The Food and Drug Administration Medical Device Review Process

Clearance of a Clot Retriever for Use in Ischemic Stroke

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The Food and Drug Administration (FDA) is responsible for protecting the public health by assuring the safety and effectiveness of a variety of medical products, including drugs, devices, and biological products, and for advancing public health by helping to speed innovations that make treatments more effective, safer, and more affordable. The Center for Devices and Radiological Health (CDRH) in the FDA is responsible for premarket and postmarket regulation of medical devices. On August 11, 2004 the FDA gave market authorization to the first medical device specifically indicated to retrieve blood clots from the brain in ischemic stroke for patients who fail or are ineligible for intravenous tissue plasminogen activator (tPA). This article summarizes the FDA regulatory process for marketing medical devices in general and provides background on the FDA clearance of a clot retriever for ischemic stroke.

FDA Medical Device Regulations

There are several types of marketing applications that a medical device manufacturer may submit to CDRH. Most medical devices reach the market through either the premarket approval (PMA) process or the premarket notification process (510(k)). In fiscal year 2003, the FDA gave market authorization to 4132 devices through the 510(k) program and 31 devices through the PMA program.

Medical device manufacturers submit PMAs for novel devices, also referred to as Class III. These devices tend to be higher risk or raise new types of safety and effectiveness questions that must be answered before approval for marketing. Data in a PMA application must demonstrate a “reasonable assurance” of safety and effectiveness. Manufacturers submit 510(k)s for devices similar to those already on the market. Data in a 510(k) submission must demonstrate that the new device is substantially equivalent in safety and effectiveness to a Class II device already on the market.

Based on the incremental nature of device development, the majority of device applications cleared under the 510(k) program are based on nonclinical testing with no clinical data. Although the majority of PMA applications do contain clinical data, study designs are not prescribed by regulations. Rather, a hierarchy of “valid scientific evidence” is described in law, ranging from well-controlled investigations, partially controlled studies, and objective trials without matched controls to well-documented case histories conducted by qualified experts and reports of significant human experience with a marketed device.

As will be explained in the following section, many devices are developed as tools for the user community, and the development program is aimed at demonstrating the device is a safe and effective tool for the user community. The clinical community will often continue to study the medical device after marketing to develop a more refined understanding of the patient population most likely to benefit and to quantify that benefit.

Development Process for Medical Devices

Development of medical devices differs significantly from that of drugs. Many devices are first designed and developed as “tools” to accomplish a task that is already established practice, which means that the intended patient population and anticipated effects of the device are known or understood before testing begins. This is in contrast to the drug development process, in which a new molecular entity may be identified before the identification of any of its potential clinical applications. For devices developed as tools, FDA evaluation may most appropriately focus on assessing the ability of the device to perform its intended function safely and effectively. Use of a new device may be challenging for the practitioner as a result of novel deployment techniques and the incorporation of novel delivery tools. Patient selec-
tion may also prove challenging. Therefore, developing instructions for use and physician training are critical to the safe and effective use of a novel device. This is in contrast to drug development and evaluation. Whether in the clinical trial setting or in practice, relatively few drugs require extensive clinician training in methods of administering the drug.

These differences between device and drug development processes can also explain some of the differences in trial design. Important objectives of clinical trials for devices include evaluation of the delivery technique and of physician training.

For example, sutures have long been used in performing surgical anastomosis. To enable the surgeon to more rapidly perform anastomosis in various clinical settings, surgical clips were developed. FDA clearance is based on a combination of bench and animal performance testing, and in some cases clinical data, aimed at showing the performance characteristics (substantial equivalence) of clips used for anastomosis are equivalent to those of sutures for the same intended use. As another example, consider robotic devices intended to provide the surgeon with the ability to manipulate, cut, and suture tissue via a computer-assisted surgical system. Although the original FDA clearance of this device was based on data collected on the device performance during 2 specific surgical procedures (laparoscopic cholecystectomy and Nissen fundoplication), these 2 procedures were already performed laparoscopically, and the clearance was based on a demonstration of device performance. FDA clearance was not based on clinical outcomes in either of these 2 examples, but rather a demonstration that the device, in the hands of a trained surgeon, can be safely used to perform the surgical tasks. These clearances also underscore the importance of appropriate instructions for use, physician training, and human factor issues, including assessing and providing information on the user learning curve. In both of these examples, the clinical community has continued to study the use of these types of devices after their marketing authorization.

Effectiveness is an important consideration in FDA review of premarket applications for medical devices. It is important to note that for many devices, the clinical utility is obvious from its usefulness as a tool to complete tasks or functions that are already being performed by clinicians.

