On February 2, 2024, FDA published the final rule to amend the Quality System (QS) regulation in 21 CFR part 820 (89 FR 7496, effective February 2, 2026). The revised 21 CFR part 820 is now titled the Quality Management System Regulation (QMSR). The QMSR harmonizes quality management system requirements by incorporating by reference the international standard specific for medical device quality management systems set by the International Organization for Standardization (ISO), ISO 13485:2016. The FDA has determined that the requirements in ISO 13485 are, when taken in totality, substantially similar to the requirements of the QS regulation, providing a similar level of assurance in a firm's quality management system and ability to consistently manufacture devices that are safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act).

This guidance document was issued prior to the effective date of the final rule. FDA encourages manufacturers to review the current QMSR to ensure compliance with the relevant regulatory requirements.

FDA notes that in particular, the QMSR does not utilize certain terms from the previous QS regulation, such as "Design Change," and "Design History File (DHF)." The elements that comprise those terms are now described in ISO 13485:2016, Clause 7.3 and its subclauses, which are incorporated by reference in the QMSR.

On June 14, 2023, FDA issued a guidance titled "Content of Premarket Submissions for Device Software Functions."[1] This final guidance supersedes the Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, issued on May 11, 2005. The final guidance issued on June 14, 2023, provides information regarding the recommended documentation sponsors should include in premarket submissions for FDA's evaluation of the safety and effectiveness of device software functions. In particular, the final guidance includes information to help determine a device's Documentation Level (formerly known as Level of Concern). The purpose of the Documentation Level is to help identify the minimum amount of information that would support a premarket submission that includes device software functions.

Within the framework of the superseded guidance, peripheral vascular atherectomy devices were considered a device with a Moderate Level of Concern. Based on the device's risk in the context of the device's intended use, as discussed in the final guidance "Content of Premarket Submissions for Device Software Functions," peripheral vascular atherectomy devices should generally address the recommendations for a Basic Documentation Level. The actual Documentation Level for your device may vary based on the specifics of your device. Certain novel or unusual indications, applications, or technological characteristics (e.g., atherectomy devices with software to control the device's cutting/lasing functions) may warrant a higher Documentation Level. If you are uncertain what Documentation Level may be appropriate given the device's indications, applications, or technological characteristics, sponsors should discuss

[1] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-device-software-functions.

with the responsible review division as an Enhanced Documentation Level may be more appropriate. For more information about Documentation Level and recommended documentation for a premarket submission, sponsors are encouraged to review the guidance "Content of Premarket Submissions for Device Software Functions."

Contains Nonbinding Recommendations

Peripheral Vascular Atherectomy Devices - Premarket Notification [510(k)] Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on May 20, 2021.

A draft select update to this document was issued on July 13, 2020.

This document supersedes "Peripheral Vascular Atherectomy Devices - Premarket Notification [510(k)] Submissions: Guidance for Industry and Food and Drug Administration Staff" issued February 13, 2020

For questions about this document, contact OHT2: Office of Cardiovascular Devices/Division C: Division of Coronary and Peripheral Interventional Devices/Plaque Modifications Team at (301) 796-2520.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

GRZAN

Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2018-D-2494. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please include the document number 16013 and complete title of the guidance in the request.

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Peripheral Vascular Atherectomy Devices - Premarket Notification [510(k)] Submissions

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or we) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

This guidance document provides recommendations for 510(k) submissions for peripheral vascular atherectomy devices. The recommendations reflect current review practices and are intended to promote consistency and facilitate efficient review of peripheral vascular atherectomy submissions.

For the current edition of the FDA-recognized consensus standards referenced in this document, see the FDA Recognized Consensus Standards Database Web site at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm. For more information regarding use of consensus standards in regulatory submissions, please refer to FDA guidance, "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices - Guidance for Industry and Food and Drug Administration Staff."[1]

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/appropriate-use-voluntary-consensus-standards-premarket-submissions-medical-devices.

II. Background

Atherectomy is an interventional procedure performed to remove atherosclerotic plaque from diseased arteries. The mechanism of plaque removal ranges from cutting, shaving, sanding, or vaporizing.[2,3] Atherectomy devices vary in design and complexity and there are currently four main categories of atherectomy devices:[4,5]

1. Directional: Directional atherectomy involves the resection of atherosclerotic plaque with a cutting device in the longitudinal plane. Directional atherectomy typically removes plaque in a single plane with multiple passes.

