on therapies for treating breast cancer in men. Because male breast cancer is rare (consisting of 1% of breast cancer cases), the majority of breast cancer research is performed in women. Additionally, few therapies are approved for men with breast cancer, leading to off-label prescribing of products approved for women and potentially contributing to treatment access issues. While the National Comprehensive Cancer Network (NCCN) Compendium generally recommends that male breast cancer patients receive the same treatments as female breast cancer patients, it also lists specific recommendations for male patients in terms of genetic counseling and surgical interventions highlighting differences in treatment considerations between men and women.70

Proposed Therapy

The therapy is an oral inhibitor of cyclin-dependent kinases (CDKs) 4 and 6. CDKs 4 and 6 are regulators of the cell cycle that trigger tumor cell progression.31,71

Patient and Provider Perspectives

Because breast cancer often affects women, men with breast cancer often face stigma from having a disease that may be perceived as a woman’s disease.72 Some men with breast cancer feel as if they are infiltrating women’s spaces. These men do not feel like part of the breast cancer community at clinics and rehabilitation centers, which can contribute to reduced access.72 Some clinics with gynecologists who treat breast cancer will not take male patients due to anticipated billing issues.72 The stigma surrounding breast cancer might also lead to the provider assuming that the patient is a woman, which can contribute to feelings of isolation in male breast cancer patients.72 Perceptions of the disease might also make providers less likely to diagnose breast cancer in men because it is so rare.

Evidence

Prior Evidence

This approval was based on prior evidence, including two randomized pivotal trials across the PALOMA program as well as additional evidence, including clinical pharmacology and non-clinical toxicology studies to support the biological plausibility.29 Additional information about the clinical trials can be found in Table G2.

New Evidence: Strengths and Limitations

New evidence to support this labeling change was obtained from postmarketing safety report data, insurance billing data, and electronic health record (EHR) data, and demonstrated clinical benefit for use in men.73 Additionally, the safety profile for use of ibrance® in men was found to be consistent with the safety profile for its use in women.74 Additional information about the studies can be found in Table G2.

*Compendia, resources to guide use of a drug after it has been prescribed off label, contain recommendations for the treatment of oncology patients.
Regulatory Decision

The labeling change to include men as a new population was largely based on prior evidence generated from the PALOMA trials and was supported by the RWE studies. In the approval package for Ibrance®, FDA states, “The effectiveness of palbociclib is expected to be the same in both women and men based on the mechanism of action for palbociclib. Given the extensive established efficacy and safety of the use of palbociclib in women observed in randomized clinical trials, the additional EHR data provided in this application for the use in men, modest as it is, does support the expansion of the palbociclib indication to provide for the treatment of men with metastatic breast cancer.”

This supplemental application was novel in that all new evidence included was from RWD sources.

Table G1. Clinical context for Ibrance® approval in males

<table>
<thead>
<tr>
<th>DISEASE59</th>
<th>TREATMENT ALTERNATIVES</th>
<th>THERAPY</th>
<th>PATIENT PERSPECTIVE72</th>
<th>PROVIDER PERSPECTIVE72</th>
</tr>
</thead>
</table>
| • Biologically similar in men and women  
  • Expected new cases in 2019: 2,670  
  • Expected deaths in 2019: 500 | Limited treatment options | Oral inhibitor of CDKs 4 and 661,71 | • Unmet need  
  • Stigma  
  • Access to care | • Stigma  
  • Perception of disease |

Table G2. Prior evidence and RWE for Ibrance® approval in males

<table>
<thead>
<tr>
<th>PRIOR EVIDENCE59</th>
<th>RWE72</th>
</tr>
</thead>
</table>
| • PALOMA-2 RCT  
  – Study design: randomized double-blind parallel-group multicenter trial  
  – Population: postmenopausal women with ER+, HER2- advanced or metastatic breast cancer  
  – Intervention: Ibrance® in combination with letrozole versus a placebo with letrozole  
  – Primary outcome: investigator-assessed progression-free survival evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) | • Postmarketing reports, insurance billing data, and EHR data sourced from:  
  – IQVIA insurance database  
  – Flatiron Health breast cancer database  
  – Pfizer global safety database |
| • PALOMA-3 RCT  
  – Study design: randomized double-blind parallel-group multicenter trial  
  – Population: women with HR+, HER2- advanced or metastatic breast cancer with disease progression after previous endocrine therapy  
  – Intervention: Ibrance® in combination with fulvestrant versus placebo in combination with fulvestrant  
  – Primary outcome: progression-free survival evaluated according to RECIST |  
  • Clinical pharmacology studies  
  • Non-clinical toxicology studies |
DISCLAIMER: The following evaluation of the Invega Sustenna® approval process is an interpretation of the evidence conducted by this Center. This interpretation does not represent the opinions of the sponsors, manufacturers, or any third parties involved in the regulatory submission, nor does it represent the opinions of the FDA.

