An Example of US Food and Drug Administration Device Regulation

Medical Devices Indicated for Use in Acute Ischemic Stroke

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Abstract—The Food and Drug Administration has established requirements 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 promoting public health by expediting the approval of treatments that are safe and effective. The Center for Devices and Radiological Health is the center within the agency that is responsible for pre- and postmarket regulation of medical devices. In this article, we review current regulation of medical devices, research and development programs, pre- and postmarket perspectives, and future considerations of medical devices, particularly as they relate to devices targeting acute ischemic stroke as an example of the process. We also review the Center for Devices and Radiological Health’s historical perspective of acute ischemic stroke trials and clinical trial design considerations used in prior studies that have led to US market clearance as they are related to currently marketed devices indicated for acute ischemic stroke. (Stroke. 2007;38:1988-1992.)

Key Words: acute stroke ■ stroke ■ treatment

The US 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 promoting public health by expediting the approval of treatments that are safe and effective. More than 20 000 firms worldwide produce over 80 000 brands and models of medical devices for the US market. The Center for Devices and Radiological Health (CDRH) is a center within FDA that is responsible for pre- and postmarket regulation of medical devices in the US.

According to the National Institute of Neurological Disorders and Stroke (NINDS), about 700 000 people have a stroke each year, a leading cause of long-term disability and the third leading cause of death for Americans after heart disease and cancer. The regulation of medical devices by CDRH includes devices indicated for stroke. This article will review research and development of such devices, pre- and postmarket evaluation, and provide an FDA perspective on future development.

Device Classification

Medical devices are categorized into 3 classes with regulatory control increasing from Class I to III. The device classification regulations define the regulatory requirements for a general device type. Most Class I devices are exempt from FDA notification; Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval (PMA). Humanitarian use devices (HUDs) are
marketed for a limited population in an entirely separate process termed a Humanitarian Device Exemption (HDE). The majority of medical devices reviewed by CDRH are evaluated under premarket notification (510(k)).

**PMA Process**

A second regulatory pathway for marketing of medical devices is the PMA process. This market approval process is required for most Class III devices. These devices are typically referred to as significant risk devices that support or sustain human life, are important in preventing health impairment, or present risk of serious injury or death in case of failure. The PMA approval process requires that the manufacturer has demonstrated, through preclinical and clinical data, a reasonable assurance of safety and effectiveness when used for the label indication in the intended population. In FY 2005, FDA authorized marketing of 3148 devices with 510(k) clearance and 32 devices through the PMA program. Neurological devices have comprised ~5% of all medical devices authorized for marketing.4

Approval of a device through the PMA process represents a rigorous type of device marketing application required by FDA and is based on a determination by FDA that the PMA application contains valid scientific evidence to assure that the device is safe and effective for its intended use(s) (21CFR814 [Subpart C]). An approved PMA is, in effect, a license granting the applicant (or owner) permission to market the device. The PMA applicant is usually the company, also called sponsor) who owns the rights, or has authorized access, to the data and other information submitted in support of safety and effectiveness. In some cases, before approving or denying a PMA, an FDA advisory committee composed of nonagency experts (special government employees), may review the data submitted in support of the PMA. A public meeting provides a venue for making a recommendation whether to approve the submission. After carefully weighing the evidence contained in the submission and recommendations from the advisory panel, the FDA will notify the applicant of its decision. In those instances where a PMA is approved and after FDA notifies the applicant that the PMA has been approved, a notice is published on the Internet announcing the data on which the decision is based, providing an opportunity for the public to petition FDA within 30 days for reconsideration of the decision.5 To assist potential users in understanding the basis for PMA approval, FDA provides a Summary of Safety and Effectiveness that identifies the type of safety and effectiveness data as the basis for each approval decision. The clinical community will often continue to study the medical device after marketing (post-market surveillance), to develop a more refined understanding of the patient population most likely to benefit.

Medical device regulation requires 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. The Center for Devices and Radiological Health, by law, considers valid scientific evidence to include all of the following: well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, to determine whether there is reasonable assurance that the device is safe and effective (21CFR 860.7). The agency has considered whether these guidelines are in conflict with adequate scientific integrity and believes there can be several approaches to addressing regulatory requirements.

**HDE**

In 1996 the FDA finalized rules (21 CFR part 814 [Subpart H]) regarding HUDs. In contrast to the PMA, a HUD designation requires that <4000 individuals in the United States per year are eligible for use of the device under the proposed indications. After approval of an HUD designation, the device must receive a Humanitarian Device Exemption to allow the intended use. Unlike a PMA approval, the sponsor of an HDE is not required to provide clinical data to demonstrate reasonable safety and effectiveness but must provide sufficient information demonstrating that the device does not pose unreasonable risks and that there is probable benefit of use that outweighs the risks. These data must be interpreted in light of currently available treatment options. Lastly, the sponsor must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that the device could not be brought to market without HUD status. A device approved under an HDE for marketing, however, remains restricted as an investigational device limited to the specific indications stated in the product labeling. Investigators are required to obtain approval from their Institutional Review Boards for use of the device in each case.

