The Food and Drug Administration (FDA) evaluates applications for new human drugs, biologics, and complex medical devices. Companies must obtain FDA approval to legally market these products. In August, the FDA gave Concentric Medical clearance to market its Merci Retriever system to “remove blood clots from the brain in patients experiencing an ischemic stroke.” Given that the FDA is charged with “protecting the public health by assuring the safety, efficacy, and security of . . . biological products and medical devices . . .,” “advancing public health by helping to speed innovations that make medicines . . . more effective, safer, and more affordable,” and “helping the public get the accurate, science-based information they need to use medicines . . . to improve their health,” the FDA’s decision to approve the Merci Retriever system is of concern. The pathways to approval are reviewed by Felten et al in the accompanying article and are outlined in Figure 1.

The decision to approve the Merci Retriever was based on data from the MERCI (Mechanical Embolus Removal in Cerebral Ischemia) Trial; the approval was granted through the 510(k) process. The Merci Retriever system includes a flexible nickel titanium (nitinol) wire that obtains a helical shape once it is passed through the tip of the guidance catheter. In practice, the catheter/wire is passed distal to the thrombus, the catheter is removed, and the helical configuration assumed by the wire; the clot is then trapped in the helix and withdrawn from the vasculature (Figure 2). The 510(k) clearance means that the Merci Retriever was felt to be substantially equivalent to a predicate device. In this case, the predicate device was the Concentric Retriever, which itself received 510(k) clearance by the FDA in May 2001 for “use in the retrieval of foreign bodies in the peripheral, coronary, and neuro vasculature.”

The MERCI investigators compared their treated patient population to the placebo arm of the PROlyse in Acute Cerebral Thromboembolism (PROACT II) study to determine the safety and efficacy of mechanical embolectomy. Because only 18% of patients in the placebo arm of PROACT II (n=59) showed evidence of recanalization, the MERCI investigators felt that a recanalization rate of 30% would be indicative of success. Similar to PROACT II, MERCI included patients with M1 and M2 occlusions, but MERCI also included patients with occlusions of the supraclinoid internal carotid artery and the vertebral basilar system, making direct comparisons of outcome difficult.

In the data presented to the FDA, the intention-to-treat population in the MERCI trial included 121 patients, although 7 patients could not be treated for a variety of reasons. The catheters were judged to be substantially equivalent to other predicate devices.

The data presented by Concentric Medical to the FDA in support of the Merci Retriever is publicly available on the FDA’s Web site (http://www.fda.gov/). The intent of the MERCI Trial was to broaden the indication for the Concentric Retriever to include the removal of thrombi from the cerebral vasculature in patients with stroke. Because the submission for approval of the Merci Retriever was a 510(k) submission, the advisory panel members, including the authors, were not asked to vote on the approvability of the device, as would be the case with a PMA. The advisory panel meeting was therefore perfunctory, but the discussion clearly revealed a general level of discomfort with the approval of the device. The trial itself was a prospective nonrandomized study that included patients with ischemic stroke that could be treated within 8 hours of symptom onset; the primary hypothesis of the trial was that the retriever could access and revascularize occluded vessels “while minimizing adverse events.” Serious device-related events were considered to be vessel perforation, vascular dissection, and embolization of clot to another vessel segment.

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In the data presented to the FDA, the intention-to-treat population in the MERCI trial included 121 patients, although 7 patients could not be treated for a variety of reasons. The
“per-protocol population” therefore includes 114 patients. A total of 265 devices were used to treat the 114 patients and the recanalization rate of the target vessels was 53.5%. Device-related events included fracture of 7 retrievers with 6 device tips detaching in patients. Serious device-related events occurred in 3.5% of patients; 2 patients experienced stroke in previously uninvolved vascular territories and 2 patients had vascular dissection/perforation (both cases were complicated by hemorrhage). In addition, 4 patients had “procedure-related” complications (related to angiography and deployment of the balloon) for an overall 7% rate of device or procedure related complications.

Neurological outcome, which should be the most important outcome in a stroke treatment trial, was a secondary end point in the MERCI study and was again determined by comparing the outcome of treated patients to the placebo arm of PROACT II.2 In MERCI, the overall mortality at 90 days was 39%; among patients in whom embolectomy was unsuccessful, the mortality

Figure 1. Potential pathways for device approval.

Figure 2. Merci Retriever (http://www.concentric-medical.com/).
Concentric Medical. It is unclear how much the Retriever will likely prove to be of significant financial benefit to the vasculature) are uncommon, the recent FDA approval of the Merci Retriever (ie, retrieval of foreign objects from given that stroke is common and other indications for use of the retriever system in patients with stroke. And the semantics of this approval, however, will not limit the use of the retriever for the "removal of clots," not for the treatment of stroke. Thus, there is currently no evidence that using the procedure actually harmed people in whom recanalization could not be established (which was nearly half of the population).

