

Regulation of Carotid Artery Stents and Embolic Protection Devices in the United States

A history of, and perspectives on, FDA regulation of carotid stents and associated embolic protection devices over the years.

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Carotid artery stents and embolic protection devices (EPDs) have had a relatively complicated regulatory history in the United States. Although stents and EPDs labeled for use in stenotic carotid arteries have been on the market for almost 10 years, the full implications associated with the approval, marketing, and clinical use of these devices can be nuanced and challenging to appreciate, particularly for those less familiar with the medical device regulatory paradigm. In this article, we provide an overview of the FDA regulatory review process as it affects these two important product areas, along with a brief history of key approval/clearance milestones. In addition, we attempt to clarify how the regulatory status of these devices can have or does not have an impact on clinical practice.

OVERVIEW OF PREMARKET MEDICAL DEVICE REGULATION

Since 1976, the FDA's Center for Devices and Radiological Health (CDRH) has been charged with regulating the marketing of medical devices in the United States.¹ The CDRH follows a risk-based classification system for medical devices, which establishes the pre- and postmarket regulatory processes that have an impact on all devices of a given type. Carotid stents are classified into the highest-risk category (Class III), and as such, FDA approval of a Premarket Approval (PMA) application for each carotid stent is required before that device can be marketed and promoted for this use. PMA approval is

based on a determination that there is a reasonable assurance that the device is both safe and effective when used according to its approved labeling to treat the indicated patient population. In contrast, EPDs are classified as moderate-risk devices (Class II), for which FDA clearance through the Premarket Notification [510(k)] process is required before marketing. Different from PMA approvals, 510(k) clearance is given if the EPD is shown to be "substantially equivalent" in intended use, design, and performance to another currently marketed EPD.

Regardless of the pathway required for marketing, FDA approval and clearance decisions are predicated on the presentation and review of valid scientific evidence demonstrating either safety and effectiveness or substantial equivalence, as appropriate. As part of the review process, the FDA considers what kinds of information are appropriate, yet least burdensome to support the use of the device for the proposed patient population, keeping in mind the risks posed to the patient and the benefits provided by the treatment, particularly with respect to available treatment alternatives.² When new questions of safety and effectiveness arise, such as when a device involves first-of-a-kind technology or a novel indication for use, the FDA may also solicit input from an Advisory Panel composed of external experts in relevant device or clinical areas. These nonbinding recommendations from the Panel represent additional perspectives for the review team as they weigh the risks and benefits of a given product.