2. Rotational: Rotational atherectomy devices typically employ a high-speed concentrically rotating cutting blade or burr coated with abrasive material. These devices use differential and circumferential cutting blades to debulk plaque.

3. Orbital: Although similar to rotational atherectomy devices, orbital atherectomy devices employ a 360° rotational coil with a rough burr that "sands" off plaque. The orbital motion allows the burr to remove plaque as it moves through the lesion. Unlike rotational atherectomy, the orbit of this type of atherectomy device changes with rotational speed.

4. Laser: Laser atherectomy systems use a high-energy light beam to vaporize plaque. The device typically consists of a fiber-optic catheter that attaches to a laser generator.

The choice of atherectomy device depends on plaque location, vessel characteristics, length of disease segment, plaque quantity, plaque texture, and physician experience.

We encourage members of industry to engage the Office of Product Evaluation and Quality (OPEQ) via the Q-Submission Program to obtain feedback on specific device indications and operation characteristics. For more information on Q-Submissions, please see the FDA guidance, "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program;"[6] here in after, Q-Submission Guidance).

Atherectomy devices used in the peripheral vasculature require a premarket notification [510(k)] submission before marketing (see 21 CFR part 807). This document supplements other FDA documents regarding the specific content requirements and recommendations of a premarket

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[2] Mustapha, Jihad A. "Atherectomy Today: Go Slow to Finish Fast." *Endovascular Today*, October 2011, pp. 56-66.
[3] Akkus, Nuri I., Abdulrahman Abdulbaki, Enrique Jimenez, and Neeraj Tandon. "Atherectomy Devices: Technology Update." *Medical Devices: Evidence and Research*, vol. 8, 2015, pp. 1-10.
[4] Akkus, Nuri I., Abdulrahman Abdulbaki, Enrique Jimenez, and Neeraj Tandon. "Atherectomy Devices: Technology Update." *Medical Devices: Evidence and Research*, vol. 8, 2015, pp. 1-10.
[5] Quevedo, Henry C., Salman A. Arain, Gholam Ali, and Nidal Abi Rafeh. "A Critical View of the Peripheral Atherectomy Data in the Treatment of Infrainguinal Arterial Disease." *Journal of Invasive Cardiology*, vol. 26, no. 1, 2014, pp. 22-29.
[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

notification (510(k)) submission. You should also refer to 21 CFR 807.87 and FDA's guidance, "Format for Traditional and Abbreviated 510(k)s."[7]

III. Scope

The scope of this document is limited to atherectomy devices used in the peripheral vasculature, regulated under 21 CFR 870.4875 and with the product code listed in the table below:

Product Code	Regulation Number	Name
MCW	870.4875	Intraluminal Artery Stripper

Because of the higher-risk anatomical location, atherectomy devices used in the coronary vasculature are class III devices, which require a premarket approval (PMA) application before marketing. (see sections 513(a)(1)(C) and 515 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360c(a)(1)(C) and 360e) and 21 CFR part 814). Atherectomy devices indicated for use in the coronary vasculature are outside the scope of this guidance document; however, some of the information provided in this guidance document may be applicable to atherectomy devices with coronary indications. For more information on FDA's recommendations for review of coronary atherectomy devices, please contact the Plaque Modification Devices Team, Division of Health Technology 2C, within the Office of Health Technology 2.

Peripheral atherectomy devices are used to establish significant luminal gain in stenotic peripheral plaque by removing plaque as the device's primary function. A new peripheral atherectomy device might not strictly fall into one of the four categories listed in the Background Section above; however, the information provided in this guidance may still be helpful in developing a risk analysis and performance testing strategy.

Medical devices used to facilitate passage of a guidewire through or around chronic total occlusions or devices used for plaque modification via reshaping, compression, and cracking of the plaque to change the plaque volume, but do not intentionally remove plaque (such as devices that primarily achieve luminal gain through balloon angioplasty or cutting/scoring), are not considered atherectomy devices and are outside the scope of this guidance document.

IV. Premarket Submission Recommendations

A. Device Description

We recommend that you identify your device by regulation and product code as described in Section III above, and include the information described below. As part of the device description, we also recommend that you identify all accessories and describe their function(s).

[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/format-traditional-and-abbreviated-510ks.