There are currently no PMAs cleared for treatment of acute ischemic stroke. However, the FDA has recently approved two HDEs for intracranial stent systems for the treatment of symptomatic and medically refractory intracranial atherosclerotic disease, a very select patient population with an extremely high stroke risk: the Wingspan Stent System (Boston Scientific, 2005) and NeuroLink System (Guidant, 2002).

**Research and Development of Medical Devices**

The first step that manufacturers take in the research and development of their device is the determination of whether
their product is, in fact, a medical device. A medical device is
defined as an instrument, apparatus, implement, etc, intended
for use in the diagnosis of disease, or other conditions, or in
the cure, mitigation, treatment, or prevention of disease, in
man or other animals, or intended to affect the structure or
any function of the body of man or other animals, and which
does not achieve any of its primary intended purposes
through chemical action within or on the body of man or other
animals and which is not dependent on being metabolized for
the achievement of any of its primary intended purposes.

Once a product is determined to be a medical device, the
sponsor of a device may then investigate whether there is a
legally marketed predicate. Often, medical devices are first
designed and developed as “tools” to accomplish a task that
is already an established practice, which means that the
intended patient population and anticipated effects of the
device are known or understood before testing even begins.

During the research and development of a medical device,
sponsors may approach FDA for guidance on the suitable
design of a clinical or nonclinical study. Investigational
devices for the treatment of stroke are usually evaluated by
the Office of Device Evaluation’s (ODE), Division of Gen-
eral, Restorative, and Neurological Devices (DGRND), one
of five divisions in CDRH, responsible for regulating medical
devices. Clearance of a Class II medical device is typically
based on both bench and animal performance testing. In some
cases, the FDA may require a clinical study to demonstrate
adequate performance characteristics, or substantial equiva-
Ience to a legally marketed predicate device. Safety and
effectiveness are important considerations in FDA’s review
of premarket applications for medical devices.

Regardless of the medical device or regulatory pathway
necessary to market the medical device, sponsors and principal
investigators usually collect clinical data for each of the
applications in a clinical study permitted by the FDA with
approval of a protocol providing an Investigational Device
Exemption (IDE). In most cases, if there is reasonable
assurance that a device is safe (ie, the probable benefits to
health from use of the device for its intended uses and
conditions of use outweigh the probable risks), the FDA will
allow a clinical investigation to proceed.

In general, devices indicated for the treatment of acute
ischemic stroke have been categorized as significant risk
devices and therefore warrant study under an IDE application.
In addition to the requirement for having an FDA-approved
IDE, sponsors of such trials must comply with the regulations
governing institutional review boards (21 CFR Part 56) and
informed consent (21 CFR Part 50).

Acute Ischemic Stroke

FDA’s role is to regulate medical devices, drugs, and biolog-
ics, but not regulate the practice of medicine. There have been
several clinical studies conducted to evaluate medical prod-
ucts for acute ischemic stroke. Prolyse in Acute Cerebral
Thromboembolism (PROACT II),6 the Mechanical Embolus
Removal in Cerebral Ischemia (MERCI) Retrieval Study,7
and other trials8,9,10 support investigation of acute stroke,
generally within the first few hours of stroke onset. Based on
this experience, initial treatment in IDE stroke trials usually
occurs within hours of symptom onset. Defining the exact
time of symptom onset is an important component of all study
protocols to ensure identification of appropriate subjects. For
those studies or devices with a therapeutic time window
beyond intervals studied in prior studies, evidence is encour-
aged from either preclinical or clinical testing to support
treating subjects for FDA approval of an IDE.

An issue in the investigation of acute ischemic stroke is the
difficulty in recruiting subjects, particularly when there is a
need to provide a cohort of control subjects treated with the
current standard of care for ischemic stroke especially if a
time restriction for use of the device is set. An unbiased way
to interpret the outcomes of a medical device study can be
obtained with a randomized controlled and double-blinded
study to reliably infer the use of a device. Simple comparison
of pretreatment versus posttreatment assessments, without a
control group, may not provide adequate proof of a reason-
able assurance of safety and effectiveness. Therefore, in some
cases, prospective randomized controlled studies are encour-
aged. Although we are aware of the difficulty in the design
and recruitment of subjects for acute ischemic stroke, alter-
nate methods may be considered only when valid methods of
inference are used and there are valid reasons for not using a
randomized control group (eg, evaluation of medical device
to restore blood flow). In some cases, study designs using
single-arm nonrandomized clinical protocols with compari-
son of study results to historical or concurrent matched
controls may be acceptable if they are scientifically sound
and address the relevant safety and effectiveness concerns
important to the proper use of the device by the community.
In those cases where alternative study designs are presented,
early collaboration with the FDA and discussion of new
statistical issues with FDA, before study initiation, are
strongly recommended.