TABLE 1. APPROVED CAROTID STENTS IN THE UNITED STATES

Product Name		Indications for Use	Date of First Carotid Approval
Abbott Vascular	Acculink/ RX Acculink Carotid Stent System	Indicated for use, in conjunction with Abbott Vascular's AccUNET or Emboshield family of embolic protection systems, for the treatment of patients at high and standard risk for adverse events from carotid endarterectomy who require carotid revascularization, have a reference vessel diameter within 4–9 mm at the target lesion, and meet the criteria outlined below: High Surgical Risk —Patients with neurological symptoms and $\geq 50\%$ stenosis of the common or internal carotid artery by ultrasound or angiogram, or without neurological symptoms and $\geq 80\%$ stenosis of the common or internal carotid artery by ultrasound or angiogram. Standard Surgical Risk —Patients with neurological symptoms and $\geq 70\%$ stenosis of the common or internal carotid artery by ultrasound or $\geq 50\%$ stenosis of the common or internal carotid artery by angiogram, or without neurological symptoms and $\geq 70\%$ stenosis of the common or internal carotid artery by ultrasound or $\geq 60\%$ stenosis of the common or internal carotid artery by angiogram.	High Surgical Risk: August 30, 2004 Standard Surgical Risk: May 6, 2011
	Xact Carotid Stent System	Indicated for use, in conjunction with the Emboshield embolic protection system, for the improvement of the lumen diameter of carotid arteries in patients considered at high risk for adverse events from carotid endarterectomy who require percutaneous carotid angioplasty and stenting for occlusive artery disease and meet the criteria outlined below: (1) Patients with carotid artery stenosis ($\geq 50\%$ for symptomatic patients by ultrasound or angiography or $\geq 80\%$ for asymptomatic patients by ultrasound or angiography), located between the origin of the common carotid artery and the intracranial segment of the internal carotid artery; and (2) Patients must have a reference vessel diameter ranging between 4.8 and 9.1 mm at the target lesion.	September 6, 2005
Boston Scientific Corporation	Carotid Wallstent Endoprosthesis	Indicated for use, in conjunction with Boston Scientific embolic protection devices, for the treatment of patients at high risk for adverse events from carotid endarterectomy due to either anatomic or comorbid conditions who require carotid revascularization in the treatment of ipsilateral or bilateral carotid artery disease and meet the criteria outlined below: (1) Patients with neurological symptoms and $> 50\%$ stenosis of the common, internal carotid artery and/or the bifurcation by ultrasound or angiogram, or patients without neurological symptoms and $> 80\%$ stenosis of the common, internal carotid artery and/or the bifurcation by ultrasound or angiogram; and (2) Patients with a reference vessel diameter within the range of 4 and 9 mm at the target lesion.	October 23, 2008
	NexStent Carotid Stent System	Indicated for use, in conjunction with the Boston Scientific Filter Wire EZ embolic protection device, for the treatment of patients at high risk for adverse events from carotid endarterectomy who require carotid revascularization and meet the criteria outlined below: (1) Patients with neurological symptoms and $\geq 50\%$ stenosis of the common or internal carotid artery by duplex ultrasound or angiogram or patients without neurological symptoms and $\geq 80\%$ stenosis of the common or internal carotid artery by ultrasound or angiogram; and (2) Patients must have a reference vessel diameter within the range of 4 and 9 mm at the target lesion and a stenosis less than 30 mm in length.	October 27, 2006

TABLE 1. APPROVED CAROTID STENTS IN THE UNITED STATES (CONTINUED)

Product Name		Indications for Use	Date of First Carotid Approval
Cordis Corporation	Precise/ Precise RX/ Precise Pro RX Carotid Stent System	Indicated for use, in conjunction with the Cordis Angioguard Emboli Capture guidewire system, for the treatment of patients at high risk for adverse events from carotid endarterectomy who require carotid revascularization and meet the following criteria: (1) Patients with neurological symptoms and $\geq 50\%$ stenosis of the common or internal carotid artery by ultrasound or angiogram OR patients without neurological symptoms and $\geq 80\%$ stenosis of the common or internal carotid artery by ultrasound or angiogram; and (2) Patients must have a vessel diameter of 4–9 mm at the target lesion. The vessel distal to the target lesion must be within the range of 3 and 7.5 mm to allow for placement of the Cordis Angioguard Emboli Capture guidewire.	September 22, 2006
	Protégé GPS/ Protégé RX Carotid Stent System	Indicated for use, in conjunction with Covidien embolic protection devices, for the treatment of patients at high risk for adverse events from carotid endarterectomy who require percutaneous carotid revascularization and meet the following criteria: (1) Patients with carotid artery stenosis ($\geq 50\%$ for symptomatic patients by ultrasound or angiography or $\geq 80\%$ for asymptomatic patients by ultrasound or angiography) of the common or internal carotid artery; and (2) Patients must have a reference vessel diameter within the range of 4.5 and 9.5 mm at the target lesion.	January 24, 2007
Medtronic, Inc.	Exponent Carotid Stent System	Indicated for use, in conjunction with a Medtronic Vascular embolic protection system, for improving carotid luminal diameter in patients at high risk for adverse events from carotid endarterectomy who require carotid revascularization and meet the criteria outlined below: (1) Patients with neurological symptoms and $\geq 50\%$ stenosis of the common or internal carotid artery by either ultrasound or angiogram, or patients without neurological symptoms and $\geq 80\%$ stenosis of the common or internal carotid artery by either ultrasound or angiogram; and (2) Patients having a vessel with reference diameters between 4.5 and 9.5 mm at the target lesion.	October 23, 2007

For both carotid stents and EPDs, the supportive scientific evidence typically includes not only nonclinical data but also clinical data, especially for first-generation devices. FDA approval of an Investigational Device Exemption (IDE) is required before initiating any clinical study in the United States that involves the use of a significant-risk device for an indication for which it has not yet been approved or cleared for marketing. Clinical data collected outside the United States can also be used to support premarket submissions, although the extent to which these data can be leveraged for US regulatory purposes frequently depends on additional factors such as how the patient demographics and clinical practice patterns in the countries in which the data were collected compare to those in the United States.

