Current Considerations on Real-World Evidence Use in FDA Regulatory Submissions

Examples and decision making from the Center for Devices and Radiological Health's Peripheral Interventional Devices Branch.

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In specific circumstances, real-world evidence can contribute to a fuller understanding of the benefits and risks of medical device use in patients in real-world clinical practice, as a means of supporting regulatory decision making. The US Food and Drug Administration (FDA) recognizes the wealth of data available from clinical experience, and ongoing efforts to balance premarket and postmarket data collection and consider the potential benefits and risks represent an attempt to streamline the regulatory approval process while generating robust and meaningful evidence to support the safety and effectiveness of devices.

As currently defined by the FDA, *real-world data* are data relating to patient health status and/or the delivery of health care that are routinely collected from a variety of sources, which can include data derived from electronic health records, claims and billing information, product and disease registries, patient-generated data including home-use settings, and other sources. *Real-world evidence* is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data.

The use of real-world evidence has many potential benefits, including swifter identification of safety problems following the introduction of a device into the general marketplace, the ability to better understand the benefit-risk profile of devices, and the reduction of time and cost of evidence generation to support regulatory submissions. However, there are also some potential limitations that may discourage the use of real-world evidence as a primary source of clinical evidence, which may include data relevance, quality, reliability, and bias.[1] Because of these factors, careful consideration is needed when determining the appropriateness of using real-world evidence to support regulatory submissions. In this article, we provide examples of when the use of real-world evidence, either pre- or postmarket, has adequately supported the expansion of indications of previously approved peripheral vascular devices.

PREMARKET USE OF REAL-WORLD EVIDENCE

The Peripheral Interventional Devices Branch of the Division of Cardiovascular Devices at the FDA has considered real-world evidence sufficient to support the approval of several recent regulatory submissions for both marketing approval as well as postmarket surveillance. As noted in the real-world evidence guidance document, a good example where real-world evidence may be valuable is for the expansion of the indications for use of an approved or cleared device, particularly when the studied indication is similar to the approved indications (eg, longer lesion lengths, specific lesion types).[1] This strategy has successfully been employed

to expand the indications for use of the three following peripheral products:

- **In.Pact Admiral paclitaxel-coated percutaneous transluminal angioplasty (PTA) balloon catheter (Medtronic).** To support the safety and effectiveness of the In.Pact Admiral drug-coated balloon (DCB) for treating in-stent restenosis (ISR), Medtronic compared data from the ISR cohort of the IN.PACT Global Study with an uncoated PTA ISR group derived from the Society for Vascular Surgery's Vascular Quality Initiative (VQI). This prospectively designed, propensity score–matched comparative study demonstrated superior effectiveness of the DCB cohort to the PTA cohort to support an indication expansion to include treatment of ISR in the superficial femoral artery (SFA) and proximal popliteal artery.[2]

- **Zilver PTX drug-eluting peripheral stent (Cook Medical).** Data from a global, single-arm study, as well as a Japanese postmarket surveillance study, supported an expansion of the indications of the Zilver PTX device for treating a maximum SFA/proximal popliteal artery lesion length of 140 mm/limb to up to 300 mm total. Both studies assessed the use of the Zilver PTX device in real-world populations (eg, limited inclusion and exclusion criteria). Patients were treated per standard of care and assessed for clinically driven symptoms. The extensive clinical evidence supported the safe and effective use of this device in longer lesions.[3]

- **Lutonix 035 DCB PTA catheter (Bard Peripheral Vascular, Inc.).** Data from two real-world registries, including the Global SFA Registry—which included both ISR and long lesion cohorts—and Global Long Lesion Registry, were evaluated to support an indication expansion to include ISR and lesions lengths up to 300 mm. Both studies analyzed the use of the Lutonix DCB in real-world populations that were treated per standard of care and assessed for clinically driven symptoms. The clinical evidence supported the safe and effective use of this device in ISR and long lesions.[4]

