Innovation in Regulation Applied to Descending Thoracic Aortic Endografts

FDA Regulatory Review Scientist Dorothy B. Abel discusses what led to the unique expanded approval of a thoracic endograft and a landmark postapproval study.

In September 2013, the US Food and Drug Administration (FDA) broadened its approval of the Gore TAG thoracic endoprosthesis (Gore & Associates, Flagstaff, AZ) to remove the exclusion of repair of dissections of the descending thoracic aorta from the indications for use. Originally approved for the treatment of aneurysms in the descending thoracic aorta (its previous iteration having received the first thoracic approval in 2005), the device's approval was previously expanded to the repair of isolated lesions of the descending thoracic aorta, a designation that included all types of isolated lesions (eg, traumatic transections, intramural hematomas, penetrating ulcers), but excluded dissections.

The pathway that led to these approvals was unique. FDA regulatory agents, leading aortic experts from a variety of specialty backgrounds, and industry representatives with otherwise competing interests worked collaboratively over a number of years with a common goal of identifying the outstanding questions with the endovascular treatment of thoracic aortic pathologies and the appropriate mechanisms to answer these questions. Some will be addressed postmarket using an innovative postmarket study. To learn more about the approval pathway and the goals of the postapproval study, Endovascular Today *asked Dorothy B. Abel to share her insights.*

The nature of the Gore TAG's expanded indication approval appears to be distinctly different from other FDA device approvals. The language is broader and less specific with respect to particular disease or injury states. Is it fair to say that this is a unique approval?

I agree that the approval of the broad indication is atypical compared to the labeling for most endovascular implants. Labels traditionally reflect the selection criteria for a clinical study, including the type and location of the lesion treated and any anatomical limitations. For example, the initial approval of thoracic endografts was for the treatment of aneurysms of the descending thoracic aorta in patients with suitable anatomy for endovascular repair. The description of *suitable anatomy* was spelled out in the indications for use statement for each device.

Can you explain why the FDA used this approach for expanding the indications for thoracic endografts in particular?

This innovative approach for evaluating and labeling thoracic endografts has been in the works for many years, as described in the August 2009 FDA Insights column in *Endovascular Today*. In 2008, we met with representatives from industry, the Society for Vascular Surgery, the Society of Thoracic Surgery, the Society of Interventional Radiology, and the American Association of Thoracic Surgeons to discuss how to best evaluate endografts to support labels that would cover the many ways they were being used since their first approval for the treatment of aneurysms in 2005. There was general consensus that it would be difficult to complete separate studies for every lesion type that could be treated with an endograft. Also, well-defined clinical guidelines for when to treat every type of lesion were not available;

that is, there was a lack of information to drive the development of appropriate selection criteria for such studies.

What solution was suggested to get more uses of these devices on label?

Based on the discussion during the meeting, the FDA agreed to the concept of allowing a broad indication for an individual endograft for the treatment of descending thoracic lesions (rather than specifying the lesion types in the device label) with the submission of adequate safety and effectiveness data for the treatment of aneurysms, transections, and acute complicated type B dissections.

Why were these particular lesion types selected?

We agreed that aneurysms, acute complicated type B dissections, and transections were the most common and clinically significant descending thoracic aortic pathologies treated with endografts. Also, appropriate studies were relatively easy to develop, as the criteria for treatment were well established for these pathologies.

What information did you expect to get from each of the studies?

Data from clinical studies for the treatment of aneurysms and acute complicated type B dissections would address delivery and deployment, as well as seal and fixation, within a broad range of anatomical variation. Transection data would include the evaluation of focal aortic lesions in more angulated, smaller aortas and the problems of bird-beaking and collapse that were reported in the literature, most commonly with the treatment of transections.

Why didn't you require clinical data for the other pathologies, including chronic dissections?

Although it would be preferable to have data for every lesion type and reason for treatment, the outcomes from the aneurysm, transection, and acute complicated type B dissection studies provide useful insight into the expected device performance for the treatment of all types of descending thoracic aortic lesions. Additionally, the absence of reports in the literature describing unique device-related problems associated with the treatment of chronic dissections and other less common lesion types supported this unique regulatory strategy.

