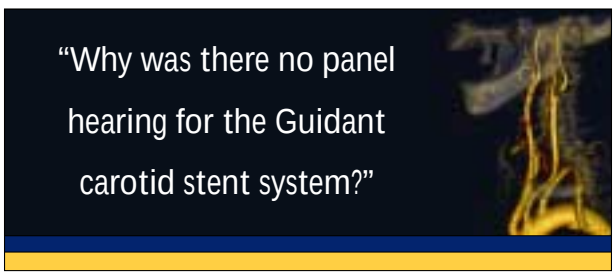
FDA Approval of Carotid Artery Stenting

Dorothy B. Abel, Acting Chief of the FDA's Peripheral Vascular Device Branch, and Glenn Stiegman, Biomedical Engineer of the Peripheral Vascular Device Branch, discuss the issues surrounding the recent approval of the Guidant's carotid stent system.

On August 31, 2004, the FDA announced that it had approved Guidant Corporation's (Indianapolis, IN) carotid stent system, which is composed of the RX Acculink Carotid Stent System and the RX Accunet Embolic Protection System. Prior to this recent announcement, the devices were only approved for use in investigational device exemption clinical trials. The Acculink and Accunet are indicated for the treatment of patients at high risk for adverse events from carotid endarterectomy who require carotid revascularization and who meet the following criteria: (1) patients with neurological symptoms and ≥50% stenosis of the common or internal carotid artery by ultrasound or angiogram, or patients without neurological symptoms and ≥80% stenosis of the common or internal carotid artery by ultrasound or angiogram; and (2) patients must have a reference vessel diameter within the range of 4 mm and 9 mm at the target lesion.

Endovascular Today: Many people were surprised by this recent approval. In April, Cordis (a Johnson & Johnson company, Miami, FL) appeared before the FDA's Circulatory System Devices Panel, which voted 6-5 in favor of approval. Why was there no panel hearing for the Guidant carotid stent system?

Glenn Stiegman: There are three criteria for determining whether the FDA will request that a new device be submitted to a panel:



(1) We do not have the knowledge or experience to properly evaluate the types of safety and effectiveness questions posed by the new device without panel input;

(2) The specific PMA raises a new issue that is best addressed by employing the breadth of knowledge and experience afforded by convening an advisory panel meeting; or

(3) The data establishing the clinical performance of the device reveals unanticipated safety and effectiveness questions that would best be addressed through panel deliberations.

With Guidant's clinical trial, we felt that there were no such issues. We thought that the panel that met in April for the Cordis study had already outlined everything that we would want to ask, and no new issues needed to be addressed.

EVT: Why was Cordis required to appear before the panel first?

Dorothy B. Abel: Because Cordis was the first to reach that stage in their PMA.

EVT: Is there a lesson here? If a company goes to panel first, and is subjected to the time, expense, and pressures associated with that process, and then watches as another company obtains approval before them, might they not conclude that it is better to be second, and obtain approval without going before the panel?

DBA: No company knows definitively whether they will be required to appear before the panel until after they submit their application. The FDA did not prospectively determine that we would send the first applicant to panel, but not the others. This determination hinged on how thoroughly the panel discussed global issues regarding the technology for the first application. As another example, for abdominal aortic endografts, the first four applicants went to panel; the FDA has now publicly stated that as long as future applications did not present any new issues, the applicants will not be going to panel. Previously, the FDA has had a unique issue with respect to each endograft applicant such that we deemed it appropriate to obtain panel input. So, I don't think this approval will result in a lot of jockeying to be second to file a PMA for a new technology.

EVT: Did it matter that the SAPPHIRE trial had randomized data, whereas ARCHeR did not?

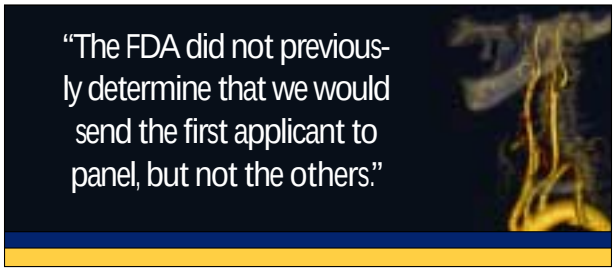
GS: No. Each PMA stands on its own; from the beginning we knew what Guidant was trying to accomplish, and they clearly demonstrated that with their clinical trial.

EVT: Is it correct that the FDA is approving stents through a PMA process and distal protection devices through a 510(k)?

GS: Yes.

EVT: Why the difference?

GS: The embolic protection filter system is predicated on filter systems used in the coronary arteries that were cleared for marketing through the 510(k) process. The manufacturers have established the link between the two procedures with actual clinical data showing that the devices are substantially equivalent in safety and efficacy. In contrast, vascular stents are class III devices and their safety and effectiveness must be demonstrated prior to approval.



DBA: The difference between 510(k)s and PMAs has been explained in previous articles. In summary, with a PMA you are demonstrating that the product is reasonably safe and effective, whereas with a 510(k), you are claiming that your device is substantially equivalent to a predicate device; that is, a device that is legally marketed in the US. Whether a device is reviewed under a 510(k) or a PMA is based on the risk-based regulatory classification of the device. Because embolic protection devices are only used during the procedure and they have already been cleared for use in coronary procedures, they have been classified as class II devices and are reviewed under the 510(k) process.

EVT: Now that a carotid stent system has been approved, will the other distal protection devices go through the 510(k) pathway?

GS: If the distal protection system can be determined to be substantially equivalent to a previously 510(k)-cleared system, it will go through the 510(k) process. The stent, however, will continue to go through the PMA process.

