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Anthony J. Furlan and Marc Fisher

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Section Editors: Marc Fisher, MD, and Antoni Dávalos, MD

Devices, Drugs, and the Food and Drug Administration Increasing Implications for Ischemic Stroke

Anthony J. Furlan, MD; Marc Fisher, MD

The approval process at the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has been of little interest previously to stroke neurologists, but an increasing number of devices are being approved for stroke prevention (carotid stents, patent foramen ovale closure) and now also for acute ischemic stroke intervention. Felten et al provide a review of the CDRH approval process and give their perspective concerning the recent approval of the Concentric Merci Retriever in acute ischemic stroke. Drs Becker and Brott were members of the FDA advisory panel that reviewed the MERCI (Mechanical Embolus Removal in Cerebral Ischemia) Trial and approval application. Despite concerns raised by the advisory panel, the Merci device was ultimately approved by CDRH. It is not our purpose to arbitrate the specific concerns raised by the advisory panel or to question the CDRH decision; readers can judge the strength of the evidence for themselves. However, we do wish to consider some of the implications of this decision for patient care and stroke clinical research.

The Merci Retriever was approved for clot removal in brain arteries and not as a therapeutic modality for acute ischemic stroke. This distinction is critically important. The MERCI Trial relied on historical controls (mostly data from PROlyse in Acute Cerebral Thromboembolism [PROACT] II) for demonstration of safety, recanalization efficacy, and clinical outcome.¹ Although not the primary end point, it is useful to summarize clinical outcomes in the MERCI Trial. The median baseline National Institutes of Health (NIH) Stroke Scale score was 17 in the PROACT II controls and 19 in the MERCI patients, implying that the MERCI patients had more severe strokes. This could partly reflect the inclusion of patients with internal carotid and vertebral basilar occlusions in MERCI. The overall 90-day favorable outcome in MERCI, defined as a modified Rankin score of ≤ 2 , was 31%, which is not significantly better than the rate in the middle cerebral artery controls in PROACT II (25%). In patients who recanalized, the favorable outcome was 53%. The 24-hour symp-

tomatic brain hemorrhage rate was 8%, very similar to the 10% rate in PROACT II, in which patients received intra-arterial (IA) prourokinase. The 90-day mortality rate was 27% in the PROACT II controls and 40% in the MERCI Trial. The conclusions we draw from MERCI are that despite the 54% partial or complete immediate recanalization rate (63% at 1 hour in PROACT II), there was no overall evidence of improved patient outcome at 90 days. There was a suggestion of improved outcome in patients who recanalized. The symptomatic brain hemorrhage rate was similar to patients given an IA thrombolytic agent, and the 90-day mortality was higher in the MERCI trial.

Although these results could reflect case mix and insufficient sample size, it also reinforces that safely re-establishing brain reperfusion alone does not guarantee meaningful clinical improvement in patients with acute stroke. Additionally establishment of clinical efficacy for reperfusion therapy beyond 3 hours from stroke onset with either device, drug or both, will require a randomized, controlled trial stratified by stroke severity and site of occlusion that also includes patients still capable of responding to reperfusion therapy (ie, patients with ischemic but still salvageable tissue, the ischemic penumbra). Reperusing irreversibly injured brain tissue will not improve outcome and may lead to an increased risk of hemorrhage. If the Merci Retriever can be used in conjunction with advanced imaging technology that can identify the ischemic penumbra, then it is possible that clinical efficacy could be established beyond 3 hours. Such a trial, Magnetic Resonance and REcanalization of Stroke Clots Using Embolectomy (MR RESCUE), is ongoing, and it will be interesting to see how rapidly patient recruitment occurs.

The approval of the Concentric Merci Retriever for use in ischemic stroke highlights important differences in the FDA approval process between CDRH and the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). Although the 3 pillars of approval are safety, mechanism of action, and clinical

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From the Department of Neurology (M.F.), University of Massachusetts Medical School, Worcester, Mass; and the Head Section of Stroke and Neurocritical Care (A.J.F.), Department of Neurology, Cleveland Clinic, Cleveland, Ohio.