**Invega Sustenna® (Janssen)**

**Regulatory Context**

Invega Sustenna® (paliperidone palmitate) was approved first as an oral tablet, then as a long-acting injectable (LAI) antipsychotic (Figure H1).* In 2018, Invega Sustenna® was approved for a labeling change to include information comparing a long-term monotherapy treatment versus an oral antipsychotic therapy. Specifically, Invega Sustenna® was studied in a broader population including adults with schizophrenia who had recent incarcerations and largely included adults with substance abuse issues. Traditionally, these populations are not included in clinical trials, even though they represent a significant number of schizophrenia patients. This trial sought to increase relevancy by including a more representative population and using a real-world assessment of benefit, particularly given the challenges with adherence to treatment in these populations.

*Invega Sustenna® is indicated to treat both schizophrenia and schizoaffective disorder. It is the only once-monthly monotherapy LAI approved for schizoaffective disorder.*

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*Duke-Margolis Center for Health Policy | HealthPolicy.Duke.edu*
Clinical Context

Disease Background

Schizophrenia prevalence is approximately equal in men and women and occurs in about 1.1% of people in the United States.\textsuperscript{49,75} True prevalence of schizophrenia can be difficult to determine due to misdiagnosis and conflation with other mental disorders. DSM-5 characterizes schizophrenia as a spectrum with presence of two or more of the following symptoms within a month: delusions, hallucinations, disorganized speech (such as frequent derailment or incoherence), grossly disorganized or catatonic behavior, and negative symptoms (diminished emotional expression or avolition).\textsuperscript{76} For diagnosis, at least one of the symptoms exhibited must be delusions, hallucinations, or disorganized speech.

Schizoaffective disorder consists of an uninterrupted period of illness of schizophrenia symptoms in conjunction with a major depressive or manic mood episode.\textsuperscript{76} Diagnosis of schizophrenia and schizoaffective disorder are also evaluated in terms of additional criteria, outlined in DSM-5. Additional clinical context information can be found in Table H1.

Current Therapies and Level of Unmet Need

Pharmaceutical treatment options for people with schizophrenia include first- and second-generation antipsychotics, clozapine, mood stabilizers, combination therapies, and LAIs.\textsuperscript{75}

Proposed Therapy

Paliperidone palmitate hydrolyzes over time to paliperidone, which is a centrally active antagonist of the dopamine type 2 receptors and serotonin type 2 receptors.\textsuperscript{50}

Patient and Provider Perspectives

Provider perspective can often overshadow patient perspective in this case, with treatment decisions made without patient or caregiver input 67% of the time.\textsuperscript{77} Patients with less severe mental impairment are more likely to be a part of treatment decisions, and some providers emphasized that patients should have treatment autonomy.\textsuperscript{77} The most common reason for accepting an LAI antipsychotic was a benefit to adherence, which can include the convenience of taking the medication once or a few times per month rather than daily. Patients refused LAIs due to fear of needles, a lack of understanding of the disease or treatment option, the requirement that the drug be received at a site, and the lack of a guarantee of effectiveness of the drug. If a patient was resistant to trying an LAI, some providers ceased discussion in order to preserve the relationship with the patient or for fear of coercing the patient into trying a particular treatment. Providers expressed concerns over the side effects of LAIs and that patients cannot be immediately taken off the therapy if they experience a negative reaction. Providers recognized the adherence benefits associated with prescribing LAIs rather than oral antipsychotics, as adherence is a predictor of recovery for schizophrenia patients.\textsuperscript{77,78}
Evidence

Prior Evidence

Prior evidence was based on four short-term RCTs in patients with schizophrenia and one long-term, double-blind, placebo-controlled randomized withdrawal trial in patients with schizoaffective disorder. Additional information about the clinical trials can be found in Table H2.

