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

December 19, 2019

Duke | MARGOLIS CENTER *for* Health Policy

Table of Contents

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.

Acknowledgments

The Duke-Margolis Center would like to thank several individuals for their contributions to this white paper. This paper's development was guided by the collaboration of the working group members listed on page iv. The working group's extensive subject-matter expertise and insightful comments were integral to the development of this paper. We are also appreciative of the broader Real-World Evidence Collaborative Advisory Group who provided their guidance throughout development of this white paper. We would like to thank those who participated in the Duke-Margolis private workshop, "Improving RWE Study Credibility and its Role in Totality of Evidence," held in June 2019 (a list of attendees can be found in Appendix A). In addition, we are grateful to Patricia Green and Sarah Supsiri from the Center for their communications and events guidance. We would like to thank Kerry Stenke from the Duke Clinical Research Institute for her support in developing graphics for this white paper. Finally, we acknowledge Rachael Lussos from Graham Associates and Liz Wing from the Duke Clinical Research Institute for their editorial assistance.

Any opinions expressed in this paper are solely those of the authors and do not represent the views or policies of any other organizations external to Duke-Margolis. Funding for this work is made possible through the generosity of the Margolis Family Foundation, which provides core resources for the Center, as well as a combination of financial and in-kind contributions from Real-World Evidence Collaborative members, including AbbVie; Eli Lilly and Company; Genentech, a member of the Roche Group; GlaxoSmithKline; Johnson & Johnson; Merck & Co.; Novartis; Teva; and UCB. For more information on the Real-World Evidence Collaborative, visit https://healthpolicy.duke.edu/real-world-evidence-collaborative.

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.

Gregory Daniel, PhD, MPH, receives consulting fees from Genentech, Inc., the Reagan-Udall Foundation, and AbbVie Inc.

Rachel E. Sherman, MD, MPH, is an independent board member for Aptinynx and has served as an advisor to Medidata.

WHITE PAPER

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

DUKE-MARGOLIS AUTHORS

Nirosha Mahendraratnam

Kerra Mercon

Joy Eckert

Morgan Romine

Adam Kroetsch

Katherine Frank

Rachel Sherman

Gregory Daniel

Mark McClellan

WORKING GROUP

Jean Marie Arduino
Merck & Co.

Shrujal Baxi
Flatiron Health

Marc Berger
ISPOR

David Blaser
PatientsLikeMe

Stephanie Chiuve
AbbVie

Jennifer Christian
IQVIA

Susan Colilla
Teva Pharmaceuticals

William Crown
OptumLabs

Shannon Ferrante
GlaxoSmithKline

Kevin Haynes
HealthCore

Stacy Holdsworth
Eli Lilly and Company

Solomon Iyasu
Merck & Co.

Linda Kalilani
UCB

Ryan Kilpatrick
AbbVie

Carol Koro
Merck & Co.

Martin Ladouceur
Evidera

Grazyna Lieberman
Genentech

Nicole Mahoney
Flatiron Health

Panagiotis Mavros
Janssen

Emily O'Brien
Duke Clinical Research Institute

Sally Okun
PatientsLikeMe

Christina Parrinello
Flatiron Health

Amy Rudolph
Novartis

Patricia Saddier
Merck & Co.

Meghna Samant
Flatiron Health

Khaled Sarsour
Genentech

Kristin Sheffield
Eli Lilly and Company

Caroline Tai
Evidation Health

David Thompson
Syneos Health

Eileen Mack Thorley
PatientsLikeMe

Kathleen Villa
Evidation Health

Yiting Wang
Janssen Research and Development

Vince Willey
HealthCore

Richard Willke
ISPOR

David Wormser
F. Hoffmann-La Roche

Keele Wurst
GlaxoSmithKline

ADVISORY GROUP

Ryan Kilpatrick
AbbVie

Carlos Garner
Eli Lilly and Company

Bray Patrick-Lake
Evidation Health

Debra Schaumberg
Evidera

Nicole Mahoney
Flatiron Health

Jacqueline Law
Genentech

John Graham
GlaxoSmithKline

Richard Platt
Harvard Medical School

Marcus Wilson
HealthCore

Marc Berger
ISPOR

Richard Willke
ISPOR

Nancy Dreyer
IQVIA

Joanne Waldstreicher
Johnson & Johnson

Solomon Iyasu
Merck & Co.

Barbara Bierer
The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard

Eleanor Perfetto
National Health Council

Amy Rudolph
Novartis

Paul Bleicher
OptumLabs

Sally Okun
PatientsLikeMe

David Thompson
Syneos Health

Riad Dirani
Teva Pharmaceuticals

David Miller
UCB

Stephanie Reisinger
Veradigm Health

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. 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.

---

* 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.

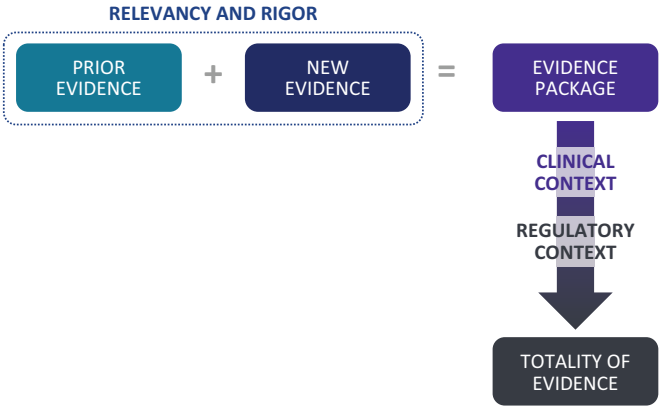


Figure 1. The totality of evidence approach for evaluating the risks and benefits of a medical product

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.