Correspondence to Dr Marc Fisher, Department of Neurology, University of Massachusetts Medical School, 19 Belmont St, Worcester, MA 01605-2982. E-mail fisherm@ummhc.org

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efficacy, each FDA center weighs these quite differently. Concerns about the FDA device approval process were first raised by the Temple Report of 1993.² The Temple Report recommended that the principles of sound clinical trial design, including appropriate controls, statistical design, data management, and end points, should be applied to devices as well as drugs. However, notably, the Temple Report also stated that “randomized trials are not a routine requirement but will often prove practical and desirable.” Furthermore, “assuming there are no other choices and that the natural history of patients getting the device is known to be dismal, so that no treatment or placebo is not an acceptable treatment, any (device) study would of necessity be a single arm historically controlled trial.” After the Temple Report, the FDA introduced changes that brought device approval more in parallel with drug approval. However, when this resulted in delays in device approval unacceptable to industry, Congress passed the FDA Modernization Act (FDAMA) in 1997.³ FDAMA included language requiring the FDA to consider “the least burdensome means” when approving the marketing of a new device. This often does not include a randomized controlled clinical efficacy trial, even for the more rigorous premarketing assessment application. Although CDRH adopted the “least burdensome” FDAMA mandate,⁴ neither CDER nor CBER has approved pharmacological agents based only on historical controls and without clinical efficacy being demonstrated in randomized controlled trials. The key reason for this difference is that device approval typically is based on a mechanistic (“tool”) end point (eg, thrombus removal, closing a hole, reducing a stenosis), whereas drug approval has required the much tougher end point of clinical efficacy based on randomized trials.

The negative implications of the CDRH device approval process for randomized clinical efficacy trials have been increasingly recognized.⁵ After a device is approved by CDRH, interventionalists are often reluctant to randomize to a medical control arm in a clinical trial. Off label use of approved devices has been especially recognized by the FDA as a major impediment to the conduct of randomized clinical efficacy trials.⁵ Although the reluctance of interventionalists to participate in randomized clinical trials may have some ethical basis, reimbursement for a CDRH-approved device by the Center for Medicaid and Medicare Services (CMS) provides a powerful financial disincentive to the participation in or the performance of randomized clinical efficacy trials.⁵

The traditional FDA arguments for reviewing devices differently from drugs are summarized by Felten et al. However, there are circumstances in which such distinctions become artificial. To use the current example, the distinction between a device and a pharmacological agent such as tissue plasminogen activator or prourokinase becomes blurred when the criterion is simply safe and effective clot removal in brain arteries. Ironically, although there is no demonstrated difference in either recanalization efficacy or safety between the Merci Retriever and pro-urokinase, and the prourokinase data are based on randomized controlled trials rather than historical controls, the FDA approval process has resulted in approval of a device for this purpose but not the drug.

We suggest that CBER and CDER should consider a “least burdensome” mechanistic approval option for pharmacological agents similar to the CDHR process for devices (eg, approving a thrombolytic agent based on demonstrated safe and effective recanalization). This important emerging issue was addressed recently by an FDA advisory panel on the design of clinical trials for endovascular devices to treat and prevent acute ischemic stroke and the Stroke Therapy Academic Industry Roundtable (STAIR) IV conference.^{6,7} We also suggest that “mechanistic approval” of either a device or a drug should be provisional and lead to only limited reimbursement by CMS. Full reimbursement by CMS for a device, just as for a drug, should be linked to unequivocal demonstration of clinical efficacy. Furthermore, in our opinion, there is no justification for CDRH, CDER, and CBER to grant approval using differing standards of clinical efficacy.⁸ The highest level of evidence for clinical efficacy for a device or a drug remains a randomized, controlled, adequately powered clinical trial. Less strict alternatives, such as historical controls, objective performance criteria, and validated surrogate end points, should be considered by CDRH, CDER, and CBER, but the circumstances under which such alternatives might be acceptable for approval should be standardized across FDA centers.

Although NIH, CDRH, and CMS have collaborated in studies such as Carotid Revascularization Endarterectomy Versus Stent Trial to fulfill premarket reimbursement and to provide proof of clinical efficacy requirements, such collaboration remains the exception rather than the rule with devices. We suggest that the path to approval at CDER and CBER may be too inflexible and may discourage pharmaceutical participation in stroke research. We believe that the evolution of new stroke therapies requires a similar evolution in the FDA device and drug approval process. A more homogeneous and consistent approach across FDA centers would help advance the care of patients with stroke and other serious and life-threatening conditions.

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