New Evidence: Strengths and Limitations

New evidence consisted of the Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) trial, a randomized pragmatic trial in people with schizophrenia with recent incarceration. To increase this study’s pragmatism, researchers recruited non-traditional trial patients from homeless shelters, soup kitchens, jail-release programs, and jail-diversion programs. In this study, patients were randomized to a flexibly dosed monthly injection of Invega Sustenna® or a flexibly dosed oral antipsychotic. Researchers found that Invega Sustenna® delayed treatment failure when compared to oral antipsychotics. Additional information about the studies can be found in Table H2.

Regulatory Decision

The labeling change provided real-world clinical context about a broader population in the clinical studies section of the label. This population would not have been feasible to study in an RCT. Through a totality of evidence approach, the RWE study contributed evidence that a once-monthly LAI monotherapy was effective compared to a daily oral antipsychotic among schizophrenia patients with a broad inclusion criteria.

Table H1. Clinical context for including new evidence in the clinical studies section of the label for Invega Sustenna®

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>TREATMENT ALTERNATIVES</th>
<th>THERAPY</th>
<th>PATIENT PERSPECTIVE</th>
<th>PROVIDER PERSPECTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Equally prevalent in men and women</td>
<td>• First-generation antipsychotics</td>
<td>• Paliperidone is a centrally active dopamine type 2 receptor antagonist and serotonin type 2 receptor antagonist</td>
<td>• Autonomy</td>
<td>• Benefits to adherence</td>
</tr>
<tr>
<td>• 1.1% prevalence in U.S.</td>
<td>• Second-generation antipsychotics</td>
<td></td>
<td>• Convenience of treatment</td>
<td>• Fear of coercion</td>
</tr>
<tr>
<td></td>
<td>• Clozapine</td>
<td></td>
<td>• Fear of injections</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Combination therapy</td>
<td></td>
<td>• Lack of understanding about disease or therapy</td>
<td>• Maintaining relationship with patient</td>
</tr>
<tr>
<td></td>
<td>• LAI antipsychotic agents</td>
<td></td>
<td></td>
<td>• Patient autonomy</td>
</tr>
</tbody>
</table>
Table H2. Prior evidence and RWE for including new evidence in the clinical studies section of the label for Invega Sustenna®

<table>
<thead>
<tr>
<th>PRIOR EVIDENCE</th>
<th>RWE⁴⁹,⁵⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Three short-term (13-week) RCTs (schizophrenia)</td>
<td>• PRIDE</td>
</tr>
<tr>
<td>– Study design: randomized double-blind placebo-controlled fixed-dose trial</td>
<td>– Study design: randomized prospective open-label event-monitoring board-blinded parallel-group study</td>
</tr>
<tr>
<td>– Population: acutely relapsed adult inpatients who meet DSM-IV criteria for schizophrenia</td>
<td>Screening phase of ≤2 weeks</td>
</tr>
<tr>
<td>– Primary outcome: change of positive and negative symptoms of schizophrenia and general psychopathology measured by the Positive and Negative Syndrome Scale (PANSS)</td>
<td>15-month randomized open-label treatment phase</td>
</tr>
<tr>
<td>– Intervention</td>
<td>– Population: adults aged 18–65 with DSM-IV schizophrenia, confirmed by Mini-International Neuropsychiatric Interview version 6</td>
</tr>
<tr>
<td></td>
<td>Taken into custody</td>
</tr>
<tr>
<td></td>
<td>≥2 times within 2 years</td>
</tr>
<tr>
<td></td>
<td>≥1 incarceration within 2 years</td>
</tr>
<tr>
<td></td>
<td>Release from custody within 90 days of screening</td>
</tr>
<tr>
<td>PSY-3007: comparing initial deltoid injection of 234 mg and 3 fixed doses (39 mg/4 wk, 156 mg/4 wk, 234 mg/4 wk) of Invega Sustenna® to placebo</td>
<td>– Intervention: comparing Invega Sustenna® (paliperidone palmitate) with oral antipsychotics (aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, and risperidone)</td>
</tr>
<tr>
<td>PSY-3003: comparing 3 fixed doses (78 mg/4 wk, 156 mg/4 wk, 234 mg/4 wk) of Invega Sustenna® to placebo</td>
<td>– Primary outcome: time to treatment failure</td>
</tr>
<tr>
<td>PSY-3004: comparing 3 fixed doses (39 mg/4 wk, 78 mg/4 wk, 156 mg/4 wk) of Invega Sustenna® to placebo</td>
<td></td>
</tr>
<tr>
<td>• SCH-201</td>
<td></td>
</tr>
<tr>
<td>– Study design: short-term (9-week) double-blind randomized placebo-controlled fixed-dose trial</td>
<td></td>
</tr>
<tr>
<td>– Population: acutely relapsed adult inpatients who meet DSM-IV criteria for schizophrenia</td>
<td></td>
</tr>
<tr>
<td>– Intervention: comparing 2 fixed doses (78 mg/4 wk and 156 mg/4 wk) of Invega Sustenna® to placebo</td>
<td></td>
</tr>
<tr>
<td>– Primary outcome: change of positive and negative symptoms of schizophrenia and general psychopathology measured by PANSS</td>
<td></td>
</tr>
<tr>
<td>• PSY-3001</td>
<td></td>
</tr>
<tr>
<td>– Study design: long-term double-blind placebo-controlled flexible-dose study</td>
<td></td>
</tr>
<tr>
<td>– Population: adults who met DSM-IV criteria for schizophrenia</td>
<td></td>
</tr>
<tr>
<td>– Intervention: randomized to same dose of Invega Sustenna® as stabilization phase (39 mg/4 wk, 78 mg/4 wk, or 156 mg/4 wk) or placebo until relapse</td>
<td></td>
</tr>
<tr>
<td>– Primary outcome: time to relapse</td>
<td></td>
</tr>
<tr>
<td>• SCA-3004</td>
<td></td>
</tr>
<tr>
<td>– Study design: long-term double-blind placebo-controlled flexible-dose randomized-withdrawal trial</td>
<td></td>
</tr>
<tr>
<td>– Population: adults who met DSM-IV criteria for schizoaffective disorder, confirmed by structured clinical interview for DSM-IV disorders</td>
<td></td>
</tr>
<tr>
<td>– Intervention: comparing Invega Sustenna® (78 mg, 117 mg, 156 mg, 234 mg) to placebo</td>
<td></td>
</tr>
<tr>
<td>– Primary outcome: time to relapse</td>
<td></td>
</tr>
<tr>
<td>• Clinical pharmacology studies</td>
<td></td>
</tr>
<tr>
<td>• Non-clinical toxicology studies</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX I. HYPOTHETICAL CASE STUDY: BIOLOGIC APPROVED FOR CROHN’S DISEASE