In addition, we recommend that you provide the following information, if applicable to your device:

- description of the mechanism of operation;
- description of technological characteristics;
- identification of configurations and models;
- listing of materials;
- identification of coatings; and images or engineering drawings.

We recommend that you describe the technical and performance specifications of the device and include a brief description of the device design in this section. This should include, as applicable, details about how your atherectomy device achieves its desired rotational speed. We recommend the specifications identify applicable dimensional characteristics, operating limitations (e.g., rotational speed, energy output, wavelength, orbital lumen diameter) and any other functional, physical, and environmental considerations of the device. If your submission includes multiple device models, we recommend that you identify all device models and configurations. You should also provide images or engineering drawings of the device and accessories that include dimensions and tolerances to fully describe and characterize the device and describe any unique device features. Please also identify if your device uses software and if so, the extent of software control on your device.

As part of your device description, we recommend that you provide a list of all device components, their respective materials, and their contact duration. We recommend identifying both the generic material(s) of construction and the unique material identifier(s). You should also provide the level of blood contact (i.e., direct, indirect, or no contact) for each component.

B. Predicate Device Comparison

For devices reviewed under the 510(k) process, manufacturers must compare their new device to a similar legally marketed predicate device to support its substantial equivalence (21 U.S.C. 360c(i); and 21 CFR 807.87(f)). This comparison should provide information to show how your device is similar to and different from the predicate. Side by side comparisons, whenever possible, are desirable. See Table 1 below for an example of how this information may be organized. This table is not intended to represent an exhaustive list of comparative parameters; you should provide all relevant device descriptive characteristics as outlined in the "Device Description" section, above.

Table 1: **Predicate Device Comparison.**

Description	Subject Device	Predicate Device (Kxxxxxx)
Indications for Use		
Mechanism of Operation		
Materials		
Dimensional Characteristics		
Rotational Speed		
Energy Wavelength		
Other Relevant Characteristics		

As part of your comparison, we recommend that you clearly explain the intended clinical environment and intended use of the device, including target vasculature.

C. Software

Significance: Software in atherectomy devices may include a variety of functions ranging from ensuring that malfunctions that could be hazardous do not occur (e.g., cause injury, erroneous diagnosis, or delay in delivery) to directly controlling device cutting/lasing output. Adequate software performance testing provides assurance that the device is safe for the user, operator, and the patient.

Recommendation: Refer to the FDA software guidance, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices"[8] for a discussion of the software documentation that you should provide in your submission. The software guidance outlines the type of documentation to be provided based on the "level of concern" (LOC) associated with the device. We generally consider the software of atherectomy devices to present a moderate LOC. However, new or unusual indications, applications, or technological characteristics (e.g., atherectomy devices with software to control the device's cutting/lasing functions) may result in a higher level of concern. If you believe that the software in your device presents either a "minor" or a "moderate" LOC as defined in the software guidance, you should provide a scientific justification that supports your rationale of the LOC based on the possible consequences of software failure.

We recommend that you provide a full description of the software/firmware supporting the operation of the subject device in accordance with the Software Guidance, commensurate with the appropriate level of concern. This recommendation applies to original device/systems as well as to any software/firmware changes made to already-marketed devices. Changes to software must be revalidated and reverified in accordance with Design Controls (21 CFR 820.30(g)(i)) and documented in the Design History File (21 CFR 820.30(j)). Some software changes may warrant the submission of a new 510(k). For further information on this topic, please refer to "Deciding When to Submit a 510(k) for a Software Change to an Existing Device."[9]

As appropriate, you should also provide information on the Cybersecurity aspects of your device. For more information on this topic, please see the FDA guidance, "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices."[10]

If the device includes off-the-shelf software, you should provide the additional information as recommended in the FDA documents titled, "Off-the-Shelf Software Use in Medical Devices"[11]

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[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-content-premarket-submissions-software-contained-medical-devices

[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-software-change-existing-device

[10] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-management-cybersecurity-medical-devices-0

[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/shelf-software-use-medical-devices

and "Cybersecurity for Networked Medical Devices Containing Off-The-Shelf (OTS) Software,"[12] which provide additional information regarding medical devices using off-the-shelf software.