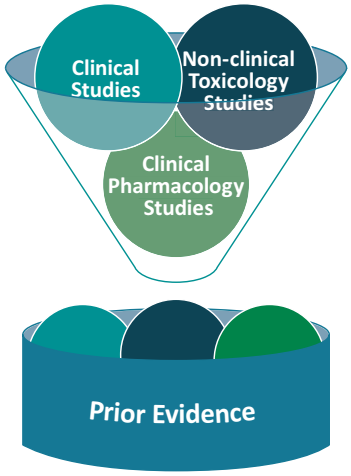


Figure 2. Components of an evidence package that is submitted to support a product approval

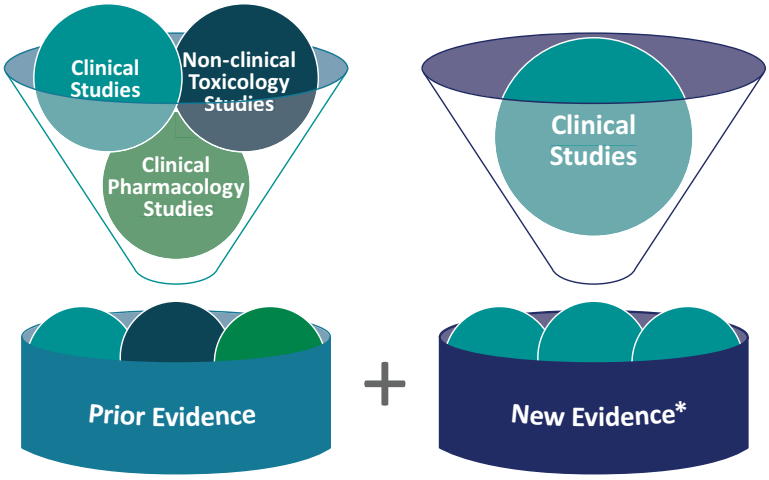


Figure 3. Components of the prior and new evidence packages submitted to support an effectiveness labeling change

*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.

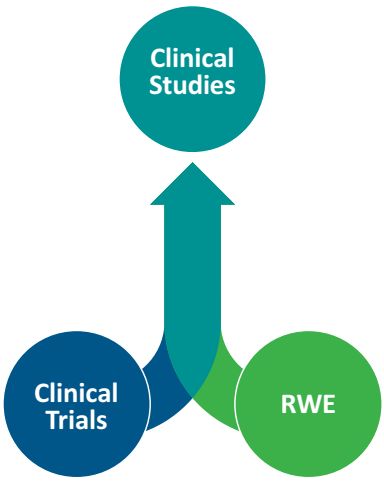


Figure 4. Clinical studies can consist of clinical trials or RWE

* 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.

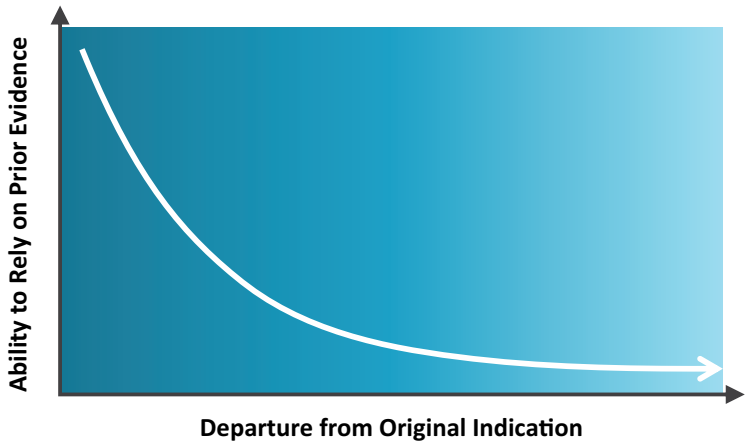


Figure 5. Weight of prior evidence is informed by the proximity of the labeling change to the original indication

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.

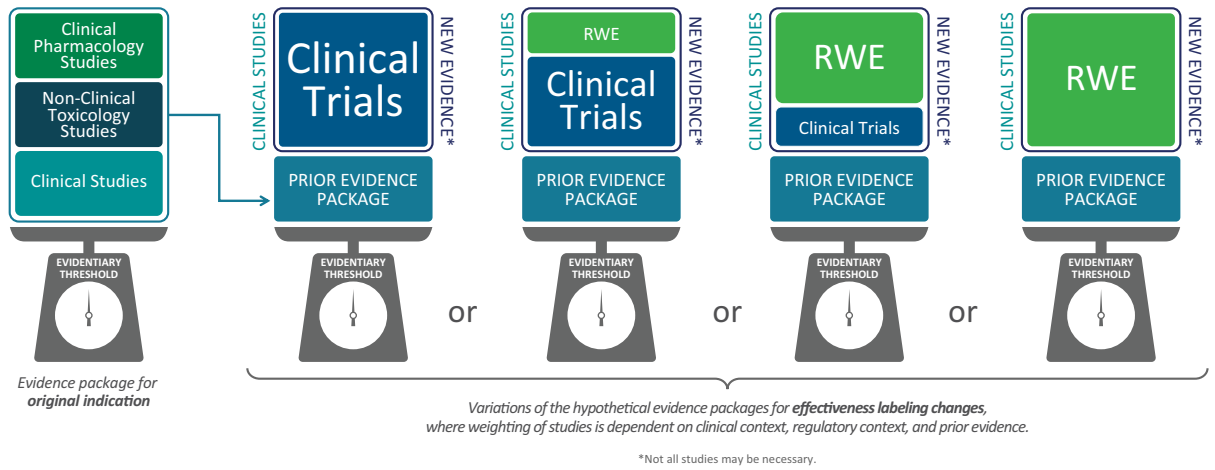


Figure 6. Hypothetical weighting of prior evidence and new evidence in various evidence packages evaluated through a totality of evidence approach for an original approval and an effectiveness labeling change. The size of the boxes corresponds to the relative amount of weight provided by each piece of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