An additional critical difference between device and drug development lies in the interpretation of safety events seen in a clinical trial. A control group may not be needed to interpret some of the types of safety information developed in a clinical trial. For example, for many devices, a control group may not be needed to identify adverse events related to device deployment or use.

This summary overview of device development and FDA medical device regulations provides background for describing the recent FDA clearance of a device intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke who are ineligible or who failed intravenous tPA therapy.

Mechanical Thrombectomy in Ischemic Stroke
The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial was designed as a least burdensome method of obtaining safety and effectiveness information that could lead to FDA clearance of a tool with the specific indication of mechanical thrombectomy in the neurovasculature. The device is a catheter with a helically coiled tip to grasp the clot for removal, previously given a marketing authorization for retrieval of foreign bodies misplaced during interventional radiological procedures in the neurovasculature and peripheral and coronary vascular systems. The MERCI trial was designed, not to evaluate the safety and effectiveness of clot retrieval as a treatment, but rather, to evaluate whether the Merci Retriever, in the hands of a trained interventional neuroradiologist, could be used safely to retrieve clots. The trial provided an assessment of device design and performance and the adequacy of the instructions for use. It also provided valuable clinical data to aid neurologists and interventional neuroradiologists in making decisions about the risks of using such a treatment in an individual patient in whom the treating physician believed revascularization is warranted with the goal of achieving restoration of blood flow to ischemic but salvageable tissue (penumbra).

For example, Concentric Medical used the findings from the MERCI trial to make modifications to the design of the device to increase its safety and effectiveness. Early in the trial, tip fracture (the breakage of the helical coil from the wire) was an infrequent but troubling occurrence, associated with serious adverse events in a limited number of cases. Based on an analysis of these events, Concentric Medical modified its device (to increase the strength at the common fracture site) and the training and instructions for use to emphasize the risks associated with overtorquing the device during clot extraction.

An FDA advisory panel was convened to review the data submitted in a 510(k) submission for the Merci Retriever for the indication of removing thrombus in patients experiencing ischemic stroke. During their thoughtful and thorough deliberations, the panel discussed the nature and frequency of serious adverse events that occur during the instrumentation of the neurovasculature and removal of clots in patients experiencing ischemic stroke. These events included vessel perforation, dissection, and embolization of clot into a previously uninvolved territory. The frequency of these events, along with the frequency of successful removal of the target clot, are 2 critical pieces of information needed by physicians treating stroke patients to make a decision as to whether mechanical thrombectomy is appropriate. Subgroup analysis examined the interaction of clot location and other clinical factors on revascularization success and serious adverse events, and although the study was small, these analyses did not show a difference in safety and efficacy in all studied vessels. The trial design also collected some clinical outcome data (modified Rankin score [mRS] mortality), although clinical outcomes were not the primary end point. The FDA advisory panel raised concerns about the high mortality rate in MERCI compared with results of published thrombolytic trials. However, the mortality rates in MERCI were consistent with the high rates documented in published series of patients with angiographically confirmed large vessel occlusions. The clinical outcome data (mRS), although lacking a control group for comparisons, demonstrated a trend of improved...
outcome from stroke in patients with successful revascularization.

As noted above, the advisory panel expressed concerns about the trial design and some of the results, and the FDA considered comments made by our advisory panels very carefully when evaluating the evidence submitted by the manufacturer. However, we also noted that panel members from clinical specialties most likely to use this device expressed a desire to have the Merci Retriever available to them as an additional tool in their armamentarium to treat individual patients who might benefit.

**Summary**

Many medical devices are properly evaluated as tools to accomplish a specific task. The incremental changes in design and the criticality of deployment techniques to safety and effectiveness are key features of medical devices that make them inherently different from drugs. Medical device regulation provides (and in fact, requires) the FDA to tailor the data requested from a manufacturer to address the specific safety and effectiveness questions that need to be addressed before a marketing authorization can be granted. In the case of the Merci Retriever, Concentric Medical provided data to demonstrate that the device is a safe and effective tool developed to meet the needs of the user community that could be used for removal of thrombus in the neurovasculature. The clinical trial that supported this clearance provided important safety information that led to improvements in the device design and in the instructions for use before marketing. The clinical user community may choose to conduct further research to develop more definitive outcome data for patients undergoing mechanical thrombectomy with devices such as the Merci Retriever. As these data are collected, to better refine the patient population and to quantify the expected benefit, FDA clearance of the Merci Retriever allows the device to be available as a useful tool for clinicians to treat patients for whom they believe mechanical thrombectomy may be of benefit, thus potentially reducing the devastating impact of ischemic stroke on the public health.

Key Words: acute care, stroke, ischemic
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Stroke. 2005;36:404-406; originally published online December 29, 2004;
doi: 10.1161/01.STR.0000153063.54972.91

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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