Food and Drug Association Approval Process for Devices Used in Endovascular Treatment of Stroke

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Abstract

Purpose of the Review
This article reviews the Food and Drug Administration’s (FDA’s) process for approval of new medical devices and describes the evolution of endovascular devices used for the treatment of acute ischemic stroke.

Recent Findings
Several recent studies have established the benefit of endovascular treatment of acute ischemic stroke from emergent large vessel occlusion. This has led to endovascular treatment becoming the usual care in acute stroke management and has generated greater-than-ever interest in the development of newer and more effective devices.

Summary
In the United States, the FDA is the regulatory authority that is empowered with the approval and monitoring of new medical devices for widespread use in the population. The FDA categorizes medical devices into 3 classes based mainly on their potential risks to patients and/or users; class I devices pose the least risk and have the least stringent approval process, while class III devices pose the highest risk and undergo the most stringent and time-consuming approval process. There are 4 main pathways to approval: premarket notification, also known as the 510(k) pathway; premarket approval (PMA), de novo, and Humanitarian Device Exemption pathway. These pathways are described in detail in the article. The FDA also mandates postmarketing surveillance to identify any untoward and unexpected long-term complications.
The unprecedented growth of endovascular treatments for acute ischemic stroke that we have witnessed over the past decade is critically dependent on the innovations in stroke thrombectomy devices and technologies. Increased collaboration among the medical device industry, physician-scientists, and engineers has resulted in creating next-generation devices with improved recanalization rates and safety profiles. The critical part of this partnership includes the complex regulatory oversight process of ensuring that the new devices are safe and effective in order to become available in the armamentarium of a practicing neurointerventionalists.

Founded in 1906, the Food and Drug Administration (FDA) has been tasked with ensuring that various drugs and devices are safe and effective before they become available in the market for widespread clinical use in the United States. Within the FDA, the Center for Devices and Radiological Health was formed in the 1980s with the goal of specifically overseeing the manufacturing and approval and ensuring the safety of the medical devices. Under the Center for Devices and Radiological Health, the Division of Neurological and Physical Medicine Devices is assigned as the point of contact for submissions involving medical devices related to the field of neurology and neurosurgery. In the 2012 issue of the Neurology® supplement, clinical trial design for endovascular ischemic stroke interventions, including patient selection criteria, outcome measures, use of innovative outcome measures, control groups, and specific challenges related to ethical issues, was discussed in detail. In this article, we describe the FDA approval process and focus specifically on devices used in endovascular stroke therapies (Figure).

Definitions
What Is a Medical Device?
The first step in the approval process is to identify whether the new treatment modality falls under the definition of a device or a drug because they have very different approval processes. The FDA defines a medical device as follows:

An instrument, apparatus, machine, implant, or other similar or related article, which is (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of a disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Classification of Medical Devices
The FDA categorizes medical devices into 3 classes based mainly on their indications for use and potential risks to patients or users (Table 1). Devices that pose the lowest risk are grouped under class I, and devices that most the highest risk are grouped under class III. Devices that sustain or support life such as pacemakers belong to class III.

Understanding what class to which a medical device belongs is an important first step because that determines what pathway to pursue approval for the device. These classes have a different level of oversight, with class I requiring the least stringent process and class III undergoing the most stringent and time-consuming process. The FDA has established a searchable database in which the manufacturers or device sponsors can establish the class to which a new device belongs and what regulatory pathway to use to pursue approval.

Most class I devices are exempt from requiring clinical data for approval and require only general controls, which include good manufacturing practices, registration of devices, labeling of the device, and reporting of adverse events. The goal is to provide a reasonable assurance of effectiveness and safety. Most class II devices need to demonstrate only that they perform as expected and can undergo premarket notification (PMN), also known as the 510(k) process, which usually does not require high-level clinical evidence.

Most class III devices and some class II devices are subject to the premarket approval (PMA) process, which is the most stringent process of all. Under this process, the sponsor is required to prove both the safety and efficacy of the device with high-level clinical trials.

Approval Process
Several distinct approval pathways exist depending on the intended indications for a new device, its safety profile, and the existence of a predicate device. PMN or 510(k) Pathway
The PMN process is less rigorous compared to the PMA process. The main objective of this pathway is to ensure that a device performs as intended. PMN takes less time and funding compared to a full PMA process. In 2016, the FDA reclassified the Neurovascular Mechanical Thrombectomy Device for...
Acute Ischemic Stroke Treatment into class II with special controls under the de novo pathway. This has enabled the subsequent devices to pursue PMN instead of full PMA via the de novo pathway. The first neurovascular thrombectomy device approved was Merci Retriever (Concentric Medical, Mountainview, CA) in August 2004 (Table 2). It was approved for patients who were ineligible for or who failed IV tissue plasminogen activator. Merci Retriever was approved under the 510(k) pathway, with the Concentric retriever used as a predicate device that was approved for “retrieval of foreign bodies in the peripheral, coronary, and neuro vasculature.” The approval of Merci Retriever led to subsequent approvals for Solitaire (Medtronic, Minneapolis, MN) and Trevo (Stryker, Kalamazoo, MI) retrievers and Penumbra (Penumbra, Inc, Alameda, CA) under the 510(k) pathway with Merci Retriever used as a predicate device.