DISCLAIMER: This hypothetical case study is not intended to be used as a regulatory or evidence-generation strategy to support effectiveness claims. Rather, the intent is to foster a discussion on the potential of RWE. To evaluate the ability of RWE to contribute to the evidence package, as evaluated through a totality of evidence approach, some questions have been developed for readers’ consideration.

Questions for Consideration

1. Can RWE be used to adequately answer the research question informing the labeling change?
   a. If yes, why?
   b. If not, why not?
2. Under what conditions, if any, might an RCT be required as part of a new evidence package for these case studies?
3. What additional studies may strengthen the new evidence package?

Regulatory Context

Consider a hypothetical biologic (IBDBIO2) currently approved for inducing and maintaining remission in adult patients with moderately to severely active Crohn’s disease (CD). The sponsor is seeking a labeling change to add a new indication, inducing and maintaining remission in adult patients with moderately to severely active ulcerative colitis (UC).

Clinical Context

Disease Background

UC and CD are both autoimmune diseases and types of inflammatory bowel disease that significantly impact quality of life.\(^8^0\) UC affects only the large intestine, or colon, whereas CD affects any part of the gastrointestinal tract. UC manifests in recurring colon mucosal layer inflammation.\(^8^0\) CD and UC affect men and women equally (Table I). The prevalence of UC and CD is varied; however, one estimate indicates that UC and CD prevalence increased between 2000 and 2011 from 214 to 286 cases per 100,000 persons for UC and from 174 to 247 cases per 100,000 persons for CD.\(^8^1\)

CD and UC share similar symptoms, with about 10% to 15% overlap. While typical phenotypes differ for UC and CD, most biologics are effective in treating both diseases. Additionally, C-reactive protein (CRP) levels correlate with response in UC and CD patients, although no gold-standard biomarker exists. Additional clinical context information can be found in Table I.\(^1\)
**Current Therapies and Level of Unmet Need**

Tumor necrosis factor (TNF) inhibitors, or anti-TNFs, are a typical monoclonal antibody (MAB) treatment option for patients with moderately to severely active UC. However, patients can suffer from primary non-response (PNR), in which the patient never responds to treatment after induction. The incidence of PNR ranges from 10%–30%. Patients can also suffer from secondary loss of response (LOR), in which the patient responds to treatment after induction but stops responding to treatment at a later time. The incidence of LOR is difficult to determine, as it varies depending on whether it is measured in terms of dose intensification or drug discontinuation. PNR and LOR are managed by intensifying the dose, adding immunomodulators, or switching to a therapy in a different class. If patients repeatedly suffer from PNR or LOR, the existing therapies can be exhausted. Surgical bowel removal is the last resort. Anti-TNFs can also be associated with a small increased risk of lymphoma, especially when the biologic is combined with another immunosuppressant.