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

Participant List

Elodie Baumfeld Andre
Pfizer

Stella Chang
Veradigm Health

Stephanie Chiuve
AbbVie

Jennifer Christian
IQVIA

William Crown
OptumLabs

Ruthie Davi
Acorn AI, a Medidata company

Kevin Haynes
HealthCore

Stacy Holdsworth
Eli Lilly and Company

Albert Kraus
Pfizer

Martin Ladouceur
Evidera

Grazyna Lieberman
Genentech

Nicole Mahoney
Flatiron Health

Panagiotis Mavros
Janssen

Brian Mayhew
Novartis

David Miller
UCB

Marko Mychaskiw
Teva Pharmaceuticals

Emily O'Brien
Duke Clinical Research Institute

Sally Okun
PatientsLikeMe

Christina Parrinello
Flatiron Health

Andrew Robertson
Sanofi

Khaled Sarsour
Genentech

Kristin Sheffield
Eli Lilly and Company

Caroline Tai
Evidation Health

David Thompson
Syneos Health

Yiting Wang
Janssen Research and Development

Richard Willke
ISPOR

David Wormser
F. Hoffmann-La Roche

Keele Wurst
GlaxoSmithKline

Duke-Robert J. Margolis, MD, Center for Health Policy

Gregory Daniel

Adam Kroetsch

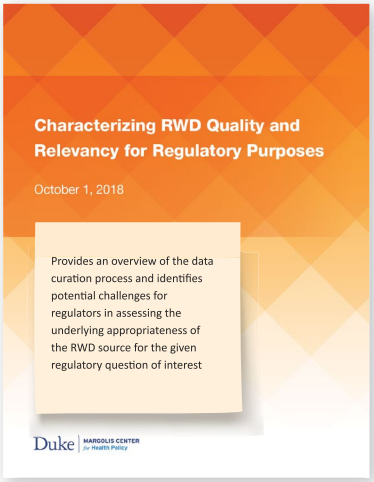
Nirosha Mahendraratnam Lederer

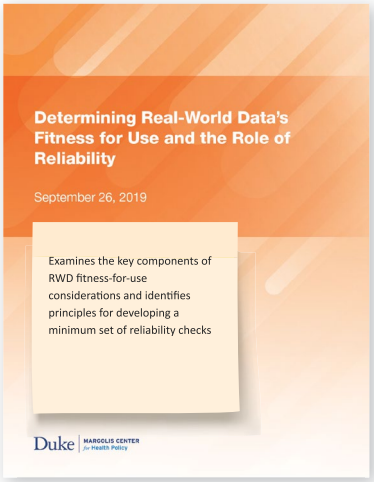
Kerra Mercon

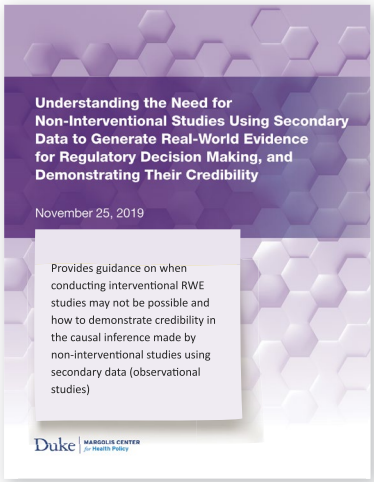
Morgan Romine

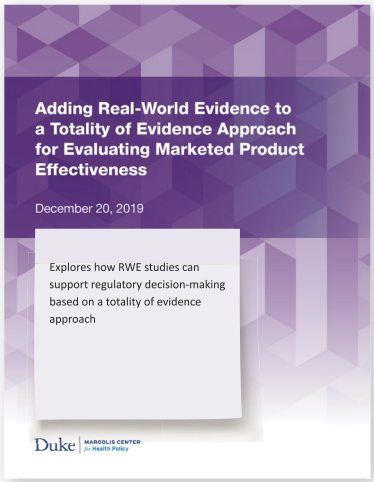
Rachel Sherman

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









APPENDIX C. EXAMPLES OF DRUG APPROVALS AND LABELING CHANGES USING EVIDENCE GENERATED FROM NON-TRADITIONAL STUDY DESIGNS

Table C1. RWE studies

PRODUCT	SPONSOR	DISEASE	STUDY DESIGN
Bavencio® (avelumab)[15-17]	Pfizer and Merck KGaA	Metastatic merkel cell carcinoma	1. Open-label single-arm multicenter trial 2. RWE-generated historical control as benchmark
Blincyto® (blinatumomab)[18-21]	Amgen	B-cell precursor acute lymphoblastic leukemia	1. Open-label single-arm multicenter trial 2. RWE-generated historical control
Brineura® (cerliponase alfa)[22-24]	Biomarin	Infantile batten disease	1. Non-randomized single-arm dose-escalation study 2. Non-randomized comparison with natural history cohort
Carbaglu® (carglumic acid)[25,26]	Recordati Rare Diseases Inc.	Hyperammonemia	Retrospective unblinded uncontrolled case series
Cordarone® (amiodarone hydrochloride) tablets[27,28]	Sanofi	Arrhythmia	Retrospective open-label self-controlled study
Ibrance® (palbociclib)[29-33]	Pfizer	Male breast cancer	Retrospective cohort study using EHR data, insurance billing data, and postmarketing studies
Intravenous ganciclovir[34,35]	Exela Pharma Sciences	Acquired immunodeficiency virus syndrome (AIDS) and cytomegalovirus (CMV) retinitis	Retrospective non-randomized study
Luthathera® (lutetium Lu 177 dotatate)[36,37]	Advanced Accelerator Applications, a Novartis company	Somatostatin receptor (SSTR) positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs)	1. Randomized open-label, active-controlled multicenter trial 2. Retrospective study
Omegaven® (fish oil triglycerides)[38,39]	Fresenius Kabi	Parenteral nutrition-associated cholestasis	1. Open-label single-center trial 2. Open-label single-center trial 3. Historical control
Tepadina® (thiotepa)[40,41]	Adienne SA	Pediatric class 3 beta-thalassemia	Retrospective observational trial
Yescarta® (axicabtagene ciloleucel)[42-44]	Kite, a Gilead company	Diffuse large B-cell lymphoma	1. Open-label single-arm multicenter trial 2. Retrospective analysis of patients receiving standard of care as benchmark
Zostavax® (zoster vaccine live)[45,46]	Merck	Herpes zoster (shingles)	1. Randomized double-blind placebo-controlled trial (ages 50–59) 2. Randomized double-blind placebo-controlled trial (age >60) 3. Prospective observational cohort study

Table C1. RWE studies (continued)

PRODUCT	SPONSOR	DISEASE	STUDY DESIGN
Large Simple Trials/Pragmatic Trials			
Savaysa® (edoxaban)[47,48]	Daiichi Sankyo, Inc.	Atrial fibrillation	Randomized double-blind multinational non-inferiority study
Invega Sustenna® (paliperidone palmitate)[49,50]	Janssen	Schizophrenia, schizoaffective disorder	Prospective randomized open-label active-controlled parallel-group trial
Inactivated polio vaccine[51-53]	National Foundation for Infantile Paralysis (March of Dimes)	Polio	Randomized blinded placebo-controlled trial with additional observed controls

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

PRODUCT	SPONSOR	DISEASE	STUDY DESIGN
Altace® (ramapril)[54,55]	King Pharmaceuticals, Inc.	Hypertension, heart failure	Randomized double-blind placebo-controlled multicenter multinational trial
Capoten® (captopril)[55]	Bristol Myers Squibb	Hypertension, heart failure	Randomized double-blind placebo-controlled trial
Darzalex® (daratumumab)[56,57]	Janssen	Multiple myeloma	1. Open-label single-arm trial (phase II) 2. Open-label dose expansion dose-escalation trial
Keytruda® (pembrolizumab)[58,59]	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)[55,60]	Roussel–Uclaf and Knoll Pharmaceuticals	Hypertension, heart failure	Randomized double-blind placebo-controlled trial
Vasotec® (enalapril)[55]	Merck	Hypertension, heart failure	Randomized double-blind placebo-controlled trial
Zestril® (lisinopril)[55,61]	Zeneca Pharmaceutical	Hypertension, heart failure	Randomized controlled multicenter open trial
Zykadia® (ceritinib)[62,63]	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

STUDY DESIGN	DEFINITION
Single-arm	All trial participants received the experimental treatment[64]
Open-label	Trial participant and researcher knew which treatment was assigned to the participant[65]
Meta-analysis	A statistical analysis of combined results from multiple studies[66]

APPENDIX E. CLINICAL CONTEXT CONSIDERATIONS

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.