In these three examples, real-world evidence was submitted to expand the indications of marketed peripheral vascular products. When deciding if real-world evidence was appropriate for this type of indication expansion, the review division weighed the benefits and risks of these treatments compared with alternatives for the newly indicated population to evaluate whether there may be any additional risks associated with the new indications statement that might necessitate a more traditional clinical study. The risks identified for these indications expansions were evaluated and mitigated through additional bench and preclinical evaluations. Safety data were also leveraged from the pivotal clinical trial used to support the original approval in the same vascular location. Within the benefit-risk framework, regulatory decisions are made in part based on the relevance and reliability of the data source. Some regulatory decisions will have different evidentiary needs, depending on the stage of device development and the benefit-risk profile. In these cases, the team judged that the real-world evidence collection and analysis methods ensured the relevance and reliability of the data. Therefore, the review division determined that using real-world evidence was appropriate and least burdensome to support the reasonable assurance of safety and effectiveness for the inclusion of ISR lesions and long lesions in the indications statements.

For examples such as these, a presubmission discussion with the review division is often beneficial to determine the acceptability of using supportive real-world evidence and to discuss the proposed prospective analysis strategy. As part of this strategy, developing a prospective analysis plan (eg, propensity scoring against a concurrent registry control) with prespecified success criteria is advantageous to generate quality analyses, reduce potential bias, and further support labeling.

POSTMARKET USE OF REAL-WORLD EVIDENCE

Real-world evidence may also be a valuable tool in conducting postapproval device surveillance. When limited data are available or additional questions remain from the pivotal trial, the use of registry data may be an efficient and effective way to answer any remaining questions, such as to support a condition of approval requirement for that marketing application. The use of real-world evidence data in the postmarket setting may also allow for reduced premarket data collection. The benefits of using real-world evidence for postmarket use as compared with a more traditional postapproval study may include swifter enrollment and the potential for generation of more useful real-world data. Although subjects from these data sources represent a more real-world population, the follow-up, end-

points, comparators, and event adjudication for these data sources could be designed to be similar to the prospectively designed postapproval study, if needed, in order to ensure data quality. This type of real-world evidence for postmarket use has recently been used effectively in the following examples:

- **LifeStent vascular stent system (Bard Peripheral Vascular, Inc.).** The LifeStent's indications for use were expanded to include lesions in the mid and distal popliteal artery based on data collected from a prospective, multicenter, physician-sponsored study in addition to an agreement by the sponsor to conduct a postmarket surveillance registry of 74 United States patients through the VQI Peripheral Vascular Intervention Registry through 24 months to evaluate clinical outcomes in a real-world population.[5]

- **In.Pact Admiral paclitaxel-coated PTA balloon catheter.** For the previously discussed ISR indication, a postmarket registry was included as a condition of approval for surveillance of 300 DCB ISR patients through the VQI for 36 months. The purpose of this study is to evaluate the outcomes in the United States patient population, as the premarket data set came from European subjects.[6]

With these two examples, data from these registries will provide additional assurance of safety and effectiveness in a real-world population and longer-term data. Real-world evidence was determined to be appropriate for these postapproval commitments, as the data quality and reliability was ensured based on the prospective design of the studies. It is also assumed that the enrollment and data collection for these studies will be quicker and will allow for a swifter evaluation of the results of these registry data. As previously noted, a presubmission discussion with the review division is often beneficial to determine the acceptability of using supportive real-world evidence for postapproval commitments.

CONCLUSION

Leveraging real-world evidence in both the pre- and postmarket setting can be an effective way for the FDA to evaluate the benefit-risk profile of devices at various points in the total product life cycle. This approach has numerous benefits, including the potential reduction of cost and time of evidence generation to support regulatory decisions. Inclusion of the real-world evidence in the labeling could also help physicians make better-informed treatment decisions. However, as compared to well-controlled clinical trials, there are limitations due to the underlying relevance, quality, and reliability of the data sources and additional confounding factors related to real-world clinical practice. Therefore, careful consideration should be taken when determining whether real-world evidence is appropriate to support a regulatory submission. The FDA encourages companies to submit their proposals through the presubmission process to determine whether the use of real-world evidence is an appropriate strategy for their specific device and indication. ■

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