FDA has recognized various voluntary consensus standards that support medical device interoperability which is one way to ensure appropriate functional, performance, and interface requirements of these devices. If your device has the ability to exchange and use information through an electronic interface with another medical/nonmedical product, system, or device, you should provide the additional information as recommended in the FDA guidance, "Design Considerations and Pre-market Submission Recommendations for Interoperable Medical Devices."[13]

Overall, the documentation related to the software contained in the medical device should provide sufficient evidence to describe the role of the software included in the device and performance testing to demonstrate that the software functions as designed.

D. Biocompatibility

Significance: Peripheral vascular atherectomy devices contain patient-contacting materials, which, when used for their intended purpose, may induce a harmful biological response.

Recommendation: You should determine the biocompatibility of all patient-contacting materials present in your device. If your device is identical in composition and processing methods to atherectomy devices with a history of successful use, you may reference previous testing experience or the literature, if appropriate. For some device materials, it may be appropriate to reference a recognized consensus standard or provide a Letter of Authorization (LOA) for a device Master File (MAF).

If you are unable to identify a legally marketed predicate device with similar location/duration of contact and intended use that uses the same materials and manufacturing (including sterilization and packaging) as used in your device, we recommend you conduct and provide a biocompatibility risk assessment. The assessment should explain the relationship between the identified biocompatibility risks, discuss the information available to mitigate the identified risks, and identify any knowledge gaps that remain. You should then identify any biocompatibility testing or other evaluations that were conducted to mitigate any remaining risks. We recommend that you follow the FDA guidance, "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process'," [14] which identifies the types of biocompatibility assessments that should be considered and recommendations regarding how to conduct related tests.

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[12] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cybersecurity-networked-medical-devices-containing-shelf-ots-software

[13] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-and-pre-market-submission-recommendations-interoperable-medical-devices

[14] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and.

Per ISO 10993-1: *Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process* and Attachment A of FDA's guidance on ISO-10993-1, atherectomy devices are external-communicating devices in contact with circulating blood for a limited contact duration. Therefore, the following endpoints should be addressed in your biocompatibility evaluation:

- Cytotoxicity.
- Sensitization.
- Irritation or intracutaneous reactivity.
- Acute systemic toxicity.
- Material mediated pyrogenicity.
- Hemocompatibility (i.e., hemolysis, complement activation, and thrombogenicity).

Please note that genotoxicity assessment may be requested if the atherectomy device contains novel patient-contacting materials that have not been previously evaluated for use in contact with circulating blood in legally marketed medical devices.

The following additional considerations are recommended regarding sample preparation for atherectomy devices. For biocompatibility testing conducted using extraction samples, we recommend the following:

- Determine the appropriate amount of test material, as outlined in *ISO-10993-12: Biological evaluation of medical devices – Part 12: Sample preparation and reference materials* or an equivalent method, using surface area to extractant volume ratios (mass to extractant volume ratios should only be used if use of mass may result in a test article with a larger surface area to extract volume ratio than what is recommended by ISO 10993-12.
- Use both polar and nonpolar extractants, where applicable.
- Explain any changes in the post-extraction vehicle (compared to pre-extraction), including color, presence of any particulates, etc.
- Describe the details of storage conditions (e.g., storage time, temperature), if applicable.

E. Sterility

Significance: Peripheral vascular atherectomy devices come in contact with blood and should be adequately sterilized to minimize infections and related complications.

Recommendation: For atherectomy devices labeled as sterile, we recommend that you provide information for the final, sterilized device in accordance with the FDA guidance, "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile"[15] (subsequently referred to as "Sterility Guidance").

[15] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-and-review-sterility-information-premarket-notification-510k-submissions-devices-labeled.

F. Pyrogenicity

Significance: Pyrogenicity testing is used to help protect patients from the risk of febrile reaction caused by gram-negative bacterial endotoxins and chemicals that can leach from a medical device (e.g., material-mediated pyrogens).

Recommendation: To address the risks associated with the presence of bacterial endotoxins, atherectomy devices should meet pyrogen limit specifications by following the recommendations outlined in the FDA Guidance, "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile." You should also follow the recommendations in "Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers."[16] To address the risks associated with material-mediated endotoxins, follow the recommendations in FDA's guidance "Use of International Standard ISO-10993-1, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing'."[17]

Peripheral vascular atherectomy devices should be labeled as "non-pyrogenic" as they come into contact with circulating blood. We recommend that both bacterial endotoxins and material-mediated pyrogenicity be addressed. Devices in contact with the cardiovascular system should meet pyrogen limit specifications discussed in the FDA guidance, "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile."[18]

G. Shelf Life and Packaging

Significance: Shelf life testing is conducted to support the proposed expiration date through evaluation of the package integrity for maintaining device sterility and/or evaluation of any changes to device performance or functionality.

