
Dr Peña et al provide a regulatory perspective on the Food and Drug Administration’s (FDA) device approval process. Reflecting the growing importance of the topic, this is the second such review and accompanying editorial comment to appear in Stroke, the first being prompted by the FDA’s clearance of the MERCI retriever device. For those more familiar with the FDA’s requirements for the introduction of a new pharmaceutical, the differences in the regulatory approach for device approval are striking.

The FDA’s Premarket Notification 510(k) clearance process is the most frequently used and requires that a new device be substantially equivalent to a legally marketed predicate device (ie, the new device is substantially similar in design, function, and indication for use). The approval can be based entirely on preclinical data; no human testing is necessarily required. The assumption is that the new device represents an incremental change and does not compromise safety as compared with the older one. It might or might not have purported advantages as compared with a device or devices that are already in use for the same or similar purpose. Whether the new device is truly as safe or actually has the professed advantages does not need to be established through a comparative study. The analogy to a pharmaceutical might be a new drug for a specific indication that has a slightly altered chemical structure which is anticipated to increase its potency based on the results of studies conducted in tissue culture or in laboratory animals. In contrast to the situation for devices, such a drug would not achieve regulatory approval without adequate human testing, nor should it.

The Premarket Approval (PMA) process (applicable to most Class III devices, defined as those that sustain human life, are important in preventing health impairments, or are important in improving human health and function) requires preclinical and clinical data supporting a reasonable assurance of both safety and effectiveness for the intended use. Depending on the device and indication, the clinical data can be derived from controlled trials, partially or uncontrolled studies, case histories, or reports of significant human experience with an approved device. In contrast to the PMA process, a new pharmaceutical would not be approvable in the absence of well-controlled trials showing both safety and efficacy in the intended patient population.

The illustrative example provided by Peña et al is again the FDA’s approval of the MERCI retriever, which “was cleared along the 510(k) regulatory pathway rather than the PMA process because there already existed a predicate device with a similar use.” The stroke clinician may be perplexed by this reasoning because there were not any approved devices intended to remove clots from a cerebral artery in patients with acute ischemic stroke that had been proven in randomized trials to be either safe or to be associated with improved clinical outcomes. What was the predicate device? As pointed out in the previous editorial after the MERCI device’s approval, the substantially equivalent device was the Concentric Retriever that was itself approved for removing foreign bodies in the peripheral, coronary or cerebral vasculature through the 510(k) process. The approval of these earlier devices were in turn based on other devices. None of the sequential series of so-called substantially equivalent predicate devices on which the 510(k) process for the MERCI retriever was justified had been tested or approved for the removal of blood clots from cerebral arteries in the patients with acute ischemic stroke. An analogy for a pharmaceutical might be the clearance of a thrombolytic shown to dissolve clots for use in acute stroke based on the prior approval of a different thrombolytic used in acute myocardial infarction that was in turn based on a third used for acute limb ischemia.

Although human testing is not required for approval under the 510(k) process, the FDA can require a clinical study because of “concerns about the safety and potential effectiveness of the new device.” The study required for the MERCI retriever was nonrandomized and used as a comparison group controls from PROACT-II, a trial that had been completed >5 years earlier of intra-arterial prourokinase in patients with acute ischemic stroke related to a proximal cerebral arterial occlusion. The sponsor closely and appropriately followed all relevant regulatory requirements in the conduct of this study. Neither the clinical community nor the FDA, however, would view a study of a pharmaceutical that used only historic controls as acceptable because of potentially misleading results related to differences in the study population, changes in medical therapy and other unmeasured factors.

Another key concept reviewed by Peña et al is that a device can be approved as a tool to perform a certain task, but not necessarily as a means of treatment of the condition for which the task is to be performed. Thus, without a prior study of a predicate device showing that the approach was safe or effective in improving stroke-related outcomes, and without a...
study that included a contemporaneous control group, the MERCI device was cleared for use as a tool for removing clots from a cerebral artery in the setting of an acute stroke, but not as a means of treating an acute stroke. Because the only reason to use the device in this setting is as part of an attempt to improve a patient’s outcome, the implication of this logic is that the approach would be both safe and effective. Without appropriately controlled trials, clinicians are left uncertain of the comparative benefits and risks of the strategy, but the MERCI device can now itself serve as a predicate device for others.

Dr Peña et al note that “the FDA’s role is to regulate medical devices, drugs, and biologics, but not regulate the practice of medicine,” and that “the clinical community will often continue to study the medical device after marketing (postmarket surveillance) to develop a more refined understanding of the patient population most likely to benefit.” This, however, is not a requirement. Once the ‘genie is out of the bottle,’ (and after its use has been approved for reimbursement), enthusiasts often will embrace the new device, and only serious safety issues or the advent of another device will halt its use. Even when subsequent studies are undertaken, large numbers of patients can be exposed to the device in the interim. The availability of an “approved” device can also compromise the design and conduct of clinical trials of other therapies (medical or interventional) for a similar indication.

As noted by Peña et al, part of the FDA’s mission is to promote public health by expediting the approval of treatments that are safe and effective. By law, the agency must consider a variety of strategies for accomplishing that goal, and it is important to acknowledge that an incremental change in a medical device is fundamentally different than a chemical modification of a pharmaceutical. The FDA’s task in striking the correct balance between getting a new device into the hands of clinicians as quickly as possible and obtaining sufficient data showing that the device is safe and effective is not trivial, but it is a critical one. It becomes problematic when a device is cleared as a tool to accomplish a task related to a clinical problem without adequate, contemporaneous controlled data showing that it leads to similar or better health outcomes as compared with alternatives. In contrast to the clearance process for the MERCI device, the FDA is requiring prospective, randomized trials of patent foramen ovale closure devices versus medical therapy for preventing recurrent strokes in patients with otherwise cryptogenic ischemic events. The FDA’s device approval process has to continue to be fair to those developing innovative new treatment strategies, but at the same time be balanced by the need to provide clinicians with the data they require when determining whether the use of a new device is appropriate.

Disclosures
L.B.G. is a consultant for Johnson & Johnson (Cordis), and a member of the FDA Peripheral and Central Nervous System Drug Advisory Committee.

References

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