CAROTID STENTING AND EPD REGULATORY HISTORY

The First Studies: High Surgical Risk

Many of the earliest clinical studies involving carotid stenting in the United States focused on patients that

were deemed to be at high risk for adverse events from surgical revascularization via carotid endarterectomy (CEA) due to pre-existing anatomic factors (eg, surgically inaccessible carotid stenosis or previous radiation therapy in the neck) or comorbidities (eg, high-stage congestive heart failure or severe coronary artery disease), as these patients were expected to derive particular benefit from the availability of a suitable nonsurgical revascularization alternative. Another important consideration in study design was the neurological symptomatic status of the subjects to be enrolled. By convention, patients were considered “symptomatic” if they experienced an ipsilateral stroke or transient ischemic attack within 6 months of enrollment, while patients were considered “asymptomatic” if they experienced no such events within the same period. Along with percent stenosis of the affected carotid artery, surgical risk status and symptomatic status continue to represent the most important attributes when identifying patient populations in carotid stenting studies, at least for regulatory purposes.

TABLE 2. CLEARED CAROTID EMBOLIC PROTECTION DEVICES IN THE UNITED STATES

Product Name		Indications for Use	Date of First Carotid Clearance
Abbott Vascular	AccUNET/ RX AccUNET Embolic Protection System	Indicated for use as a guidewire and embolic protection system to contain and remove embolic material (thrombus/debris) while performing angioplasty and stenting procedures in carotid arteries. The diameter of the artery at the site of filter basket placement should be between 3.25 and 7 mm.	August 31, 2004
	Emboshield/ Emboshield Nav6 Embolic Protection System	Indicated for use as a guidewire and embolic protection system to contain and remove embolic material (thrombus/debris) while performing angioplasty and stenting procedures in carotid arteries. The diameter of the artery at the site of the Filtration Element placement should be between 2.5 and 7 mm.	September 14, 2005
Boston Scientific Corporation	FilterWire EZ Embolic Protection System	Indicated for use as a guidewire and embolic protection system to contain and remove embolic material (thrombus/debris) while performing angioplasty and stenting procedures in carotid arteries. The diameter of the vessel at the site of filter loop placement should be between 3.5 and 5.5 mm for carotid procedures.	December 5, 2006
Cordis Corporation	Angioguard XP/ Angioguard RX Emboli Capture Guidewire	Indicated for use as a guidewire and embolic protection system to contain and remove embolic material (thrombus/debris) while performing carotid artery angioplasty and stenting procedures in carotid arteries. The diameter of the artery at the site of filter basket placement should be from 3 to 7.5 mm.	September 22, 2006
Covidien	SpideRX/ SpiderFX Embolic Protection Device	Indicated for use as a guidewire and embolic protection system to contain and remove embolic material (thrombus/debris) while performing angioplasty and stenting procedures in carotid arteries. The diameter of the artery at the site of filter basket placement should be between 3 and 7 mm.	February 17, 2006
Lumen Biomedical	FiberNet Embolic Protection System	Indicated for use as a guidewire and embolic protection system to capture and remove embolic material (thrombus/debris) produced while performing percutaneous transluminal interventional procedures in carotid arteries in high-surgical-risk patients with reference vessel diameters of 3.5 to 7 mm.	November 18, 2008
Medtronic, Inc.	GuardWire Temporary Occlusion and Aspiration System	Indicated for use in carotid arteries to: <ul style="list-style-type: none"> • Contain and aspirate embolic material (thrombus/debris) while performing angioplasty or stenting procedures. • Facilitate placement and use of diagnostic or therapeutic catheters using the GuardWire temporary occlusion catheter. • To locally infuse/deliver diagnostic or therapeutic agents with or without vessel occlusion. • The diameter of the artery where the occlusion balloon is placed should be between 3 and 6 mm. 	October 31, 2007
	Mo.Ma Ultra Proximal Cerebral Protection Device	Indicated as an embolic protection system to contain and remove embolic material (thrombus/debris) while performing angioplasty and stenting procedures involving lesions of the internal carotid artery and/or the carotid bifurcation. The reference diameter of the external carotid artery should be between 3 to 6 mm and the reference diameter of the common carotid artery should be between 5 to 13 mm.	October 15, 2009