Recommendation: With respect to package integrity for maintaining device sterility, you should provide a description of the packaging, including how it will maintain the device's sterility, and a description of the package integrity test methods and a summary of the results, but not the package test data. We recommend that package integrity test methods include simulated distribution and associated package integrity testing, as well as simulated (and/or real-time) aging and associated seal strength testing to validate package integrity and shelf-life claims. We recommend you follow the methods described in the FDA-recognized series of consensus standards, AAMI/ANSI/ISO 11607-1: *Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging* and AAMI/ANSI/ISO 11607-2: *Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly processes*.

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[16] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-pyrogen-and-endotoxins-testing-questions-and-answers

[17] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-international-standard-iso-10993-1-biological-evaluation-medical-devices-part-1-evaluation-and

[18] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-and-review-sterility-information-premarket-notification-510k-submissions-devices-labeled

With respect to evaluating the effects of aging on device performance or functionality, shelf-life studies should evaluate critical device properties to ensure that it continues to perform adequately and consistently during the entire proposed shelf life. To evaluate device functionality, we recommend you assess each of the bench tests described in Section IV.I and IV.J and repeat all tests that evaluate design characteristics that are potentially affected by aging.

We recommend that you provide a summary of the test methods used for your shelf life testing, results and the conclusions drawn from your results. If you use devices subjected to accelerated aging for shelf life testing, we recommend that you specify the way in which the devices were aged and provide a rationale to explain how the results of shelf life testing based on accelerated aging are representative of the results if the device were aged in real time. We recommend that you age your devices per ASTM F1980: *Standard guide for accelerated aging of sterile barrier systems for medical devices* and specify the environmental parameters established to attain the expiration age. For devices or accessories containing polymeric materials, you should plan to conduct testing on real-time aged samples to confirm that the accelerated aging is reflective of real-time aging. This testing should be conducted in parallel with 510(k) review and clearance with results documented to file in the design history file (i.e., complete test reports do not need to be submitted to FDA).

H. Electrical Safety and Electromagnetic Compatibility (EMC)

Significance: Most atherectomy devices are medical electrical equipment and therefore may expose the operator and patient to hazards associated with the use of electrical energy or may fail to operate properly in the presence of electromagnetic disturbance. If your atherectomy device includes a laser radiation source, laser safety conditions and standard safety considerations apply as there is a risk for ocular and skin tissue damage.

Recommendation: Peripheral vascular atherectomy devices should be tested to demonstrate that they perform as anticipated in their intended use environment. We recommend that this testing be performed as described in the currently FDA-recognized versions of the following standards for medical electrical equipment safety and electromagnetic compatibility:

- ANSI/AAMI/ES 60601-1: *Medical electrical equipment – Part 1: General requirements for basic safety and essential performance.*
- ANSI/AAMI/IEC 60601-1-2: *Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance – Collateral standard: Electromagnetic disturbances – Requirements and tests.*

If submitting a declaration of conformity to the above standards, we recommend that appropriate supporting test data and analysis be provided because this series of standards includes general methods with multiple options and, in some cases, does not include specific acceptance criteria or address assessment of results. For additional information on providing EMC information in a

premarket submission, please see the FDA guidance, "Information to Support a Claim of Electromagnetic Compatibility (EMC) of Electrically-Powered Medical Devices."[19]

When a laser atherectomy device has the potential laser radiation hazards to the eyes and skin of the patient and operator, safety measures such as the use of personal protective equipment (laser protective eyewear) and/or skin contact sensors should be included to mitigate the risk.

I. Battery Testing

Significance: If your device is battery-operated, it is important to confirm that the battery is capable of performing effectively in a clinical setting. Inadequate battery operation could lengthen the time of procedure, which could impact patient safety and treatment effectiveness.

