

# The Preclinical Testing of Endovascular Grafts

How the FDA, physicians, and industry are working together to develop new testing and performance standards.

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*The views and opinions in this article are those of the authors and do not necessarily reflect those of the US FDA, the US Department of Health and Human Services, or the Public Health Service.*



The challenges of preclinical testing are to characterize the device and hopefully predict clinical performance, or at least allow for the extrapolation of relatively short-term clinical data for the longer term. Although testing of endovascular grafts has been adequate for characterization, in

some cases this testing has fallen short with respect to predicting clinical failures. The FDA has been working with manufacturers, clinicians, and other scientists to optimize endovascular graft preclinical testing.

## IN THE BEGINNING

When endovascular grafts were first being developed in the US in the early 1990s, the testing guidance available was limited to standards and guidances for vascular grafts and vascular stents. Although these documents were useful tools for initiating test plans, it was imperative that each manufacturer conduct an independent risk assessment to identify the additional necessary testing for their specific design. Furthermore, there were limitations on the understanding of the *in vivo* environment into which these devices would be introduced. As such, testing plans were inconsistent between manufacturers, and often the testing was not adequate to predict clinical performance.

## THE 2001 WORKSHOP

In an effort to improve preclinical testing, the FDA held a workshop 3 years ago, hoping to define the environment within which the devices needed to function and to identify the key parameters or issues that were not incorporated in bench testing. Although important characteristics that

affect clinical performance (eg, neck angulation) were identified, no agreement was reached on the following:

- the amount and significance of vessel/endograft compliance on device performance;
- the significance of forces other than those generated by pressure (eg, those generated by blood flow); and
- whether devices should be tested only within the limitations of the labeling or if the preclinical testing should address probable clinical use conditions.

Areas identified as needing additional consideration included the following:

- how to define, measure *in vivo*, describe, or quantify the characteristics identified;
- how to appropriately model these characteristics in preclinical testing given the extreme diversity of the parameters and the interrelationship between the parameters; and
- how to balance between “ideal” and what is practical.

Much time was spent discussing durability testing, the limitations of this testing, and possible ways to improve it.

This workshop succeeded in bringing the stakeholders together to define the problems and to identify areas of agreement and disagreement. The discussions from this workshop were considered while drafting the test methods for evaluating endovascular grafts for the International Organization of Standardization (ISO) standard for these devices.

## THE ISO STANDARD

The official title of the endovascular graft standard is ISO 25539-1: 2003 Cardiovascular implants—Endovascular devices—Part 1: Endovascular prostheses. This standard will be amended to include test methods in the near future. ISO standards reflect the state of the art and are not intended to establish new methods of testing. Given this limitation, the information from the 2001 FDA workshop appears primarily as informative notes within the standard. For example,

several notes have been included that recommend additional testing be considered to incorporate the effects of neck angulation on device performance.

Although incorporating the test methods in the standard will not resolve all of the outstanding limitations of endovascular graft preclinical testing, the future addition of test methods should greatly improve the consistency of testing among manufacturers. In addition, as these test methods were developed and reviewed by a vast number of experts in the field, use of the methods will also globally improve the preclinical testing of endovascular grafts.

### THE 2004 WORKSHOP

At the conclusion of the first FDA workshop, the feedback received was overwhelmingly in favor of the FDA hosting future workshops on this topic. Due to popular demand, availability of significant additional clinical experience as compared to 2001 and the continuing need to improve preclinical testing, a second workshop was held in July 2004. In preparation for this workshop, manufacturers were asked to provide information related to the following topics which were to be the subjects of discussion during the sessions of the workshop: (1) animal studies; (2) sealing and fixation effectiveness; and (3) implant integrity or durability. The intent was to provide a compiled summary of the testing that had been conducted to date regarding these areas to serve as a basis for the discussion during the workshop.

The objectives for the workshop for each of the sessions were as follows: (1) describe the testing that had been done in the past; (2) determine what had been learned from these studies; (3) identify issues or concerns that had not been adequately addressed; (4) propose modifications to address these limitations; and (5) discuss how to implement the proposed modifications. Each session started with one or two presentations, followed by a brief summary of the compiled manufacturers' responses and discussion with invited participants and audience members. During the discussion, tables were completed in real time to capture the information discussed related to the session objectives. Ultimately, a summary of the discussion and outcome of the workshop will be published in a more detailed article and provided on the FDA Web site, which can be accessed at <http://www.fda.gov/cdrh/meetings/072804workshop/>.

Although there was much discussion regarding the utility of animal studies, most participants agreed that studies are needed to evaluate tissue reaction and inflammatory response, as well as to evaluate the performance of the delivery system. There was disagreement with respect to the duration of study needed. As a result, several different strategies were discussed, including incorporating interim endpoints to justify stopping a study and the use of nonde-

structive evaluations. In addition, it was suggested that it may be possible to develop an atherosclerotic disease or aneurysm model in order to better simulate the clinical environment; however, such a model would need to be validated before it would be useful.

Many potential modifications to current bench testing methodologies were discussed, including:

- testing to the worst case;
- evaluating parameters over a range of values to provide tolerance limits;
- identifying maximum and minimum acceptance criteria; and
- setting appropriate boundary conditions for each parameter.

In addition, many participants and audience members agreed that research needs to be conducted to develop test methods that incorporate anatomical characteristics not addressed by current testing, including changes in vascular morphology, pre-existing vessel tortuosity, atherosclerotic/diseased vessels, and aortic neck angulation.

Before the close of the workshop, timeframes for completing work were proposed. For example, industry-sponsored development of test methods to modify migration resistance testing to incorporate vessel morphology should be accomplished on an individual basis now, and mainstream acceptance should be obtained in several years.

### THE FUTURE

Manufacturers have come a long way in improving preclinical testing. Many indicated that new testing is being performed to better simulate clinical use and patient anatomy. Some manufacturers have further developed their test methods to the point of being able to duplicate clinical failures on the bench. These methods are being used to improve current designs. Unfortunately, these test-method advances are not being shared. In the future, it may be possible to improve communication by developing a Web-based system to consolidate information on defining the environment, improving testing methodologies, and sharing current research. In addition, the ISO standard may be modified to include the appropriate information as this device area evolves. Continued collaboration among industry, academia, regulators, clinicians, testing facilities, and other stakeholders will continue to improve the predictability of endovascular graft performance based on preclinical testing. ■

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