With respect to chronic dissections, the lack of adequate control data and the variability in the patient population would complicate interpretation of study data. Also, the main question regarding the treatment of chronic dissections is when to treat, not the expected performance of an endograft when used to treat a chronic dissection. These issues could not reasonably be addressed in a premarket study, considering the relatively small number of patients that could realistically be enrolled. It was agreed that additional information on the real-world use of endografts to treat all type B dissections would best be captured postmarket.

What will the postapproval studies consist of for devices with the broad thoracic indication?

The planned postapproval study (PAS) is as unique as the approval of the broad indication. As described in the approval order for the Gore TAG, the PAS may include enrollment of patients treated with the TAG device or any other thoracic endovascular graft. The study will only include acute and chronic type B dissection study arms because the outstanding questions are specific to the treatment of dissections. Long-term data have already been collected for the treatment of aneurysms with the TAG device, and postmarket data were not required with the previous expansion of the indications to include other isolated lesions.

The PAS will enroll 200 acute and 200 chronic type B dissection patients, with follow-up out to 5 years. Dissection-related mortality, device technical success, and device procedural success will be the primary endpoints. Although this study will include an evaluation of device performance, the more interesting aim of the study is to provide an overall assessment of the treatment of type B dissections using endografts, including false lumen characteristics over time and the need for additional dissection-related interventions.

With any trial or study, there are challenges in defining key terms and criteria, and this is certainly the case in the thoracic arena. How were key terms and endpoints decided upon for the PAS?

The same approach used to establish the plan for the premarket evaluation of thoracic endografts for the broad indication has been used in developing the postmarket plan. The manufacturers, clinicians, and FDA have worked together to develop an acceptable protocol, including endpoints and definitions appropriate for the evaluation of endografts for the treatment of type B dissection.

What are some of the most notable definitions?

The most important new definitions are those initially proposed by Dr. Mike Dake for false lumen perfusion. These definitions include the source of the blood flow,

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similar to the definitions of endoleaks described by Dr. Geoff White for the treatment of aneurysms. For example, primary intimal tear false lumen perfusion (PIT FLP) is defined as flow from a proximal aortic source through the primary intimal tear, into the aortic false lumen (similar to a type IA endoleak after treatment of aneurysms). Rather than using the term *type II endoleak* for perfusion originating from the left subclavian artery, proximal branch false lumen perfusion (PB FLP) is defined as flow into the aortic false lumen via retrograde flow from aortic arch branch vessels. Use of the new definitions will avoid assumptions regarding the significance of the false lumen perfusion, since PB FLP is less likely to be benign as compared to a type II endoleak after aneurysm treatment.

Other definitions are particularly important, as the hope is that the study will be conducted within an existing registry; concise data requirements are needed to minimize reporting bias. For example, the definition for dissection-related interventions describes the types of interventions that will be considered dissection related, rather than relying on a determination by the site.

Why might the nature of this approval potentially be unique to this device type, the anatomy, and its related disease states?

I'm not sure how often the question of when to treat a problem can be separated from device performance. For the TAG device, we have reasonable assurance of safety and effectiveness of the device for treating a thoracic aortic lesion, if the lesion needs to be treated. In other words, we have evidence to support the use of the TAG device as a treatment option if there is a decision to treat. Given the diversity of thoracic lesions and the many variables to consider in determining the time to treat, insights on this question can better be addressed through non–device-specific studies (eg, the INSTEAD study).

For all endovascular devices, we need to determine the most reasonable and feasible evaluation plan, addressing the variables that could affect device performance, such as lesion length, size or severity, as well as other factors that could affect the benefit/risk profile of the device, including the availability of alternative treatment options and the risk tolerance of the patient population. For thoracic endografts, meeting this regulatory challenge was possible only because of the dedication of the clinical advisors and the collaboration of the otherwise competitive device manufacturers. ■

Dorothy B. Abel is a Regulatory Review Scientist with the US FDA Center for Devices and Radiological Health in Silver Spring, Maryland. Ms. Abel may be reached at (301) 796-6366; dorothy.abel@fda.hhs.gov.