Recommendation: We recommend that you describe all batteries used in the system. Your description should include performance characteristics (e.g., usable battery amp-hour capacity, shelf-life, and life testing under worst-case usage). For evaluation of battery safety and performance, we recommend providing the following:

(1) Risk Management

We recommend you include in your risk analysis any risks related to the battery and its function in the system and the system's associated risks (e.g., premature battery depletion leading to excessive battery replacement or even replacement of the atherectomy catheter, itself, to complete a procedure).

(2) Qualification Testing

We recommend evaluating the suitability and performance of the battery for the intended use. The tests should reflect the risks identified in the risk analysis and should also assess the characteristics and general reliability of the battery when subjected to stresses anticipated under normal usage and worst-case condition. For qualification testing, we recommend referencing the standards listed below:

- IEC 62133: *Secondary cells and batteries containing alkaline or other non-acid electrolytes – Safety requirements for pore sealed secondary cells, and for batteries made from them, for use in portable applications*;
- IEC 60086-4: *Primary batteries – Part 4: Safety of lithium batteries*;
- UL 2054: *Standard for household and commercial batteries*; and
- UL 1642: *Standard for lithium batteries*.

(3) Performance Testing Considerations

When conducting the qualification testing, we recommend taking the following into consideration if your device is battery-powered:

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[19] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/information-support-claim-electromagnetic-compatibility-emc-electrically-powered-medical-devices.

- If a battery is pre-installed in the device (e.g., in the atherectomy catheter handle), it is important to note that a battery may self-discharge, even if the device is not turned on; this could limit the shelf-life of the device. We recommend that you evaluate the device at the proposed shelf-life. Specifically, the atherectomy catheter should have an expiration date consistent with the shelf-life of the battery and the catheter's sterility.
- If a battery is part of the sterile device system, sterilization of the battery at extreme conditions (e.g., high temperatures) could affect the battery's properties and limit performance. We recommend taking the conditions into consideration during your qualification testing.
- If a replacement battery is needed to complete a full procedure, we recommend that you ensure that replacing a worn-out battery with a new (or fully charged) battery does not compromise device sterility.
- If the battery drives a motor connected to a rotating device, we recommend ensuring that the battery and/or the motor does not overheat during long operations. We recommend that you provide information on how the risk of overheating is mitigated (e.g., vent holes in the battery housing). If the battery necessitates venting (e.g., if over-discharged)[20] and the battery housing includes vent holes to allow the battery to safely vent, we recommend that you provide information regarding how the risk of water ingress into the battery is mitigated.
- For testing an atherectomy device for an increase in shelf life, the battery should be periodically recharged to keep the battery voltage at an acceptable level for the duration of the shelf life test.

J. Non-Clinical Performance Testing

The purpose of the non-clinical bench testing is to ensure that the device performs as intended under the specified conditions of use at baseline (time zero) and after aging to support the proposed shelf life and that the device demonstrates substantial equivalence to the predicate device. The non-clinical performance testing recommended may vary based on the respective risk profile associated with the intended target vasculature as well as the design characteristics of your device. FDA recommends that you provide the information below to evaluate the material and performance characteristics of your final, sterilized device. If a test that is applicable to your device and listed in Section J.5 is excluded from your submission, we recommend that you provide a clinical and risk-based justification for its omission. For information on the recommended content and format of test reports for the testing described in this section, refer to FDA guidance, "Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions."[21]

[20] Venting is defined as the release of excessive internal pressure from a cell/battery in a manner intended by design to preclude rupture or explosion per IEC 62133, clause 3.10.

[21] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommended-content-and-format-non-clinical-bench-performance-testing-information-premarket.

(1) Risk Management

We recommend that you apply accepted risk management principles, such as those described in the currently recognized version of ISO 14971: *Medical devices – Application of risk management to medical devices,* while conducting the risk analysis required in 21 CFR 820 during the development of your device. We recommend you submit risk management information that identifies hazardous situations, estimates the risks (e.g., risks of device malfunction, adverse tissue reaction, infection, use error, extravasation), describes risk control measures and overall residual risk specific to your device.

The risk profile of your device depends upon its intended use. In your submission, we recommend that you provide a summary of your risk analysis. If you decide not to perform a particular test for evaluation of your device performance and/or safety profile, you should provide a clinical or scientific rationale based on your risk analysis.

(2) Test Sample Selection

If your device is available in more than one size or model, the device that is deemed the worst-case should be evaluated for each respective test. In this case, you should identify the worst-case size and provide a rationale on how the selected size is representative of your size range and models.