TABLE 2. CLEARED CAROTID EMBOLIC PROTECTION DEVICES IN THE UNITED STATES (CONTINUED)

Product Name		Indications for Use	Date of First Carotid Clearance
W. L. Gore & Associates	Gore Embolic Filter	Indicated for general use as a guidewire and embolic protection system during angioplasty and stenting procedures in carotid arteries with reference vessel diameters of 2.5 to 5.5 mm.	May 23, 2011
	Gore Flow Reversal System	Intended to provide embolic protection during carotid artery angioplasty and stenting for the patients diagnosed with carotid artery stenosis and who have the appropriate anatomy described below: <ul style="list-style-type: none"> • Adequate iliac/femoral access • Common carotid artery diameters between 6 and 12 mm • External carotid artery diameters less than 6 mm 	February 4, 2009

On April 21, 2004, the Agency's Circulatory System Devices Advisory Panel met publicly to discuss the approvability of a PMA for the Cordis Precise carotid stent system (Cordis Corporation, Bridgewater, NJ) for this high-surgical-risk indication in symptomatic patients with $\geq 50\%$ stenosis and asymptomatic patients with $\geq 80\%$ stenosis of the common or internal carotid artery.³ Clinical evidence supporting the safety and effectiveness of the device for this indication came primarily from the SAPHIRE clinical trial, a randomized noninferiority trial comparing carotid artery stenting (CAS) and CEA outcomes in the indicated population. Subjects could also be directly enrolled in either CAS or CEA registry arms of the study if the treating physician felt that the subject presented an unacceptable risk for one procedure or the other, such that randomization would not be appropriate. Although enrollment in the CEA registry arm was very low, enrollment in the CAS registry exceeded enrollment in the randomized cohort. Instead of utilizing an active control, outcomes from the registry arm were compared to a performance goal derived from historical surgical and medical data obtained from similar patient groups. The primary endpoints of the randomized and registry cohorts were the composite rate of death, stroke, and myocardial infarction (MI) at 30 days postprocedure, as well as this 30-day event rate plus the rate of death and ipsilateral stroke from 31 to 365 days.

The randomized cohort demonstrated that the CAS outcomes were statistically not inferior to those from the CEA control, according to both the 30-day (4.8% for CAS vs 9.6% for CEA) and 1-year (12% vs 19.2%) primary endpoints. The CAS registry outcomes failed to meet the prespecified performance goal, with the 95% confidence interval of 19.68% exceeding the prespecified performance goal of 16.94%. Based on these data as well as other supportive information, the panel voted 6–5 to recommend that the PMA be found “approvable with conditions” specifically for the high-surgical-risk popu-

lation. The key issues raised by the panel included the importance of ensuring the comparability of patient populations and endpoints when comparing carotid stenting data to historical surgical controls, the potential problems associated with use of a composite endpoint when comparing surgical and nonsurgical outcomes because these procedures present different risk profiles, and the importance of long-term follow-up data.