APPENDIX F. ADEQUATE AND WELL-CONTROLLED STUDY REGULATION[68]

[CODE OF FEDERAL REGULATIONS]
[TITLE 21, VOLUME 5]
[REVISED AS OF APRIL 1, 2018]
[CITE: 21CFR314.126]

TITLE 21 — FOOD AND DRUGS
CHAPTER I — FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D — DRUGS FOR HUMAN USE
PART 314 — APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

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.

[50 FR 7493, Feb. 22, 1985, as amended at 50 FR 21238, May 23, 1985; 55 FR 11580, Mar. 29, 1990; 64 FR 402, Jan. 5, 1999; 67 FR 9586, Mar. 4, 2002]

APPENDIX G. IBRANCE® CASE STUDY

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.

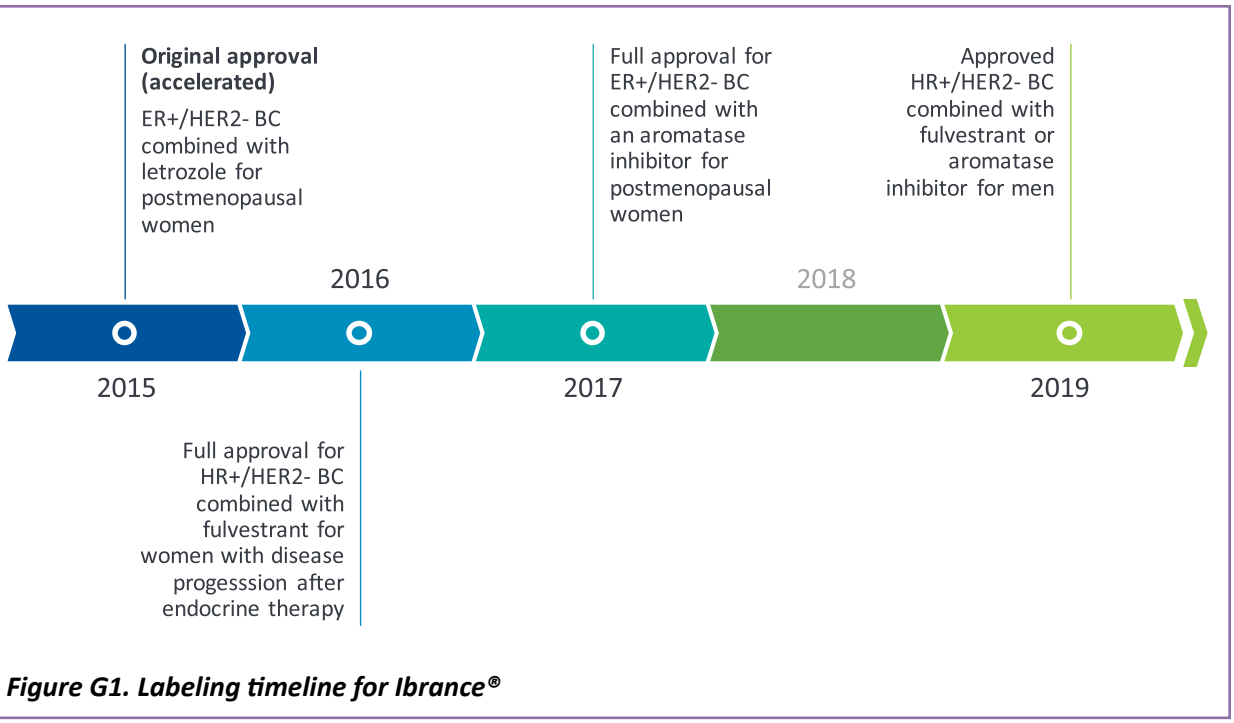


Figure G1. Labeling timeline for Ibrance®

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."[32] This supplemental application was novel in that all new evidence included was from RWD sources.

Table G1. Clinical context for Ibrance® approval in males

DISEASE[69]	TREATMENT ALTERNATIVES	THERAPY	PATIENT PERSPECTIVE[72]	PROVIDER PERSPECTIVE[72]
• 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 6[31,71]	• Unmet need • Stigma • Access to care	• Stigma • Perception of disease

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

PRIOR EVIDENCE[29]	RWE[73]
• 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) • 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	• Postmarketing reports, insurance billing data, and EHR data sourced from: – IQVIA insurance database – Flatiron Health breast cancer database – Pfizer global safety database

APPENDIX H. INVEGA SUSTENNA® CASE STUDY

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).* [50] 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.

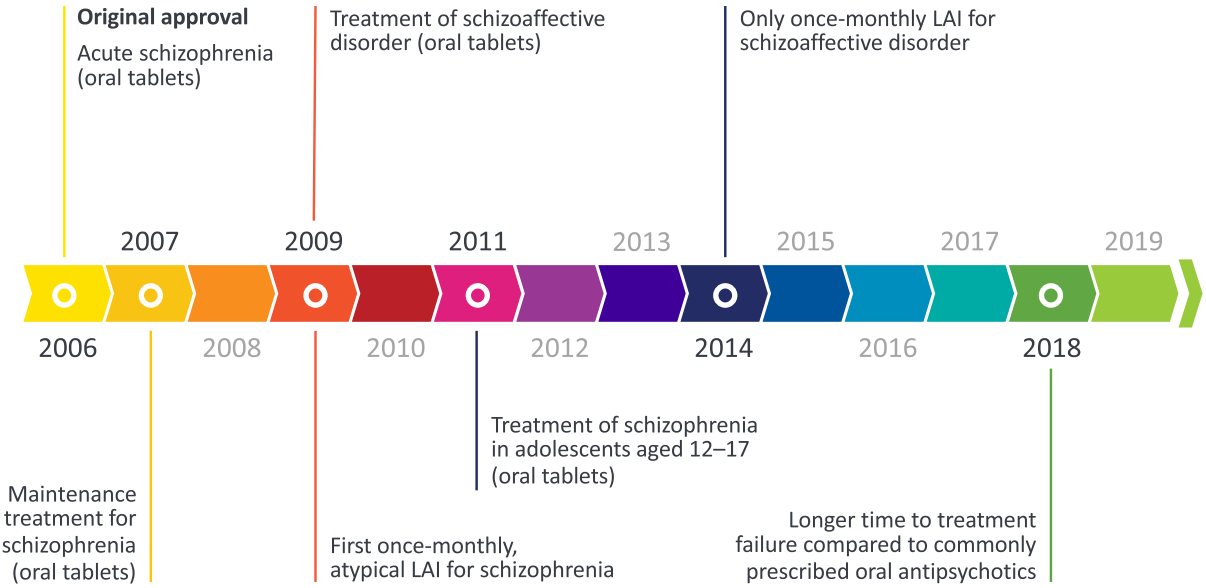


Figure H1. Labeling timeline for Invega Sustenna®

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

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.[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).[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.[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.[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.[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.[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.[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.[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.[49] 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®