(3) Test Sample Preparation: Pre-Conditioning

As previously mentioned, testing should be conducted on the final sterilized device. Before and/or during bench testing, you should apply clinically relevant pre-conditioning to the device (e.g., pre-soaking in 37°C water bath and tracking through a simulated-use model). Pre-conditioning of the device should simulate the worst-case clinical and physiological conditions that the device is expected to experience.

(4) Simulated-Use Model

Significance: The simulated-use model should adequately mimic the anatomy for which the device is intended. The use of a valid simulated use model for evaluation of device functionality helps to create a better understanding of how a device is expected to perform *in vivo* in a clinical setting.

Recommendation: Functional tests and pre-conditioning should be performed using a simulated-use model. We recommend providing the following information pertaining to your simulated-use model:

- Your simulated-use model should be rigorous enough to represent the majority of the patient population intended to be treated. Considering atherectomy devices are intended to remove plaque, we recommend incorporating simulated atherosclerotic/rigid calcified plaque in your model to represent the worst-case clinical scenario and provide a clinical/scientific rationale (i.e., based on literature or experience) for your plaque model. If the anatomical model does not contain

simulated plaque, we recommend evaluating the ability to remove plaque in a cadaver model.
- We recommend that you use a three-dimensional model to best represent the human anatomy. Furthermore, it should appropriately model the various curvatures expected to be encountered from all the proposed access sites.
- We recommend that you include detailed engineering drawings and/or photos of your anatomical model(s), including measurements for the different lengths, tubing diameters, and radii of curvatures (in millimeters) and information about the material/rigidity of your simulated use model You should also provide a clinical rationale to support the selection of the anatomical model parameters.

(5) Engineering Testing

The following are recommended engineering tests for evaluating substantial equivalence of peripheral vascular atherectomy devices. Note that the tests are not all-inclusive. Thus, it is important to ensure that unique attributes specific to your device are adequately evaluated for substantial equivalence. For catheter testing, we also recommend referencing FDA's "Class II Special Controls Guidance Document for Certain Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheters"[22] (hereinafter, PTCA Catheters Guidance).

a. Dimensional Verification

Significance: Accurate device dimensions are important to aid the physician in selecting the appropriate product size. The dimensions should meet the established specification for each device size.

Recommendation: We recommend that you provide dimensional specifications and tolerances for your device as manufactured. We recommend that the specified tolerances should be based on your risk analysis. To provide accurate and consistent measurements, we recommend the use of a calibrated tool.

The following should be evaluated for any atherectomy device:
- crossing profile;
- inner diameter;
- working length; and
- effective length;

For directional devices:
- cutter length; and
- cutter diameter;

For rotational and orbital devices:

[22] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/class-ii-special-controls-guidance-document-certain-percutaneous-transluminal-coronary-angioplasty.

- rotating component length; and
- rotating component diameter.

b. Simulated-Use Testing

Significance: Use of the device in a simulated use model, in combination with other interventional devices, as appropriate, can provide more clinically relevant information about its performance than isolated bench top performance testing. Furthermore, the device should perform safely and reliably when used as intended or according to the recommended Instructions for Use, including techniques for preparation, delivery, use, retraction, and removal. Failure to perform as expected may lead to prolonged procedure times, device damage, or patient injury.

Recommendation: The following attributes should be evaluated during simulated-use testing:

- The device integrity and performance are unaffected when used in combination with applicable ancillary devices (e.g., introducer, guiding catheter, embolic protection device).
- The device is deliverable via the intended access point (e.g., femoral access) without vascular damage.
- The device is compatible with materials and accessories expected to be used with your device (e.g., guidewire, sheath).
- The device can be appropriately prepared before use.
- The device is able to track smoothly through the tortuous path and lesions to verify ease of use. The device should be appropriately flexible to traverse the simulated-use model (with plaque) without kinking or damage.
- The device (e.g., distal component, catheter shaft, cutting component) is able to maintain structural integrity prior to delivery, during use (at all labeled rotational speeds by using all mechanisms of achieving the desired rotational speed(s) and functional modes), and during retraction.
- The catheter distal component (e.g., catheter tip) can withstand constant impact on plaque under the expected number of clinical cycles as evidenced by appropriate visual assessment. If your distal component also serves as a flushing tool, the number of tissue removal cycles the distal component can withstand should be determined. The catheter should also be evaluated for possible distal component detachment.
- The device should be visualized with appropriate imaging guidance. You should address any device changes (e.g., defects, kinks, debris) on your device before and after testing.
- If your device contains a coating, we recommend that you provide images of sufficient magnification to fully characterize the coating coverage and potential defects. Apart from standard visual inspection (e.g., 2.5X), please also conduct coating inspection at higher magnifications (e.g., 40-500X)) to clearly identify and characterize any defects in the coating. Any changes in the coating (e.g., decreased uniformity, delamination, cracks) should be addressed. Please refer to Section q below for further details.
- If your device contains software, we recommend that you validate use of the software component during simulated-use testing. Please see Section C above.