Some class III devices can use this pathway when there is already a similar device in the market that is approved by the FDA. Such an already approved device is called a predicate device. The sponsor can appeal to the FDA to reclassify a new class III device to a class II device through a §13(g) application. It is up to the FDA to make the final determination of whether a new device qualifies as having a predicate device and qualifies for PMN rather than PMA. If the FDA declines a PMN application, then the sponsor will have to pursue PMA.

### PMA Process

The PMA is the most stringent approval process by FDA that is required for any new device unless it is reclassified as a de novo device, which is discussed later. Most class III and some class II devices fall under this process. The main objective of PMA is to ensure that a device is both safe and effective. To demonstrate this, the devices typically need to undergo multiple phases of clinical trials that require several years of time and millions of dollars in funding. There are currently no stroke thrombectomy devices that have PMA approval. Examples of specific devices that have PMA and are used in other neurointerventional fields are the Pipeline Embolization Devices (Medtronic) and Surpass Flow Diverter (Stryker) used for the treatment of aneurysms. The safety and efficacy of both devices were confirmed after a series of rigorous clinical trials with clinical and angiographic follow-up extending up to 5 years. For comparison, acute stroke clinical trials typically include a much shorter follow-up period.

### De Novo Pathway

New devices that do not have a predicate are by default classified as class III and are required to undergo the PMA process. However, if a new device is thought to have low risk, a sponsor may petition for reclassifying the device into class I or II through the de novo application. If approved, this would qualify the device for the PMN process rather than PMA. Again, the FDA makes the final determination of whether a new device qualifies as a de novo device. If the application is declined, the sponsor will have to pursue PMA.

### Humanitarian Device Exemption Pathway

A device that is intended for use in a rare disease that affects <8,000 individuals per year in the United States qualifies as
Humanitarian Use Device (HUD). Humanitarian Device Exemption (HDE) is an approval pathway for a device that qualifies as an HUD. HDE is handled by the Office of Orphan Products Development. Under this pathway, the sponsor only needs to prove that there is probable benefit from the device and that the benefit outweighs the risk. The requirement to demonstrate effectiveness of a device is waived under the HDE. The rationale is that it would take many years to prove effectiveness due to the rarity of the condition. Once approved under HDE, the use of HUD requires additional approval and supervision by the local Institutional Review Board. The devices approved under HDE are subject to certain profit and use restrictions. The manufacturers can charge a price that only covers the research, development, manufacturing, and distribution costs. If this cost is more than $250, the manufacturer has to provide a report from an independent accountant to justify the higher sale price. The rationale behind this restriction is to limit voracious manufacturers from profiting from vulnerable patient populations using devices that have unproven efficacy. The FDA has approved 2 HDEs for intracranial stent systems, Wingspan (Stryker) and Neurolink (Abbott Vascular, Abbott Park, IL), for the treatment of symptomatic and medically refractory intracranial atherosclerotic disease.

### Postmarketing Surveillance

The FDA requires the sponsor to monitor for any untoward and unexpected complications arising from the use of the device after it has been made available on the market. This postmarketing surveillance helps in monitoring the long-term safety and efficacy of the devices. The FDA Medical Device Reporting regulation guides the postmarketing surveillance.7 The hospitals, health care providers, and other users of the device are required to report any adverse events to both the FDA and the manufacturer under this regulation. FDA sometimes mandates postmarket surveillance as a contingency for a new device approval. The FDA also requires device manufacturers to follow Quality Systems regulations, also known as Good Manufacturing Practices, which focus mainly on quality control during the manufacturing process of the devices.7

### Medical Device Registries

Medical device registries play a crucial role in postmarketing surveillance. The registries give us an insight into how a medical device performs outside of a clinical trial environment in the real world when used in a large number of patients. Registries shed light on safety and effectiveness data in diverse clinical settings and in understudied populations. The data collected in registries may also facilitate future hypothesis generation, innovation, and device improvements. In 2010, the FDA created the Medical Device Registry Task Force, a public-private partnership, to facilitate creation and maintenance of medical device registries. Investigator-initiated postapproval multicenter clinical registries allow data collection on real-world experience with the newly approved devices. The real-world clinical safety of the Solitaire and Trevo devices was evaluated in the North American Solitaire Stent Retriever Acute Stroke and Trevo Stent-Retriever Acute Stroke registries.8,9 Scientific societies such as the Society of NeuroInterventional Surgery and Society of Vascular and Interventional Neurology now also partner with industry to create unified registries that can be used for postmarket surveillance, including the treatment of acute ischemic stroke.