The First FDA-Approved Carotid Stent: Use in High-Surgical-Risk Patients

Although the Precise stent was the subject of the first Advisory Panel meeting for a carotid stent, the first carotid stent to be FDA approved for use in high-surgical-risk patients was the Guidant (now Abbott Vascular [Santa Clara, CA]) Acculink carotid stent system, which was approved in August 2004. For a complete listing of all US FDA-approved carotid stents and cleared EPDs, see Tables 1 and 2. Clinical evidence supporting approval was obtained from three nonrandomized, multicenter, single-arm clinical studies (ARCHEr I, II, and III).⁴ In ARCHEr I, 158 pivotal subjects were treated with the Acculink over-the-wire system without embolic protection. The primary endpoint of this study was the composite rate of death, stroke, and MI at 30 days plus the rate of ipsilateral stroke from 31 to 365 days, which was compared to a performance goal derived from published data, following an approach similar to that used for the CAS registry arm of SAPHIRE. In ARCHEr II, 278 pivotal subjects were treated with the Acculink over-the-wire system plus the Accunet embolic protection system, using the same primary endpoint and comparator as ARCHEr I. ARCHEr III introduced the rapid-exchange versions of the Acculink and Accunet systems, which were evaluated in 145 subjects by comparing the primary endpoint of the rate of death, stroke, and myocardial infarction at 30 days to the corresponding ARCHEr II outcomes. Each of these studies met its pre-

specified goal. Although data from a randomized study were not available for this device, the FDA believed that the totality of the data supported the safety and effectiveness of the Acculink device for its intended use, particularly given the benefits and risks offered by this device compared to available alternatives.

Given the relative novelty of carotid stenting in the United States, one of the conditions of PMA approval was that the manufacturer conduct a postapproval study to collect additional important safety and effectiveness data that were not considered necessary for premarket approval.⁵ One goal of the postapproval study was to investigate the long-term (> 1 year) performance of the device via collection of 3-year follow-up in a subset of the premarket cohort. Another goal was to assess the generalizability of the premarket study results to the broader physician and patient populations via the enrollment of a new subject cohort and recruitment of some less experienced clinical sites. The results from this new cohort were also used to assess the adequacy of the device training program.

One day after the Acculink carotid stent PMA approval, the Accunet EPD was cleared via 510(k) for carotid use. Along with nonclinical testing, this clearance was based on the ARChER study data.⁶ Because the majority of the clinical data in these studies were collected in subjects in whom both the Acculink and Accunet devices were used, the PMA and 510(k) reviews were inextricably linked, resulting in PMA approval and 510(k) clearance within 1 day of each other.

As of 2013, seven carotid stents have been approved for the treatment of symptomatic and asymptomatic carotid stenosis in high-surgical-risk patients. With the exception of the Cordis Precise stent family, which was supported by the randomized SAPHIRE trial, all of these approvals were based on the results of prospective single-arm clinical studies involving designs and comparisons comparable to those used in ARChER II, and postapproval studies were mandated for each PMA approval. There are 10 EPDs cleared for carotid use, including seven distal filter-based systems, one distal balloon, and two proximal protection systems. The indications for use of EPDs do not typically specify surgical risk or symptomatic status. The majority of these EPDs were studied clinically along with an investigational carotid stent, such that the results of the clinical study supported both the stent approval for high-surgical-risk use as well as EPD clearance, as with the Acculink/Accunet devices. The other EPDs were studied together with stent systems that were already approved for carotid use, with multiple such stents used in the same study in some cases.

The Regulatory Value of Nonrandomized CAS Studies

With carotid stents now approved for the high-surgical-risk population, interest from the vascular community focused more strongly on treating the much larger non-high- (or standard) surgical-risk population, those patients with symptomatic or asymptomatic carotid stenosis that are not considered to be at high risk for adverse events from surgical revascularization. Specifically, although randomized, controlled trials (RCTs) comparing CAS and CEA were considered the gold standard for evaluating the safety and effectiveness of carotid stents in these patients, it was not clear whether data collected from other types of clinical trials, such as nonrandomized, concurrently controlled studies, could also be capable of providing sufficiently valid scientific evidence to support FDA approval of this new indication. Given the challenges often associated with running randomized trials such as SAPHIRE, most notably slow enrollment due to a lack of clinical equipoise or strong physician or patient preferences (particularly when both treatments are readily available outside the study without the need for randomization), a nonrandomized study could potentially allow collection of these data in a faster and less burdensome manner.