DBA: The differentiation, again, is that the amount of regulatory oversight we need for a class III device is different than that required for a class II device. It's not just a question of whether there is an approved carotid stent out there. It's that we have determined that carotid stents are class III devices and therefore each new stent must be shown to be reasonably safe and effective before it can be approved. This involves submission of much more extensive data and manufacturing information, as well as post-market requirements that are more rigorous than for class II devices.

EVT: Post market studies are a required aspect of the carotid stenting approval process. What do they entail?

GS: Any manufacturer of an approved carotid stent will be required to perform post-market studies. These studies will provide information on the longer-term performance of the stents, information on rare events, and

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an evaluation of the performance of the stent outside of the confines of a clinical study. PMAs are approved on clinical data collected under very strict criteria of inclusion/exclusion. We all realize that once the product is out on the market, it is going to be used under conditions unlike the controlled studies. For example, stenting will be performed by interventionists or surgeons from different regions of the country with differing levels of experience. Additional study is required to gather information to ensure that the results reported in the post-market surveillance are in accord with those reported in the premarket studies.

DBA: The description of the post-market studies required is set forth in the approval order. In addition to what Glenn has mentioned, we also advise manufacturers that if during their post-approval studies they see that the device is often used outside of the labeled indication, we would expect them to submit an IDE for the different indication.

EVT: What are the stopping rules that are going to go into effect with regard to these postmarket studies?

DBA: I'm not sure if we could answer that because it isn't publicly available. There certainly are stopping rules, and generally stopping rules have to do with complication rates. The expectation for most post-market studies would be to use the information obtained to determine whether changes are needed to the training program, labeling, the device, or the manufacturing process to obtain results comparable to the pre-market studies.

EVT: Will the data from the postmarket surveillance studies be accessible by the public?

GS: One of our conditions of approval is to require the sponsor to provide a clinical update for the physician users. We specify in the conditions what type of update and the data they are to present to the clinicians.

EVT: What is the status of the approval for Cordis? I have heard their device referenced as having received conditional approval.

DBA: You don't really get a conditional approval on a PMA. The options are not-approvable, approvable, or approved. Approvable means that there are some issues that you have to take care of before you can get a full approval. There are different reasons for the approvable and an example is an approvable pending Good Manufacturing Practice (GMP) issues.

EVT: So, to interpret their press release, Cordis really has an "approvable" determination, not a conditional approval>

DBA: That would be correct.

EVT: What will be required by the FDA to expand the indication beyond the high-risk patients?

GS: Valid scientific data. Somebody would have to come in with a new study proposal wanting to look at lower-risk patients and then actually complete that study.

EVT: Would the FDA require randomized enrollment in those studies?

GS: It is possible that the FDA could approve a nonrandomized lower-risk study. Lower-risk patients, however, have the option of carotid surgery, and therefore we would prefer a randomized study because that would be the most scientifically valid method.

EVT: Under the present approval of Guidant's carotid stent system, are compassionate and emergency uses that fall outside of the inclusion criteria still approved under the IDE?

DBA: Yes. The FDA rules pertaining to compassionate and emergency use remain the same for carotid stents as they do for other devices. In the case of compassionate use, the devices can be used for patients who fall outside the

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inclusion criteria, provided that the physician obtains prior approval from the FDA to use the device for that particular case. In the case of emergency use, no prior FDA approval is required; however, the FDA needs to be notified of each emergency-use case. Having said that, however, often IDEs are closed after PMA approval of the device, unless other studies are ongoing under the IDE.

EVT: Has the FDA mandated any particular training for carotid stenting?

DBA: We do not mandate the type of training. The sponsor proposes their training, and we interact to come up with a mutually acceptable plan. In the approval order, we acknowledge that the manufacturer has provided us with a training program and we concur with the endpoints to be used to evaluate the program. The approval order further requires that the sponsor report back to us their evaluation of their program in reports to the PMA.

EVT: What was it that the FDA was looking for with regard to industry training mandates?

DBA: We were looking for industry to provide us with their strategy based on what they learned from training at the sites participating in their clinical studies, from the outcomes from their studies, and from their overall experience. We are looking for a very rigorous training program, and for them to address the different levels of experience that clinicians have.

EVT: What role will medical simulation have in training?

DBA: Medical simulation will certainly be a key aspect of the carotid stenting training, but you cannot rely exclusively on simulators. There will need to be hands-on proctoring and oversight of initial clinical use.

GS: The FDA ensures that the company looks at each site and investigator, and appreciates what worked, what didn't work, and what training regimen was most efficient in terms of getting the best results. They then need to incorporate this feedback into the most efficient and effective training program possible.

EVT: CMS recently conducted a town hall meeting regarding a possible change in their noncoverage policy for carotid artery stenting. At that meeting, they discussed the possibility of a national standard for accreditation. Does the FDA take any position on that?

GS: No.

EVT: Is there any coordination between the FDA and CMS on carotid stenting?

DBA: We've been working closely with CMS, especially in the last couple of months. We're trying to assist in terms of looking at how the postapproval information that will be collected would be of use to CMS. So the companies, medical societies, and FDA, and CMS are all trying to coordinate to a degree. We do have some limitations, however, because the FDA cannot recommend whether a procedure should be reimbursed or not. We have to be careful not to be influencing them, but we are certainly communicating with them to help them identify sources of information.

GS: Also, as you know, CMS issued a new reimbursement determination that is out for comment for the next 30 days on post-approval studies for carotid stenting. They're proposing to provide reimbursement for a particular patient population if a company wants to conduct a postapproval study, which will also help the FDA get the post-market surveillance data in a timely and efficient manner. ■

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

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