DISEASE	TREATMENT ALTERNATIVES[75]	THERAPY	PATIENT PERSPECTIVE[77]	PROVIDER PERSPECTIVE[77]
• Equally prevalent in men and women[75] • 1.1% prevalence in U.S.[49]	• First-generation antipsychotics • Second-generation antipsychotics • Clozapine • Combination therapy • LAI antipsychotic agents	• Paliperidone is a centrally active dopamine type 2 receptor antagonist and serotonin type 2 receptor antagonist[50] • Only FDA-approved LAI for schizoaffective disorder[79]	• Autonomy • Convenience of treatment • Fear of injections • Lack of understanding about disease or therapy	• Benefits to adherence[78] • Fear of coercion • Maintaining relationship with patient • Patient autonomy

Table H2. Prior evidence and RWE for including new evidence in the clinical studies section of the label for Invega Sustenna®

PRIOR EVIDENCE[50]	RWE[49,50]
• Three short-term (13-week) RCTs (schizophrenia) – Study design: randomized double-blind placebo-controlled fixed-dose trial – Population: acutely relapsed adult inpatients who meet DSM-IV criteria for schizophrenia – Primary outcome: change of positive and negative symptoms of schizophrenia and general psychopathology measured by the Positive and Negative Syndrome Scale (PANSS) – Intervention *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* *PSY-3003: comparing 3 fixed doses (78mg/4 wk, 156 mg/4 wk, 234 mg/4 wk) of Invega Sustenna® to placebo* *PSY-3004: comparing 3 fixed doses (39 mg/4 wk, 78 mg/4 wk, 156 mg/4 wk) of Invega Sustenna® to placebo* • SCH-201 – Study design: short-term (9-week) double-blind randomized placebo-controlled fixed-dose trial – Population: acutely relapsed adult inpatients who meet DSM-IV criteria for schizophrenia – Intervention: comparing 2 fixed doses (78 mg/4 wk and 156 mg/4 wk) of Invega Sustenna® to placebo – Primary outcome: change of positive and negative symptoms of schizophrenia and general psychopathology measured by PANSS • PSY-3001 – Study design: long-term double-blind placebo-controlled flexible-dose study – Population: adults who met DSM-IV criteria for schizophrenia – 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 – Primary outcome: time to relapse • SCA-3004 – Study design: long-term double-blind placebo-controlled flexible-dose randomized-withdrawal trial – Population: adults who met DSM-IV criteria for schizoaffective disorder, confirmed by structured clinical interview for DSM-IV disorders – Intervention: comparing Invega Sustenna® (78 mg, 117 mg, 156 mg, 234 mg) to placebo – Primary outcome: time to relapse • Clinical pharmacology studies • Non-clinical toxicology studies	• PRIDE – Study design: randomized prospective open-label event-monitoring board-blinded parallel-group study *Screening phase of ≤2 weeks* *15-month randomized open-label treatment phase* – Population: adults aged 18–65 with DSM-IV schizophrenia, confirmed by Mini-International Neuropsychiatric Interview version 6 *Taken into custody ≥2 times within 2 years* *≥1 incarceration within 2 years* *Release from custody within 90 days of screening* – Intervention: comparing Invega Sustenna® (paliperidone palmitate) with oral antipsychotics (aripiprazole, haloperidol, olanzapine, paliperidone, perphenazine, quetiapine, and risperidone) – Primary outcome: time to treatment failure

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.[80] 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.[80] CD and UC affect men and women equally (Table I1). 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.[81]

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 I1.

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.[82] 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%.[82] 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.[82] PNR and LOR are managed by intensifying the dose, adding immunomodulators, or switching to a therapy in a different class.[82] 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.[83]

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.[84] 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.[85] Vedolizumab may be beneficial for patients with weakened immune systems as it does not typically lead to increased infection or malignancy.[84] 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.[84]

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.[85]

Patient and Provider Perspectives

UC patients have reported a desire for treatments that allow them to perform daily activities and manage their pain.[86] 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).[87] Additionally, patients have reported concerns that providers do not recognize the effect of UC on mental health.[88]

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.[87] 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.* [89,90] 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.[90,91] 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

DISEASE[80]	TREATMENT ALTERNATIVES[82]	THERAPY	PATIENT PERSPECTIVE[86–88]	PROVIDER PERSPECTIVE[86–88]
• UC is a chronic disease, with heavy quality-of-life impact • Characterized by recurring episodes of inflammation limited to the mucosal layer of the colon • Most biologics effective at treating both diseases	• Many biologic therapies exist for UC, but patients can have either PNR or LOR and potential exhaustion of existing therapeutics • A significant number of patients do not respond to existing therapies • Surgical bowel removal is last resort • Current MABs include anti-TNFs (infliximab, adalimumab, certolizumab, and golimumab), anti-α4 integrins (vedolizumab and natalizumab), and anti-interleukin 12/23 antibodies (ustekinumab)[82,84]	• MAB with a mechanism of action different from other biologics used to treat IBD • No PML warning	• Tolerance of therapy versus symptoms • Unmet need for patients who exhaust prior treatment options • Ability to do daily activities • Pain management • Perception of disease severity • Quality of life	• Variation in treatment goals • Biologics considered last resort pharmaceutical treatment • Quality of life • Lack of efficacy with current treatments

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

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

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 FEV_1* in patients with chronic obstructive pulmonary disease (COPD) seeking to add a new indication for reducing COPD exacerbations.[92] Exacerbations are defined as two or more respiratory symptoms (cough, sputum, wheezing, dyspnea, or chest tightness) that result in a treatment change.[93] A change in treatment can include any or all of the following: antibiotics, systemic corticosteroids, or hospitalization.[93]