### Criticism of the FDA Approval Process

On one hand, the FDA is sometimes criticized for not being stringent enough in device approval; in stark contrast, on the other hand, critics voice concerns for the approval process to be slow and expensive and to impede innovation.10-13 The device manufacturers have been urging the FDA to streamline the approval process to decrease the cost and time required, so that the newer technologies can reach patients in a timely manner. On average, it takes ≈3 to 7 years for a device to reach marketplace from concept, and critics point out that in today’s world, the innovation is happening at a faster pace and the FDA approval process has failed to keep up with the pace of technologic advancements. They argue that the regulatory requirements and costs associated with a new device approval are discouraging innovation and that the United States is losing its edge in the global market as a technologic leader.

Several consumer groups and plaintiff attorneys have criticized the FDA for devices that made it to the market and then later were found to have an unacceptable adverse effect on patients. Most of these devices gained approval through a fast-track pathway such as HDE or 510(k). As described, these fast-track pathways do not require high-quality clinical data to ensure safety and effectiveness. These pathways are being criticized for being loophole in the FDA approval process. One such example of device failure is the Wingspan stent,
FDA granted approval of the Merci Retriever (corkscrew-like device) via 510(k) pathway on the basis of data from the MERCI trial.\textsuperscript{16} The predicate device was the Concentric Retriever [it received approval via 510(k) pathway in 2001]. Merci Retriever was designed by the University of California, Los Angeles. It was the first device approved by the FDA for recanalization in AIS.

**Table 2** Summary of the Evolution of Endovascular Devices Used for the Treatment of Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tr>
<td>2004</td>
<td>FDA granted 510(k) clearance to the Penumbra system (reperfusion catheter, separator, and thrombus removal ring) with the indication of revascularization in AIS within 8 h of symptom onset. Penumbra pivotal trial\textsuperscript{12} (prospective, single-arm study) compared the Penumbra system to historical control from the MERCI and Multi MERCI trials.\textsuperscript{18,19}\n<strong>The Merci Retriever (Concentric Medical) was the predicate device.</strong> A clot-grabbing device (thrombus removal ring) was also a part of the Penumbra system, but due to the small number of cases, the company excluded this device from its final submission.</td>
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<td>2007</td>
<td>FDA granted 510(k) approval to Solitaire FR stent retriever on the basis of results of the SWIFT trial\textsuperscript{20} and to Trevo stent retriever on the basis of results of the TREVO2 trial.\textsuperscript{21}\n<strong>SWIFT and TREVO2 were randomized, noninferiority trials comparing outcomes of thrombectomy within 0–8 h with either Solitaire or Merci retrieval system and Trevo or Merci, respectively. While both trials demonstrated the noninferiority of stent retrievers, the results showed higher recanalization rates and improved clinical outcomes of Solitaire and Trevo compared to Merci.</strong></td>
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<td>2008</td>
<td>FDA allowed expanded indications for Solitaire and Trevo as initial therapy for AIS with proximal anterior circulation LVO and smaller-core infarcts on the basis of the results of the randomized trial SWIFT PRIME\textsuperscript{22} via the 510(k) clearance pathway. Prior administration of IV tPA and device use within 6 h of symptoms onset were specified in this approval by the FDA.</td>
</tr>
<tr>
<td>2012</td>
<td>FDA granted approval of the Merci Retriever (corkscrew-like device) via 510(k) pathway in 2001. It was the predicate device.</td>
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<td>2013</td>
<td>FDA allowed expanded indications for Solitaire and Trevo compared to Merci.</td>
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<td>2016</td>
<td>FDA expanded the use of Solitaire to 6–16 h of time last seen well in patients ineligible for or with tPA failure after completion of DEFUSE 3.\textsuperscript{24} Similar to DAWN, the DEFUSE 3 trial compared outcomes in patients with anterior circulation stroke of 6–16 h of last known well treated with thrombectomy using Solitaire or medical therapy alone.</td>
</tr>
<tr>
<td>2017</td>
<td>FDA granted approval of the Merci Retriever (Concentric Medical) for recanalization in AIS within 8 h of symptom onset.</td>
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<tr>
<td>2018</td>
<td>FDA granted approval of the Solitaire FR stent retriever on the basis of results of the SWIFT trial and the Trevo stent retriever on the basis of results of the TREVO2 trial.</td>
</tr>
<tr>
<td>2019</td>
<td>FDA granted 510(k) approval to Solitaire FR stent retriever on the basis of results of the SWIFT trial and to Trevo stent retriever on the basis of results of the TREVO2 trial.</td>
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Abbreviations: AIS = acute ischemic stroke; DAWN = Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo Thrombectomy Procedure; DEFUSE 3 = Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution; FDA = Food Drug Administration; FR = Flow Restoration; LVO = large vessel occlusion; MERCI = Mechanical Embolus Removal in Cerebral Ischemia; SWIFT = Solitaire Flow Restoration With the Intention For Thrombectomy; SWIFT-PRIME = Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment; tPA = tissue plasminogen activator; TREVO2 = Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke. 