Other important aspects of study design that are important
to device manufacturers and will be evaluated by FDA
include selection of an adequate and representative patient
population, clinical outcome assessments by an appropriate,
validated neurological impairment scale, disability measure,
or handicap scale; device- and study design–dependent se-
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tion, clinical outcome assessments by an appropriate,
validated neurological impairment scale, disability measure,
and in some cases differences related to gender, race/ethnicity, etc are included in the labeling.

What Clearance for Marketing Means to the User

Activase (alteplase), a genetically engineered version of tissue plasminogen activator, is a medical product approved for use during the acute onset of ischemic stroke. Other advances in the management of acute ischemic stroke include recent FDA clearance of the MERCI Retriever for US marketing. In comparison to tissue plasminogen activator, the MERCI retriever is intended to remove thrombus obstructing blood flow in the neurovasculature as cause of acute ischemic stroke (the MERCI Retriever had been previously cleared by the FDA for use in the retrieval of foreign bodies misplaced during interventional radiological procedures in the neuro, peripheral and coronary vasculature). Patients who are ineligible for treatment with IV tissue plasminogen activator or who fail IV tissue plasminogen activator therapy are candidates for intervention with the MERCI retriever.

The MERCI retriever 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 510(k) device regulatory process is different from the regulatory process for drugs. In some cases, medical devices can have local effects whereas drugs can have systemic effects. Moreover, unlike the 510(k) regulatory path where one device may be similar to another and potentially appropriate for marketing clearance based on an incremental change in technology, approval of one drug based on an incremental change in molecular identity may not be appropriate because slight differences in molecular identity can have significant differences in safety and effectiveness. These characteristics highlight the potential differences between medical device and drug clearances.

Because of concerns regarding safety and potential effectiveness for the new use of the MERCI retriever, a clinical study was still required for device clearance. This study was designed as a nonrandomized study using historical data from prior clinical studies, such as PROACT II, as the control. The FDA also involved its advisory panel in the review of data for the MERCI retriever, and FDA considered comments made by advisory panel members very carefully when evaluating the evidence submitted by the manufacturer. Because the primary end point of this study was restoration of cerebral circulation and not improved clinical outcome after stroke, and because of the nonrandomized design, the MERCI retriever was cleared with an indication for use regarding cerebral revascularization after stroke and not an indication for use of acute stroke treatment. Although this may appear clinically to be an arbitrary distinction, this distinction was necessary because the data supporting market clearance was determined by radiographic evidence for accomplishing this end point and one of several considerations that the agency used in clearance of the device.

Once a device reaches the market, there is postmarket surveillance regulations with which a manufacturer must comply. These requirements include the Quality Systems (also known as Good Manufacturing Practices) and Medical Device Reporting regulations. The Quality Systems regulation is a quality assurance requirement that covers the design, packaging, labeling and manufacturing of a medical device. The Medical Device Reporting regulation is an adverse event reporting program. In the case of acute ischemic stroke, FDA continues to monitor Medical Device Reporting and other postmarket studies related to devices that are indicated for use in ischemic stroke to determine whether additional labeling or other modifications are needed to improve the safety and effectiveness profile of such devices.

Acute stroke management is a dynamic field in which medical devices will continue to play an important role in its development. Further studies are needed to evaluate outcomes for patients undergoing mechanical thrombectomy as a treatment modality.

Future Perspectives

Although the FDA has published many guidance documents on the research, development, and current thinking on several topics related to medical devices, inevitably additional guidance will be needed to identify the recommended options in the preclinical and clinical studies to support regulatory submissions targeting the treatment of ischemic stroke.

Equally important in this process is the cooperation that is necessary in the development of medical technologies between academic, industry, advocacy, and government. Through ongoing interaction of the various parties involved, validation of safety and effectiveness of new treatments is important. The regulatory controls the FDA imposes provides important assurance that this will be accomplished without unacceptable restriction of the availability of these tools to the healthcare environment. Indeed, the Food Drug Modernization Act of 1997 requires that the agency cooperates with other stakeholders to assure a “least burdensome approach” to device regulation. The agency is also committed to monitoring devices through the product’s total life cycle, cooperating with the diverse parties primarily involved at each phase of the cycle, including its research, development, and clinical investigation, performance in the real world of clinical practice after market release, and any subsequent technological improvements or changes. Despite the regulatory pathway, an evaluation of device safety and effectiveness will be needed for any device. These principles are especially important for the field of acute stroke because of the tremendous public health impact of this disease and the recent technological advances in the treatment of cerebrovascular occlusive disease.

With the proper steps and dialogue among various stakeholders, ongoing research and development of medical products will hopefully lead to more safe and effective treatments for the treatment of this devastating disease.

Disclosures

This article represents the professional opinion of the authors and is not an official document, guidance or policy of the US Government, the Department of Health and Human Services, or the Food and Drug Administration, nor should any official endorsement be inferred.
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