Clinical Context

Disease Background

COPD is a progressive pulmonary disease in which a patient has increased trouble breathing over time due to airflow limitations.[92] 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.[94] 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.[95] 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.[96] Aclidinium, glycopyrronium bromide, and umeclidinium are indicated for maintenance treatment of airflow

* Forced expiratory volume (FEV_1) 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 FEV_1/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.[97] LAMAs are associated with improved symptoms and health status and can improve pulmonary rehabilitation effectiveness.[96] 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 β_2-agonists (LABAs).[96]

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) FEV_1 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.[96] However, reduction in FEV_1 is not strongly correlated with changes in health status, breathlessness, or patient quality-of-life outcomes.[98] In a cross-sectional study, patients reported a change in breathlessness that was associated with only a 4% difference in FEV_1.[99] The change in baseline FEV_1 also cannot capture other important information that contributes to health status, such as ability to conduct functional activities.[98] FEV_1 measurements may also underestimate COPD presence in younger patients and overestimate in older patients, as decreased airflow may occur due to natural aging.[100]

Measures of FEV_1 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.[101] 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 FEV_1 is the primary outcome. Additional information about the studies can be found in Table J2.

* 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.[96] 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

DISEASE	TREATMENT ALTERNATIVES[96]	THERAPY	PATIENT PERSPECTIVE	PROVIDER PERSPECTIVE
• Characterized by airflow limitation[92] • Affects approximately 15.7 million Americans[94] • Associated with high morbidity and mortality[95]	LAMAs include tiotropium, aclidinium, glycopyrronium bromide, and umeclidinium	LAMA	• Reduction in FEV_1 is hard to understand and needs a more patient-friendly outcome • Quality of life	• Focus on disease progression • Decreased cost with decreased ER visits

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

PRIOR EVIDENCE	RWE
• Clinical trial 1 (phase II) – Study design: randomized double-blind placebo-controlled fixed-dose trial – Population: adults with COPD – Intervention: comparing drug to placebo to assess efficacy – Primary outcome: FEV_1 • Clinical trial 2 (phase III) – Study design: randomized double-blind placebo-controlled fixed-dose trial – Population: adults with COPD – Intervention: comparing drug to placebo to assess efficacy – Primary outcome: FEV_1 • Clinical pharmacology studies • Non-clinical toxicology studies	• Analysis of a large claims database comparing LAMCO to a standard of care LAMA • Analysis of a large EHR database comparing LAMCO to a standard of care LAMA • Co-primary outcomes for both analyses: proportion of patients with COPD exacerbations and the proportion of patients with hospitalizations due to COPD exacerbations

REFERENCES

1. U.S. Food and Drug Administration. Framework for FDA's Real-World Evidence Program. U.S. Department of Health & Human Services; December 2018.
2. Franklin JM, Glynn RJ, Martin D, Schneeweiss S. Evaluating the Use of Nonrandomized Real-World Data Analyses for Regulatory Decision Making. *Clin Pharmacol Ther.* 2019;105(4):867-877.
3. Sherman RE, Davies KM, Robb MA, Hunter NL, Califf RM. Accelerating development of scientific evidence for medical products within the existing US regulatory framework. *Nat Rev Drug Discov.* 2017;16:297.
4. U.S. Food and Drug Administration. Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products: U.S. Department of Health & Human Services;1998.
5. U.S. Food and Drug Administration. Labeling for Human Prescription Drug and Biological Products—Implementing the PLR Content and Format Requirements: U.S. Department of Health & Human Services; 2013.
6. Improving Transparency in Non-Interventional Research for Hypothesis Testing—WHY, WHAT, and HOW: Considerations from the Real-World Evidence Transparency Initiative: ISPOR; 2019.
7. U.S. Food and Drug Administration. Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics Guidance for Industry: U.S. Department of Health & Human Services; 2019.
8. Sasinowski FJ, Butler ML. Single-Study Approvals: Quantum of Evidence Required. *Ther Innov Regul Sci.* 2019. doi:10.1177/2168479019873918.
9. Mahendraratnam N, Silcox C, Mercon K, et al. Determining Real-World Data's Fitness for Use and the Role of Reliability: Duke-Margolis Center for Health Policy; 2019.
10. Berger M, Daniel G, Frank K, et al. A Framework for Regulatory Use of Real-World Evidence: Duke-Margolis Center for Health Policy; 2017.
11. Daniel G, McClellan M, Silcox C, et al. Characterizing RWD Quality and Relevancy for Regulatory Purposes: Duke-Margolis Center for Health Policy; 2018.
12. Mahendraratnam N, Eckert J, Mercon K, et al. 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 Center for Health Policy; 2019.
13. Federal Food, Drug, and Cosmetic Act, 21 U.S.C., §355.
14. U.S. Food and Drug Administration. Federal Register. Vol 501985:7486-7488. https://s3.amazonaws.com/archives.federalregister.gov/issue_slice/1985/2/22/7443-7513.pdf#page=38. Accessed December 5, 2019.
15. Two-Year Update of Pivotal Javelin Merkel 200 Trial Shows Continued Durable Responses with Bavencio® (Avelumab). 2018; Available at: https://www.pfizer.com/news/press-release/press-release-detail/two_year_update_of_pivotal_javelin_merkel_200_trial_shows_continued_durable_responses_with_bavencio_avelumab.
16. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Application Number: 761049Orig1s000. Multi-Discipline Review; 2017.
17. Pfizer and Merck KGaA. Bavencio [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761049s006lbl.pdf. Accessed December 4, 2019.
18. Jen E, Xu Q, Schetter A, et al. FDA Approval: Blinatumomab for Patients with B-cell Precursor Acute Lymphoblastic Leukemia in Morphologic Remission with Minimal Residual Disease. *Clin Cancer Res*. 2018.
19. Przepiorka D. BLA 125557: BLINCYTO (BLINATUMOMAB) Introductory Comments: U.S. Food and Drug Administration; 2018.
20. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Application Number: 125557Orig1s000. Medical Review(s); 2014.
21. Amgen. Blincyto [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125557s015s016lbl.pdf. Accessed December 4, 2019.
22. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Application Number: 761052Orig1s000. Summary Review; 2015.
23. U.S. Food and Drug Administration. FDA approves first treatment for a form of Batten disease. 2017; Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-form-batten-disease. Accessed December 4, 2019.

24. Biomarin. Brineura [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761052lbl.pdf. Accessed December 4, 2019.

25. Recordati Rare Diseases Inc. Carbaglu [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022562s005lbl.pdf. Accessed December 4, 2019.

26. U.S. Food and Drug Administration. Center for Drug Evaluation And Research. Application Number: 22-562. Clinical Pharmacology and Biopharmaceutics Review(s); 2009.

27. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Approval Package for: Application Number 18-972. Approval Letter(s); 1985.

28. U.S. Food and Drug Administration. 18-972 Cardarone Summary Basis of Approval Part 2; 1985.

29. Pfizer. Ibrance [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207103s000lbl.pdf. Accessed December 4, 2019.

30. IBRANCE® (palbociclib) Receives FDA Regular Approval and Expanded Indication for First-Line HR+, HER2- Metastatic Breast Cancer. 2017.

31. U.S. FDA Approves IBRANCE® (palbociclib) for the Treatment of Men with HR+, HER2- Metastatic Breast Cancer. 2019; Available at: https://www.pfizer.com/news/press-release/press-release-detail/u_s_fda_approves_ibrance_palbociclib_for_the_treatment_of_men_with_hr_her2_metastatic_breast_cancer. Accessed December 4, 2019.

32. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Approval Package for: Application Number: 207103Orig1s008; 2019.

33. Wedam S, Fashoyin-Aje L, Bloomquist E, et al. FDA Approval Summary: Palbociclib for Male Patients with Metastatic Breast Cancer. *Clin Cancer Res*. 2019:clincanres.2580.2019.

34. Exela Pharma Sciences. Ganciclovir Injection [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209347lbl.pdf. Accessed December 2019.

35. Holland GN, Buhles WC, Jr, Mastre B, Kaplan HJ. A Controlled Retrospective Study of Ganciclovir Treatment for Cytomegalovirus Retinopathy: Use of a Standardized System for the Assessment of Disease Outcome. *JAMA Ophthalmol*. 1989;107(12):1759-1766.

36. Advanced Accelerator Applications USA, Inc. Lutathera [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208700s000lbl.pdf. Accessed December 4, 2019.

37. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Application Number: 208700orig1s000. Multi-Discipline Review; 2018.

38. Fresenius Kabi. Omegaven [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/0210589s000lbledt.pdf. Accessed December 4, 2019.

39. U.S. Food and Drug Administration. Center for Drug Evaluation And Research Application Number: 210589orig1s000. Multi-Discipline Review; 2017.

40. Adienne SA. Tepadina [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208264s000lbl.pdf. Accessed December 4, 2019.

41. U.S. Food and Drug Administration. Center for Drug Evaluation and Research Application Number: 208264orig1s000. Summary Review; 2016.

42. Kite. Yescarta [package insert]. U.S. Food and Drug Administration. Available at: https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert---YESCARTA.pdf. Accessed December 4, 2019.

43. U.S. Food and Drug Administration. Center for Biologics Evaluation and Research. BLA: 125643 Summary Basis for Regulatory Action; 2017.

44. U.S. Food and Drug Administration. Center for Biologics Evaluation and Research. BLA: 125643 Statistical Review; 2017.

45. Merck. Zostavax [package insert]. U.S. Food and Drug Administration. Available at: https://www.fda.gov/media/82524/download. Accessed December 4, 2019.

46. U.S. Food and Drug Administration. Summary Basis for Regulatory Action-Zostavax2018.

47. Daiichi Sankyo, Inc. Savaysa [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf. Accessed December 4, 2019.

48. U.S. Food and Drug Administration. Center for Drug Evaluation and Research Application Number: 206316orig1orig2s000. Clinical Pharmacology and Biopharmaceutics Review(s); 2014.

49. Alphs L, Benson C, Cheshire-Kinney K, et al. Real-World Outcomes of Paliperidone Palmitate Compared to Daily Oral Antipsychotic Therapy in Schizophrenia: A Randomized, Open-Label, Review Board–Blinded 15-Month Study. *J Clin Psychiatry*. 2015;76(5):554-561.

50. Janssen. Invega Sustenna [package insert]. Available at: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=2ahUKEwjXte_9rJzmAhXBxVkKHS6TBfIQFjAAegQIBRAC&url=http%3A%2F%2Fwww.janssenlabels.com%2Fpackage-insert%2Fproduct-monograph%2Fprescribing-information%2FINVEGA%2BSUSTENNA-pi.pdf&usg=AOvVaw20mahQi1PBKu-DGzKRlZx8. Accessed December 4, 2019.

51. Dawson L. The Salk Polio Vaccine Trial of 1954: risks, randomization and public involvement in research. *Clin Trials*. 2004;1:122-130.

52. Meldrum M. "A calculated risk": the Salk polio vaccine field trials of 1954. *BMJ*. 1998;317:1233-1236.

53. Baicus A. History of polio vaccination. *World J Virol*. 2012;1(4):108-114.

54. The Acute Infarction Ramipril Efficacy Study I. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet*. 1993;342(8875):821-828.

55. Temple R. How FDA currently makes decisions on clinical studies. *Clin Trials*. 2005;2(4):276-281.

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

57. Janssen. Darzalex [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761036s003lbl.pdf. Accessed December 4, 2019.

58. Merck. Keytruda [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf. Accessed December 4, 2019.

59. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Application Number: 125514orig1s000. Summary Review 2014.

60. Køber L, Torp-Pedersen C, Carlsen JE, et al. A Clinical Trial of the Angiotensin-Converting–Enzyme Inhibitor Trandolapril in Patients with Left Ventricular Dysfunction after Myocardial Infarction. *N Engl J Med*. 1995;333(25):1670-1676.

61. Gruppo Italiano per lo Studio della Soprawivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet*. 1994;343(8906):1115-1122.

62. Novartis. Zykadia [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205755lbl.pdf. Accessed December 4, 2019.

63. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Application Number: 205755orig1s000. Other Review(s); 2014.

64. Friends of Cancer Research. Randomized and Single-Arm Trials. Available at: https://www.focr.org/randomized-and-single-arm-trials. Accessed December 4, 2019.

65. U.S. Department of Health & Human Services. AIDSinfo Glossary of HIV/AIDS-Related Terms. 9th edition; 2018. Available at: https://aidsinfo.nih.gov/contentfiles/glossaryhivrelatedterms_english.pdf. Accessed December 4, 2019.

66. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.

67. U.S. Food and Drug Administration. Expedited Programs for Serious Conditions — Drugs and Biologics Guidance to Industry: U.S. Department of Health & Human Services; 2014.

68. U.S. Food and Drug Administration. Code of Federal Regulations. 21CFR 314.126; 2018.

69. National Cancer Institute. Male Breast Cancer Treatment (PDQ®)–Health Professional Version. Available at: https://www.cancer.gov/types/breast/hp/male-breast-treatment-pdq#_71_toc. Accessed December 4, 2019.

70. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer: National Comprehensive Cancer Network; 2019.