While it is true that MERCI patients had more severe strokes (median National Institutes of Health Stroke Scale Scores [NIHSSS]=19) and comprised a more heterogeneous stroke population than the patients in PROACT II, these data certainly provide no reassurance about the safety of mechanical embolectomy, yet alone the efficacy. The risks of treatment with the Concentric clot retriever might not be limited to arterial perforation, dissection, or distal embolization; there could be unidentified risks associated with the required immediate poststroke angiography as well as with endovascular instrumentation and injury to the arterial endothelium. Unfortunately, these questions cannot be addressed with the data presented to the FDA by the MERCI investigators. Randomized trials have a distinct advantage in this setting; they can control for variables we know are likely to relate to procedure success and outcome, and they can control for important variables we have yet to identify.

Devices are different from drugs. Accordingly, the FDA convened the Neurological Devices Advisory Panel in November of 2000 to address the issue of clinical trial design for endovascular devices in the treatment of acute stroke and to make recommendations to the FDA. The FDA specifically asked the panel if surrogate end points (ie, recanalization of a cerebral vessel) would be sufficient to determine approvability of a device. The consensus of the panel was that an assessment of clinical outcomes should be required for Phase III clinical trials; the panel was not unified, however, in its view of the need for a contemporaneous control group.3

Despite these Advisory Panel suggestions, the FDA did not require Concentric Medical to provide any proof of clinical efficacy for mechanical thrombectomy in patients with stroke. Thus, there is currently no evidence that using the Merci Retriever will improve outcome in patients with ischemic stroke. The FDA approval, however, skirts the issue of "stroke therapy" by approving the Merci Retriever for the "removal of clots, " not for the treatment of stroke. The semantics of this approval, however, will not limit the use of the retriever system in patients with stroke. And given that stroke is common and other indications for use of the Merci Retriever (ie, retrieval of foreign objects from the vasculature) are uncommon, the recent FDA approval will likely prove to be of significant financial benefit to Concentric Medical. It is unclear how much the Retriever System will cost, but since at least 2 devices were used in each patient in the MERCI trial, the potential impact of the FDA’s decision to Concentric Medical is enormous.

This editorial is not an indictment of Concentric Medical; in fact, we applaud the efforts of the medical device industry for developing novel therapies for stroke. Concentric Medical cooperated fully with the FDA and did exactly what was asked of them. Since the FDA approval of the Merci Retriever, Concentric Medical has made a number of revisions to the device. Unfortunately, this modified device is now being studied in another nonrandomized trial known as “Multi-MERCI,” which is similar in design to the original MERCI trial; another 510(k) application will be submitted to the FDA for the improved device.

In order to be certain that we offer our patients effective and safe endovascular therapies, we should demand that the clinical benefits of the device and the intervention be established. Endovascular devices are not tools to be evaluated for use within an already proven stroke paradigm, because the urgent endovascular approach is not standard of care and has been shown to be successful only in PROACT II. The best evidence for safety and efficacy is provided by prospective randomized controlled trials. For example, the National Institutes of Neurological Disorders and Stroke (NINDS) recently funded a trial of mechanical embolectomy for the treatment of stroke though the Specialized Program of Translational Research in Acute Stroke (SPOTRIAS). This project is known as MR RESCUE (Magnetic Resonance and REcanalization of Stroke Clots Using Embolectomy) and is aimed at determining whether MRI can identify acute stroke patients who may benefit from having their blocked blood vessels reopened by the Merci Retriever. Patients with anterior circulation infarcts who present within 8 hours of stroke onset will be randomized to either mechanical embolectomy or medical therapy; the response to therapy will be stratified by the MR pattern at randomization (“penumbral” versus “nonpenumbral”).

The results of the MR Rescue study will provide Level I evidence regarding the benefits of mechanical embolectomy. However, intra-arterial trials such as MR Rescue, PROACT II, and MERCI are costly, and enrollment has been historically slow. Moreover, the FDA is required by law to consider evidence for safety and efficacy that does not come from randomized studies. What other types of evidence would be pertinent and acceptable? In the case at hand, the MERCI clot retriever, the treatment studied differed from standard of care treatment of stroke beyond 3 hours by requiring angiography, arterial manipulation, and use of a specific device. PROACT II placebo patients, the historical controls for MERCI, also differed from standard of care by requiring angiography and should not have been accepted by the investigators or by the FDA as the only pertinent comparison group; a medical comparison group should have been required. Contemporary randomized medical controls lacking neurological outcome data were available for severe strokes from the NINDS tPA trial for both the tPA- and placebo-treated patients; matching could have been done by baseline NIHSSS. Neurolog-
ical outcome data may also have been available to the MERCI investigators from other recently completed medical and interventional trials.

There are currently a number of different devices being evaluated for the treatment of stroke. These include devices aimed at achieving recanalization with ultrasound (both intravascular and extravascular), lasers, and water pulsation; there are also trials that combine mechanical and thrombolytic approaches to revascularization. In addition, there are devices that induce hypothermia for neuroprotection, devices aimed at improving cerebral blood without recanalizing blood vessels, and devices used to remove blood from the brain and ventricles of patients with intracerebral hemorrhage. Given the number of these devices in trial and their potential impact on the treatment of stroke, it is imperative that we set higher standards for approval of these devices. Clinical efficacy needs to be demonstrated in prospective randomized controlled trials. The FDA sets very high standards for the approval of drugs, why are the standards so different for devices?

References

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