With these considerations in mind, the FDA's Circulatory System Devices Advisory Panel met on October 11, 2007, to provide their perspective on the general topic of what kinds of clinical study designs would be suitable for evaluating carotid stenting for the standard-risk population.⁷ After presentations from the FDA, physician, and industry speakers, the expert physician Panel agreed that RCTs provide the best clinical evidence to support both the overall proof of concept of carotid stenting in the standard-surgical-risk population as well as the safety and effectiveness of individual carotid stent systems. The Panel believed that nonrandomized studies may have greater clinical and regulatory value once data from a completed RCT are available, provided factors such as bias and confounding are controlled to the greatest extent possible. Important considerations for an optimal clinical study design included sufficient long-term follow-up data, a standardized medical regimen for all subjects, current stent/EPD technology, and for noninferiority studies, the adoption of a noninferiority margin capable of detecting clinically meaningful differences in outcomes. Finally, the Panel highlighted the potential benefits and challenges of nontraditional approaches to data collection, such as leveraging non-US clinical experience and data, clinical trial networks, and collaborations among multiple device manufacturers and other stakeholders. Almost 6 years later, these perspectives still serve as a useful guide for clinical evidence development in the carotid space.

Approval for Standard-Risk Patients

On May 6, 2011, the Abbott Vascular RX Acculink carotid stent system became the first stent to receive FDA approval to expand its indication to include standard-surgical-risk patients with symptomatic $\geq 70\%$ stenosis of the common or internal carotid artery as determined by ultrasound ($\geq 50\%$ if by angiography) or asymptomatic $\geq 70\%$ stenosis ($\geq 60\%$ if by angiography).⁸ The FDA's approval was based on results from the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST), which was a two-arm, randomized clinical study of CAS using the Acculink and Accunet devices versus CEA in patients with stenoses of the carotid arteries.⁹ The subjects were randomized 1:1 to treatment with CAS as the test group or CEA as the control group. A total of 4,079 subjects (1,557 lead-in and 2,522 randomized) were enrolled at 119 US sites and 10 Canadian sites between December 2000 and August 2008. Similar to the high-surgical-risk studies, the primary endpoint for regulatory purposes was a combined safety and effectiveness endpoint of death, stroke, and myocardial infarction within 30 days postprocedure plus the rate of ipsilateral stroke from 31 to 365 days postprocedure. The primary endpoint event rates were 7.1% in the CAS arm and 6.6% in the CEA arm. The study protocol also specified several secondary analyses and subgroup analyses.

To help with the approval decision, the FDA again convened its Circulatory System Devices Advisory Panel on January 26, 2011, to contribute an independent clinical review to the approval process.¹⁰ During this day-long meeting, the Panel was asked to consider and comment on several items including the appropriateness of the indication (particularly for various subsets of the patient population stratified by age and symptom status), the clinical significance of observed differences in primary endpoint component rates between the two study arms (ie, the higher stroke rate in the CAS arm vs the higher myocardial infarction rate in the CEA arm), the stability of the outcomes after 1 year, as well as the appropriateness of the proposed labeling and postapproval study. The Panel also spent a significant amount of time discussing the availability of long-term follow-up data and the implication of long-term follow-up compliance rates.

The Panel voted 6–4 (with one abstention) that the CREST data demonstrated reasonable assurance that the RX Acculink carotid stent system is safe for use in the indicated patient population and also voted 8–2 (with one abstention) that data demonstrated reasonable assurance of effectiveness. Finally, the Panel voted 7–3 (with one abstention) that the benefits of the RX Acculink carotid stent system outweigh the risks for use in the specified patient population. The FDA review team concurred with

the Panel's recommendations and approved the device for the standard-surgical-risk population.