Other MABs indicated to treat moderately to severely active UC include anti-α4 integrin antibodies, such as vedolizumab, and anti-interleukin 12/23 antibodies, such as ustekinumab. For some anti-α4 integrins, there is an increased risk of developing progressive multifocal leukoencephalopathy (PML), a severe neurological condition that can occur during severe immunosuppression. Vedolizumab may be beneficial for patients with weakened immune systems as it does not typically lead to increased infection or malignancy. Ustekinumab may be beneficial for patients who have experienced PNR or LOR to anti-TNFs or as a first-line biologic due to failure to respond to other therapies.

**Proposed Therapy**

IBDBIO2 is a MAB with a different mechanism of action than the biologics used to treat UC currently on the market. Unlike some other biologics approved for treatment of CD and UC, IBDBIO2 does not increase the risk of developing PML.

**Patient and Provider Perspectives**

UC patients have reported a desire for treatments that allow them to perform daily activities and manage their pain. However, patients and providers have varying treatment goals. For example, a treatment goal for a physician may be reduction in inflammation, whereas a patient’s treatment goal may be more focused on quality of life (such as less time spent in the bathroom per day). Additionally, patients have reported concerns that providers do not recognize the effect of UC on mental health.

Physicians consider biologics as a last resort pharmaceutical treatment for UC due to fear of side effects, such as increased risk of infection and malignancies, but may prescribe a biologic if it is believed to significantly improve quality of life and lead to remission. Patients also might believe that biologics should be reserved for a higher severity form of UC than their current stage.
Evidence

Prior Evidence

Prior evidence consisted of clinical pharmacology, non-clinical toxicology studies, and phase II/phase III clinical trial data for CD, where the co-primary outcomes, remission and mucosal healing, were measured using the Crohn’s Disease Activity Index (CDAI) scores and the Crohn’s Disease Endoscopic Index of Severity (CDEIS) scale, respectively. Additional information about the studies can be found in Table I2.

New Evidence: Strengths and Limitations

New evidence consisting of pharmacokinetic (PK) data suggests consistency between CD and UC, motivating the exploration of IBDBIO2 for UC. First, a patient registry established from a network of practices with UC patients was created to support secondary use of the data for research purposes. EHR linkage and electronic case report forms, in addition to some patient surveys, were also available. UC diagnosis was determined in part through the Partial Mayo Score, which is used in both clinical trials and clinical practice to assess disease activity and severity. The Partial Mayo Score was collected fairly regularly, though some data were missing and time points varied due to real-world appointments. Endoscopy data were present, but limited, as is typical in clinical practice. The analysis showed that most UC patients who experienced PNR and LOR with previous treatments had positive response when using IBDBIO2. Outcomes were not available for all patients, but sensitivity analyses suggest consistent evidence for effectiveness: response and remission rates (including steroid-free remission) were comparable to pivotal trials of approved UC therapies. IBDBIO2 showed an acceptable safety profile that was comparable to pivotal UC trials and existing UC RWE studies.

Subsequently, an adequately powered, prespecified large-scale pragmatic trial was also conducted in UC patients, where patients were randomized to either IBDBIO2 or a standard of care treatment for UC to measure the comparative effectiveness of IBDBIO2. The primary outcome included colectomy surgery in the inpatient setting. The pragmatic trial showed significant benefit in tolerability of treatment and consistent effectiveness compared to standard of care therapies. Additional information about the studies can be found in Table I2.

Regulatory Decision

In determining whether IBDBIO2 should receive a labeling change to include UC patients, the regulatory decision would likely rely highly on the disease biology and clinical context, because effective alternative treatments are more limited. Due to heterogeneity in the UC population, the consistency in effectiveness and the safety profile in UC patients would also be an important consideration.

* To calculate CDAI scores, physicians collect information directly from patients on 8 items: patient-reported stool pattern, antidiarrheal use, average abdominal pain over 7 days, general well-being over 7 days, complications, finding of an abdominal mass, anemia, and weight change. Physicians then multiply each item by the weighting score. CDAI scores are used to determine the severity of CD activity, with scores of 150 or below suggesting remission.