71. Pernas S, Tolaney SM, Winer EP, Goel S. CDK4/6 inhibition in breast cancer: current practice and future directions. *Ther Adv Med Oncol*. 2018.

72. Midding E, Halbach SM, Kowalski C, et al. Men With a "Woman's Disease": Stigmatization of Male Breast Cancer Patients-A Mixed Methods Analysis. *Am J Mens Health*. 2018;12(6):2194-2207.

73. Bartlet et al. Real-world evidence of male breast cancer (BC) patients treated with palbociclib (PAL) in combination with endocrine therapy (ET). 2019 ASCO Annual Meeting.

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

75. Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: overview and treatment options. *P T*. 2014;39(9):638-645.

76. American Psychiatric Association. Schizophrenia Spectrum and Other Psychotic Disorders. In Diagnostic and Statistical Manual of Mental Disorders (5th ed.); 2013.

77. Potkin S, Bera R, Zubek D, Lau G. Patient and prescriber perspectives on long-acting injectable (LAI) antipsychotics and analysis of in-office discussion regarding LAI treatment for schizophrenia. *BMC Psychiatry*. 2013;13:261-261.

78. Greene M, Yan T, Chang E, et al. Medication adherence and discontinuation of long-acting injectable versus oral antipsychotics in patients with schizophrenia or bipolar disorder. *J Med Econ*. 2018;21(2):127-134.

79. Landmark Schizophrenia Data that Bring Hope in Breaking the Cycle of Hospitalization and Incarceration Receive FDA Approval for Inclusion in Invega Sustenna (paliperidone palmitate) Label. 2018; Available at: https://www.janssen.com/landmark-schizophrenia-data-bring-hope-breaking-cycle-hospitalization-and-incarceration-receive-fda. Accessed December 4, 2019.

80. Peppercorn M, Kane S. Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults; 2019. Available at: https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-prognosis-of-crohns-disease-in-adults. Accessed December 4, 2019.

81. Peppercorn M, Cheifetz A. Definitions, epidemiology, and risk factors for inflammatory bowel disease in adults; 2019. Available at: https://www.uptodate.com/contents/definitions-epidemiology-and-risk-factors-for-inflammatory-bowel-disease-in-adults?search=definitions-epidemiology-and-risk-factors-for-inflammatory-%20bowel-disease-in-adults&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed December 4, 2019.

82. Roda G, Jharap B, Neeraj N, Colombel J-F. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. *Clin Transl Gastroenterol*. 2016;7(1):e135-e135.

83. Crohn's and Colitis Foundation. Fact Sheet Biologics. 2018; Available at: https://www.crohnscolitisfoundation.org/sites/default/files/legacy/assets/pdfs/biologic-therapy.pdf. Accessed December 4, 2019.

84. Cohen R, Stein A. Management of moderate to severe ulcerative colitis in adults; 2019. Available at: https://www.uptodate.com/contents/management-of-moderate-to-severe-ulcerative-colitis-in-adults. Accessed December 4, 2019.

85. Card T, Xu J, Liang H, Bhayat F. What Is the Risk of Progressive Multifocal Leukoencephalopathy in Patients With Ulcerative Colitis or Crohn's Disease Treated With Vedolizumab? *Inflamm Bowel Dis*. 2018;24(5):953-959.

86. Dubinsky M, Panaccione R, Lopez-Sanroman A, et al. P024 Patient and Healthcare Provider Views on Ulcerative Colitis Treatment Goals and Quality of Life: Results of a Global Ulcerative Colitis Narrative Survey. *Gastroenterology*. 2019;156(3):S17-S18.

87. Rubin DT, Dubinsky MC, Martino S, Hewett KA, Panés J. Communication Between Physicians and Patients with Ulcerative Colitis: Reflections and Insights from a Qualitative Study of In-Office Patient-Physician Visits. *Inflamm Bowel Dis*. 2017;23(4):494-501.

88. Crohn's and Colitis Foundation. Survey of Ulcerative Colitis Patients and Gastroenterologists Indicates that Symptoms May Create a New Reality for Patients. 2017; Available at: https://www.crohnscolitisfoundation.org/news/UCNarrative. Accessed December 4, 2019.

89. Freeman H-J. Use of the Crohn's disease activity index in clinical trials of biological agents. *World J Gastroenterol*. 2008;14(26):4127-4130.

90. Dave M, Loftus EV, Jr. Mucosal healing in inflammatory bowel disease-a true paradigm of success? *Gastroenterol Hepatol (N Y)*. 2012;8(1):29-38.

91. Lewis JD, Chuai S, Nessel L, et al. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis*. 2008;14(12):1660-1666.

92. Dewar M, Curry R. Chronic Obstructive Pulmonary Disease: Diagnostic Considerations. *Am Fam Physician*. 2006;73(4):669-676.

93. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Approval Package For: Application Number: 21-395/S029. Administrative and Correspondence Documents; 2009.

94. Wheaton AG, Cunningham TJ, Ford ES, Croft JB. Employment and activity limitations among adults with chronic obstructive pulmonary disease — United States, 2013. *MMWR Morb Mortal Wkly*. 2015;64(11):289-295.

95. Sullivan J PV, Mannino DM, Siegel K, Choate R, Sullivan T. National and State Estimates of COPD Morbidity and Mortality — United States, 2014-2015. *Chronic Obstr Pulm Dis*. 2018;5(4):324-333.

96. Global Initiative for Chronic Obstructive Lung Disease. Pocket Guide to COPD Diagnosis, Management, and Prevention: A Guide for Health Care Professionals; 2019. Available at: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-POCKET-GUIDE-DRAFT-v1.7-14Nov2018-WMS.pdf. Accessed December 4, 2019.

97. Boehringer Ingelheim. Spiriva HandiHaler [package insert]. U.S. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021395s029lbl.pdf. Accessed December 4, 2019.

98. Jones P, Miravitlles M, van der Molen T, Kulich K. Beyond FEV_1 in COPD: a review of patient-reported outcomes and their measurement. *Int J Chron Obstruct Pulmon Dis*. 2012;7:697-709.

99. Cazzola Mea. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J*. 2008;31:416-468.

100. National Clinical Guideline Centre (UK). Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care [Internet]. London: Royal College of Physicians (UK); 2010 Jun. (NICE Clinical Guidelines, No. 101.) 6, Diagnosing COPD. Available at: https://www.ncbi.nlm.nih.gov/books/NBK65029/. Accessed December 4, 2019.

101. Molen TVD, Pieters W, Bellamy D, Taylor R. Measuring the success of treatment for chronic obstructive pulmonary disease—patient, physician and healthcare payer perspectives. *Respir Med*. 2002;96:S17-S21.