Consistent with the high-surgical-risk carotid stent approvals, the approval of the RX Acculink stent for the standard-surgical-risk indication was accompanied by conditions of PMA approval, including the requirement to conduct a postapproval study.¹¹ As described in the FDA's approval order for this regulatory submission, the CANOPY postapproval study was to include a minimum of 1,200 newly and sequentially enrolled standard-surgical-risk subjects at up to 350 sites. The primary endpoint was the proportion of patients with a composite periprocedural (within 30 days of the procedure) death and stroke, plus ipsilateral stroke between day 31 and 1 year (365 days), and patients were to be followed for 3 years. The objective of the postapproval study, which is ongoing, is to further evaluate long-term device performance, utility of training programs, subgroup performance within the approved patient population, and rare adverse events and generalizability of the CREST results to a broader patient population.

As of the writing of this article, the RX Acculink carotid stent system remains the only carotid stent approved for use in the standard-surgical-risk population.

REGULATORY PERSPECTIVES ON CAS/EPD MARKETING AND CLINICAL USE

Given the regulatory history of carotid stents and EPDs as summarized previously, it is important to remember that the FDA approves/clears individual devices for specific indications and does not approve/clear device classes or procedures. Because differences in stent and EPD design may result in altered clinical outcomes, the FDA evaluates the performance of each individual device to determine whether there is reasonable assurance of safety and effectiveness (for PMA devices) or substantial equivalence (for 510[k] devices) in the patient population in which it is intended to be used, and the probable benefit must outweigh the probable risk associated with use of the device in order to be marketed for that use. The approved/cleared indications and labeling reflect available data, including the patient populations studied/not studied, use with other devices (eg, EPDs), and other available evidence.

The FDA considers the labeling important for communicating information relevant to the specified indications for use, which have been supported by appropriate safety and effectiveness information. That said, physicians commonly use legally marketed medical devices in ways that are inconsistent with their cleared or approved labeling and indications, and the area of carotid stenting is no exception. With such "off-label use," the information in the device labeling may be less useful to the

clinician.¹² Because the FDA regulates the marketing of medical devices, manufacturers cannot promote a device to be safe and effective for an unapproved use. However, because the FDA does not regulate the practice of medicine, physicians may use marketed devices off-label, following what they believe is the best course of treatment for their individual patients.¹³ The FDA recognizes that prior to the first carotid stent PMA approvals, off-label use of other stents for carotid stenting procedures was commonplace. With at least one stent now approved for the standard-surgical-risk population and several more approved for use in high-surgical-risk patients, however, this may occur less frequently. Nevertheless, off-label use of devices can subject patients to unknown risks because the safety and effectiveness of the devices may not have been adequately evaluated for these uses. If manufacturers become aware of significant off-label use patterns for their devices, we would encourage them to conduct clinical studies that assess the safety, effectiveness, and performance of their device for these new uses. If sufficiently positive, such data could be used to expand the labeling of their devices to include new indications for use. In addition, treatment of patients via enrollment in a defined clinical study rather than through individual instances of off-label use allows for more robust collection and analysis of clinical data that can ultimately be shared with the medical community to develop and refine real-world patient treatment strategies.

Similarly, another significant point to remember is that the FDA does not require specific stents and EPDs to be used together. Stents are indicated for use together with the EPD with which they were studied, and EPD labeling states which stents were used in the clinical study that supported market clearance. Some EPDs were studied with a single stent and some with multiple stents. If multiple stents were used, the EPD labeling provides the clinical results stratified by the stent used. Although a manufacturer cannot promote an EPD as safe and effective when used with stents other than those with which it was studied clinically, nonclinical data can be used to support “compatibility” claims with other stents.

FUTURE DIRECTIONS

As mentioned, the FDA recognizes that treating physicians know their patients best, and the risk-benefit profile may not support EPD usage in all patients, as shown by the fact that the FDA does not require the use of an EPD during carotid procedures. The FDA does, however, appreciate open discussion of the risks and benefits of EPD use and encourages further clinical evaluation of their use, particularly as EPD technology continues to develop beyond the traditional filter basket and balloon

occlusion designs. The opportunity remains to better characterize the contributions of various EPD types and evaluate their potential clinical benefit for use in specific patient populations.