† The Partial Mayo Score includes all points of the Mayo Score, with the exception of mucosal appearance at endoscopy. The Partial Mayo Score evaluates stool frequency (normal, 1–2 stools/day more than normal, 3–4 stools/day more than normal, or >4 stools/day more than normal); rectal bleeding (none, visible blood with stool less than half of the time, visible blood with stool half of the time or more, or passing blood alone); and physician rating of disease activity (normal, mild, moderate, or severe).
Table I1. Clinical context for IBDBIO2 labeling change to include patients with UC

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>TREATMENT ALTERNATIVES</th>
<th>THERAPY</th>
<th>PATIENT PERSPECTIVE</th>
<th>PROVIDER PERSPECTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• UC is a chronic disease, with heavy quality-of-life impact</td>
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<tr>
<td>• Characterized by recurring episodes of inflammation limited to the mucosal layer of the colon</td>
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<tr>
<td>• Most biologics effective at treating both diseases</td>
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</tr>
<tr>
<td>• Many biologics therapies exist for UC, but patients can have either PNR or LOR and potential exhaustion of existing therapeutics</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>• A significant number of patients do not respond to existing therapies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Surgical bowel removal is last resort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Current MABs include anti-TNFs (infliximab, adalimumab, certolizumab, and golimumab), anti-α4 integrins (vedolizumab and natalizumab), and anti-interleukin 12/23 antibodies (ustekinumab)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• MAB with a mechanism of action different from other biologics used to treat IBD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No PML warning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tolerance of therapy versus symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Unmet need for patients who exhaust prior treatment options</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ability to do daily activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pain management</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Perception of disease severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Variation in treatment goals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Biologics considered last resort pharmaceutical treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lack of efficacy with current treatments</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Table I2. Prior evidence and RWE for IBDBIO2 labeling change to include patients with UC

<table>
<thead>
<tr>
<th>PRIOR EVIDENCE</th>
<th>RWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical trial 1 (phase II)</td>
<td></td>
</tr>
<tr>
<td>– Study design: randomized double-blinded placebo-controlled fixed-dose trial</td>
<td></td>
</tr>
<tr>
<td>– Population: adults with Crohn’s disease</td>
<td></td>
</tr>
<tr>
<td>– Intervention: comparing 3 fixed doses of a drug to placebo to assess efficacy</td>
<td></td>
</tr>
<tr>
<td>– Primary outcomes: mucosal healing (measured by CDEIS scale) and remission (measured by CDAI scores)</td>
<td></td>
</tr>
<tr>
<td>• Clinical trial 2 (phase III)</td>
<td></td>
</tr>
<tr>
<td>– Study design: randomized double-blinded placebo-controlled fixed-dose trial</td>
<td></td>
</tr>
<tr>
<td>– Population: adults with Crohn’s disease</td>
<td></td>
</tr>
<tr>
<td>– Intervention: comparing drug to placebo to assess efficacy</td>
<td></td>
</tr>
<tr>
<td>– Primary outcomes: mucosal healing (measured by CDEIS scale) and remission (measured by CDAI scores)</td>
<td></td>
</tr>
<tr>
<td>• Clinical pharmacology studies</td>
<td></td>
</tr>
<tr>
<td>• Non-clinical toxicology studies</td>
<td></td>
</tr>
<tr>
<td>• Pragmatic trial</td>
<td></td>
</tr>
<tr>
<td>– Study design: randomized open-label parallel-group trial for one year of follow up</td>
<td></td>
</tr>
<tr>
<td>– Population: adults with UC</td>
<td></td>
</tr>
<tr>
<td>– Intervention: comparing IBDBIO2 with standard of care treatments for UC (infliximab, adalimumab, golimumab, vedolizumab)</td>
<td></td>
</tr>
<tr>
<td>– Primary outcome: colectomy surgery due to treatment failure</td>
<td></td>
</tr>
<tr>
<td>• EHR-linked UC patient registry</td>
<td></td>
</tr>
<tr>
<td>– Partial Mayo Score data and some endoscopy data were available</td>
<td></td>
</tr>
<tr>
<td>– Response and remission rates were comparable to pivotal RCTs</td>
<td></td>
</tr>
<tr>
<td>– Patients who previously failed treatments had positive response</td>
<td></td>
</tr>
<tr>
<td>• PK data available suggest consistency between CD and UC</td>
<td></td>
</tr>
<tr>
<td>• Animal studies show UC effectiveness, including mucosal healing</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX J. HYPOTHETICAL CASE STUDY: LONG-ACTING BRONCHODILATOR APPROVED FOR COPD

DISCLAIMER: This hypothetical case study is not intended to be used as a regulatory or evidence-generation strategy to support effectiveness claims. Rather, the intent is to foster a discussion on the potential of RWE. To evaluate the ability for RWE to contribute to the evidence package, as evaluated through a totality of evidence approach, some questions have been developed for readers’ consideration.