which was approved for the treatment of intracranial atherosclerosis causing >50% stenosis that is refractory to medical therapy. The device was approved in 2005 under the HDE pathway on the basis of a single-arm clinical study that enrolled 45 patients and did not include a control arm. The individuals who underwent similar neurovascular procedure in the past were used as the control group. However, in 2011, the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial,\textsuperscript{14} which compared intracranial stenting to aggressive medical management, was stopped after an interim review showed high perioperative stroke risk in the stenting arm (14.7%) compared to the medical arm (5.8%). After this, the FDA revised the indication for the Wingspan stent and limited it for use in patients who have failed or are ineligible for aggressive medical management. This led to claims by several consumer groups that the Wingspan stent was released to the market prematurely without adequate safety data. However, in the FDA’s defense, the individuals evaluated in SAMMPRIS trial were different from the approval indication on the HDE. Many experts believe that the benefit noticed in the medical arm of the SAMMPRIS trial was from the significant advancement and superior performance of medical arm rather than the inferior performance of the Wingspan stent. The 30-day stroke and death rate in the medical arm of SAMMPRIS was nearly half of what was expected on the basis of the findings of Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial.\textsuperscript{14} Thus, this unexpected finding of SAMMPRIS trial is likely due to advancement in medical management rather than the inferior performance of the Wingspan stent.

There are also critics who believe that the approval process for devices is not as well regulated as that for drugs. On average, it takes \textasciitilde 12 years for new drug approval, whereas it only takes \textasciitilde 3 to 7 years for devices. Typically, drugs need to go through phases I through IV for approval, and if they fail to show...
superior safety and efficacy at any one of the phases, the drugs fail to make it further in the approval process and are dropped. In contrast, the approval process for medical devices is less stringent. The devices can bypass the rigorous clinical trials by pursuing the HDE, $10(k)$, or de novo pathway wherein they only have to show a reasonable safety profile without demonstrating the effectiveness. Even under PMA, although levels I and II are essential, it is possible to obtain PMA with level II data only. One such example is the Pipeline Embolization Device. There is also the potential for serial predicates in which a new device is approved on the basis of a predicate device that itself was approved based on yet another predicate device. Several subsequent devices later, it is possible that the new device seeking approval may be significantly different from the original device that underwent PMA. One such example is Solitaire, which was approved for neurovascular thrombectomy under $10(k)$ with Merci Retriever as its predicate device, which was in turn approved with Concentric Retriever as its predicate device, which in turn was approved with Target Therapeutics Attracter Endovascular Snare and the Microvena Corp Amplatz Goose Neck Microsnare as its predicate devices. It is interesting to note that the Snare and Microsnare were approved for retrieval of the foreign bodies in the coronary and peripheral arteries.

In response to the criticism, the US Congress passed the Act to Accelerate the Discovery, Development, and Delivery of 21st Century Cures, and for Other Purposes also known as the 21st Century Cures Act, in 2016. A major section of this law focuses on the medical devices and associated regulatory issues. The intent of this law is to decrease unnecessary regulatory hurdles and to facilitate the development of new devices. The law authorizes the FDA to use efficient and flexible approaches to facilitate the device development and approval processes. The law also enabled the use of a central Institutional Review Board to expedite the clinical trials for new device development.\textsuperscript{13,24}

Despite all the criticism, the relationship among the FDA, physician-scientists, and the medical device industry has become much stronger in recent years. The FDA has partnered with scientific societies such as the American Academy of Neurology, American Heart Association, and Society for NeuroInterventional Surgery to create interactive workshops and conference sessions to educate the researchers on how to optimize device submission processes. Selecting the correct pathway chosen for regulatory approval and staying in close dialog with the FDA can help minimize the time and money it takes for new stroke devices to reach the marketplace.

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### Appendix: Authors

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<tr>
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<td>Adnan Siddiqui, MD, PhD, FAHA</td>
<td>University at Buffalo, NY</td>
<td>Drafting and revision of the manuscript</td>
</tr>
<tr>
<td>Maxim Mokin, MD, PhD</td>
<td>University of South Florida, Tampa</td>
<td>Drafting and revision of the manuscript</td>
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