Device modifications may also improve durability and reliability or offer new features that improve patient outcomes. The debate between the favorable flexibility of the open-cell stent design versus the optimal wall apposition and plaque coverage of the closed-cell stent design continues to provide interest to the physician community, industry, and the FDA as new stent designs and better technology are developed. Additionally, as the use of drug-eluting stents expands beyond the traditional coronary space into the peripheral anatomy, use of stents with drug coatings in carotid arteries could be explored further. Drug-coated carotid stents would involve their own unique risk-benefit considerations. Although a drug-coated stent could result in improved restenosis rates, new risks such as the potential embolization of the drug coating could also result in increased complications. The FDA encourages continued dialogue between the medical community and industry as new technologies are developed.

Scientific questions also remain as to which patient populations are most likely to benefit from carotid stenting procedures. For example, while patient populations included in CAS studies have typically been defined according to their level of perceived risk for surgical revascularization, less attention has been paid to identifying risk factors for endovascular revascularization and exploring the relative value of CAS in patients with varying degrees of these risks. In addition, there remain questions about the role of CAS as well as CEA in patients with asymptomatic carotid artery stenosis, particularly given advances in medical therapy in the decades since the last of the large randomized trials comparing CEA versus medical therapy in these patients were completed. A large randomized trial focusing on the treatment of asymptomatic standard-risk patients could help to answer these important questions.

We encourage stakeholders interested in conducting a clinical study to explore these and any other CAS-related issues to involve the FDA early in the process. The FDA's Pre-Submission program provides an opportunity to obtain FDA feedback on study designs before submission of an IDE and before initiation of any clinical study that does not require an IDE, such as studies conducted outside the United States or those involving on-label use of marketed devices.¹⁴ The goal of the Pre-Submission program is to provide an efficient pathway for obtaining regulatory input with the goal of facilitating the medical device development and evaluation processes.

CONCLUSION

Carotid artery stents, EPDs, and identification of their respective indicated patient populations are evolving as device implementation and use continues to expand. As the technologies mature and expand to new patient populations, the FDA will continue to refine its recommendations for clinical trials and device approvals to best fulfill its public health mission and ensure that patients have timely access to safe and effective treatments. ■

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1. Federal Food, Drug, and Cosmetic Act and associated regulations in Chapter 21 of the Code of Federal Regulations (CFR).
2. For more information on CDRH's application of benefit-risk principles, please refer to the document, "Guidance for Industry and Food and Drug Administration Staff - Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications," published March 28, 2012.
3. Transcript from the April 21, 2004 meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee, Gaithersburg, MD.
4. Summary of Safety and Effectiveness Data for PMA P040012, for the Guidant ACCULINK and RX ACCULINK Carotid Stent System, published August 30, 2004.
5. Approval order for PMA P040012, for the Guidant ACCULINK and RX ACCULINK Carotid Stent System, issued August 30, 2004.
6. 510(k) Summary for 510(k) K042218, Guidant ACCUNET and RX ACCUNET Embolic Protection System, published August 31, 2004.
7. Transcript from the October 11, 2007 meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee, Gaithersburg, MD.
8. Approval order for PMA P040012 Supplement S034, for the Abbott Vascular RX ACCULINK Carotid Stent System, issued May 6, 2011.
9. Summary of Safety and Effectiveness Data for PMA P040012 Supplement S034, for the Abbott Vascular RX ACCULINK Carotid Stent System, published May 6, 2011.
10. Transcript from the January 26, 2011 meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee, Gaithersburg, MD.
11. Approval order for PMA P040012 Supplement S034, for the Abbott Vascular RX ACCULINK Carotid Stent System, issued May 6, 2011.
12. Abel DB. Off-label medical device use. *Endovasc Today*. 2003;2:60-61.
13. See Section 1007 of the Federal Food, Drug, and Cosmetic Act.
14. For more information on CDRH's Pre-Submission program, please refer to FDA's draft guidance document, "The Pre-Submission Program and Meetings with FDA Staff," published July 13, 2012. FDA's draft guidance represents FDA's proposed approach to this topic.