Questions for Consideration

1. Can RWE be used to adequately answer the research question informing the labeling change?
   a. If yes, why?
   b. If not, why not?
2. Under what conditions, if any, might an RCT be required as part of a new evidence package for these case studies?
3. What additional studies may strengthen the new evidence package?

Regulatory Context

Consider LAMCO, a hypothetical long-acting bronchodilator currently indicated for treating airflow obstruction as measured through FEV₁ in patients with chronic obstructive pulmonary disease (COPD) seeking to add a new indication for reducing COPD exacerbations. Exacerbations are defined as two or more respiratory symptoms (cough, sputum, wheezing, dyspnea, or chest tightness) that result in a treatment change. A change in treatment can include any or all of the following: antibiotics, systemic corticosteroids, or hospitalization.

Clinical Context

Disease Background

COPD is a progressive pulmonary disease in which a patient has increased trouble breathing over time due to airflow limitations. COPD is often due to substances that cause lung irritation over time, such as cigarette smoke or air pollution, and affects about 15.7 million Americans. COPD is associated with high morbidity and mortality and is the fourth leading cause of death in the United States. In 2010, there were 32.2 estimated hospitalizations for COPD per 10,000 patients and 72 ER visits for COPD per 10,000 patients. Additional clinical context information can be found in Table J1.

Current Therapies and Level of Unmet Need

COPD can be treated with long-acting bronchodilators, such as long-acting muscarinic agonist (LAMAs) including aclidinium, glycopyrronium bromide, umeclidinium, and tiotropium. Aclidinium, glycopyrronium bromide, and umeclidinium are indicated for maintenance treatment of airflow

* Forced expiratory volume (FEV₁) is the amount of air a person can exhale in a forced breath in one second. COPD is typically diagnosed when a patient has a FEV₁/FVC ratio of less than 70%, where FVC is forced vital capacity.
obstruction in patients with COPD. Tiotropium is indicated for maintenance treatment of bronchospasm in COPD patients as well as for reducing COPD exacerbations. For tiotropium, reduction of exacerbations was evaluated by two double-blind RCTs. LAMAs are associated with improved symptoms and health status and can improve pulmonary rehabilitation effectiveness. While other treatment alternatives exist for COPD, LAMAs were shown in clinical trials to cause a greater decrease in exacerbations as compared to long-acting β₂-agonists (LABAs).

**Proposed Therapy**

LAMCO is a LAMA currently indicated for treatment of airflow obstruction in COPD patients.

**Patient and Provider Perspectives**

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) standards recommend using: 1) FEV₁ to assess disease severity, 2) Modified British Medical Research Council (mMRC) or COPD Assessment test (CAT) to assess symptoms, and 3) history of exacerbations to categorize patients for treatment. However, reduction in FEV₁ is not strongly correlated with changes in health status, breathlessness, or patient quality-of-life outcomes. In a cross-sectional study, patients reported a change in breathlessness that was associated with only a 4% difference in FEV₁. The change in baseline FEV₁ also cannot capture other important information that contributes to health status, such as ability to conduct functional activities. FEV₁ measurements may also underestimate COPD presence in younger patients and overestimate in older patients, as decreased airflow may occur due to natural aging.

Measures of FEV₁ are intangible to patients, who have expressed a desire to understand not the measure of lung function, but rather how their lung impairment affects their quality of life as well as how they feel and function. Patients mainly desire to reduce symptoms and exacerbations, which may improve quality of life. Adding a patient-centered outcome, such as reduction of symptoms of an exacerbation, to the label can help patients quantify their disease burden.

Physicians also consider quality of life and symptom control as well as prevention of disease progression in treating COPD. A provider might be more likely to prescribe a drug that leads to fewer exacerbations, if it increases quality of life for patients and decreases medical costs.

**Evidence**

**Prior Evidence**

Prior evidence includes phase II and phase III trial data for treatment of COPD with a long-acting bronchodilator where FEV₁ is the primary outcome. Additional information about the studies can be found in Table J2.

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* mMRC is a scale that assigns a grade from 0 to 4 based on symptoms of dyspnea.

† CAT is an 8-question assessment to evaluate patient symptoms. Each item on the assessment is scored between 0 and 5, where patients are provided interpretations of a “0” score and a “5” score for each item. For example, in regard to patient energy level, patients can rate from 0 to 5, where 0 indicates “I have lots of energy” and 5 indicates “I have no energy at all.”
New Evidence: Strengths and Limitations

New evidence includes an analysis of a large claims database and an analysis of a large EHR database, both of which were prespecified and adequately powered. The primary outcomes were the proportion of patients with symptoms of COPD exacerbations and the proportion of patients with hospitalization due to COPD exacerbations. In the claims data, a validated algorithm was used to identify patients with COPD exacerbations and hospitalizations related to COPD exacerbations. Hospitalizations and symptoms of COPD exacerbations were extracted from the EHR data. Both studies demonstrated that the proportion of COPD exacerbations among patients taking LAMCO was significantly less than the proportion of COPD exacerbations in patients taking a standard of care LAMA. Additional information about the studies can be found in Table J2.

Regulatory Decision

The regulatory decision will likely largely rely on prior evidence for the previously approved LAMAs and the safety and efficacy of LAMCO. The use of RWE studies to support a labeling change for LAMCO highlights the importance of RWD to support the patient perspective by seeking to add a patient-centered endpoint to the label. LAMCO differentiates itself from other LAMAs with an indication for reduced exacerbations as it is the first to demonstrate exacerbation reduction in clinical care settings.

### Table J1. Clinical context for LAMCO labeling change to add a new indication for reducing COPD exacerbations

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>TREATMENT ALTERNATIVES</th>
<th>THERAPY</th>
<th>PATIENT PERSPECTIVE</th>
<th>PROVIDER PERSPECTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Characterized by airflow limitation</td>
<td>LAMAs include tiotropium, aclidinium, glycopyrronium bromide, and umeclidinium</td>
<td>LAMA</td>
<td>• Reduction in FEV₁ is hard to understand and needs a more patient-friendly outcome</td>
<td>• Focus on disease progression</td>
</tr>
<tr>
<td>• Affects approximately 15.7 million Americans</td>
<td></td>
<td></td>
<td>• Quality of life</td>
<td>• Decreased cost with decreased ER visits</td>
</tr>
<tr>
<td>• Associated with high morbidity and mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table J2. Prior evidence and RWE for LAMCO labeling change to add a new indication for reducing COPD exacerbations

<table>
<thead>
<tr>
<th>PRIOR EVIDENCE</th>
<th>RWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical trial 1 (phase II)</td>
<td>• Analysis of a large claims database comparing LAMCO to a standard of care LAMA</td>
</tr>
<tr>
<td>– Study design: randomized double-blind placebo-controlled fixed-dose trial</td>
<td>• Analysis of a large EHR database comparing LAMCO to a standard of care LAMA</td>
</tr>
<tr>
<td>– Population: adults with COPD</td>
<td>• Co-primary outcomes for both analyses: proportion of patients with COPD exacerbations and the proportion of patients with hospitalizations due to COPD exacerbations</td>
</tr>
<tr>
<td>– Intervention: comparing drug to placebo to assess efficacy</td>
<td></td>
</tr>
<tr>
<td>– Primary outcome: FEV₁</td>
<td></td>
</tr>
<tr>
<td>• Clinical trial 2 (phase III)</td>
<td></td>
</tr>
<tr>
<td>– Study design: randomized double-blind placebo-controlled fixed-dose trial</td>
<td></td>
</tr>
<tr>
<td>– Population: adults with COPD</td>
<td></td>
</tr>
<tr>
<td>– Intervention: comparing drug to placebo to assess efficacy</td>
<td></td>
</tr>
<tr>
<td>– Primary outcome: FEV₁</td>
<td></td>
</tr>
<tr>
<td>• Clinical pharmacology studies</td>
<td></td>
</tr>
<tr>
<td>• Non-clinical toxicology studies</td>
<td></td>
</tr>
</tbody>
</table>
REFERENCES


56. U.S. Food and Drug Administration. Center for Drug Evaluation and Research Application Number: 761036orig1s000. Pharmacology Review(s); 2015.


74. FDA Expands Palbociclib Indication in HR-Positive, HER2-Negative Breast Cancer to Include Male Patients. The ASCO Post, 2019.