c. Kink Resistance

Significance: Inability to withstand bending forces that are typical of clinical use (e.g., when the distal tip is not free to rotate, tracking the device through tortuous vascular regions) could lead to device failure or vessel damage.

Recommendation: We recommend evaluating kink resistance of the device under the worst-case radius of curvature expected during clinical use. For example, we recommend that you consider wrapping the catheter around a series of mandrels with successively smaller radii until the catheter kinks or the lumen collapses. We also recommend you provide the clinical basis for your acceptance criteria.

d. Corrosion Resistance

Significance: Corrosion of components fabricated from metal may lead to device failure or patient risk (e.g., toxicity, embolization). Visible signs of corrosion may lead to degradation of performance characteristics, even if corrosion of metallic components after exposure to corrosive environment does not lead to potential toxicity or embolization.

Recommendation: We recommend that any metallic component of the device be examined for visual signs of corrosion after an immersion test (e.g., exposure of the device to a series of saline baths at room temperature, boiling, and 37˚C beyond the maximum expected clinical use duration). For more information regarding recommendations of methodology for this testing, please refer to the currently recognized version of ISO 10555-1:2013 Intravascular catheters – Sterile and single-use catheters – Part 1: General requirements, Annex A. Although the scope of this standard is limited to intravascular catheters, the method used to evaluate corrosion resistance is applicable to atherectomy devices. Refer to the test sample conditioning methods in ISO 10555-1:2013 *Intravascular catheters – Sterile and single-use catheters – Part 1: General requirements*, Annex A for further details.

e. Heat Generation

Significance: Rotation of the device can cause heat generation caused by friction between device parts and between the rotating tip and tissues (especially if there are rigid calcified areas). Similarly, energy from the laser can also generate heat. Increased heat may lead to tissue injury or necrosis.

Recommendation: We recommend evaluating the maximum temperature rise of your device during simulated use. A clinical and/or scientific rationale for the acceptance criteria should be supported by literature (i.e., why an increase in temperature within a specific range does not impart tissue/vessel damage). If you have multiple device sizes, you should evaluate the worst-case model. For example, the largest tip at the fastest recommended rotation is expected to generate the most heat for rotational atherectomy devices.

f. Torsional Strength

Significance: Inability to withstand torsional forces that are typical of clinical use (e.g., when the distal tip is not free to rotate) could lead to device failure or vessel damage.

Recommendation: We recommend that you measure the torque strength of the atherectomy device when the distal tip is not free to rotate by rotating the proximal end of the catheter until failure. We recommend that you pre-condition the atherectomy system before evaluating torque strength by tracking through a tortuous path fixture, as described in Section (4). We recommend that you report the number of rotations to failure and the failure mode for each sample tested. Additionally, we recommend that you test the delivery system in a fixture that simulates worst-case expected anatomy. We also recommend you provide the clinical and/or scientific basis for your acceptance criteria.

g. Tensile Strength

Significance: Failure of bonds in the catheter could lead to device failure, vessel damage, and/or embolic risk caused by device remnants within the vasculature.

Recommendation: We recommend evaluating the tensile force of all the joints on your device after pre-conditioning (i.e., tracking through a simulated-use model in a water bath at 37°C). We recommend providing an image or engineering drawing with all the joints labeled. If you choose to reference standards (e.g., *ISO 10555-1: Intravascular catheters – Sterile and single-use catheters – Part 1: General requirements*) for establishing your test method, we still recommend inclusion of a clinical and/or scientific rationale to support your acceptance criteria for your device in the intended anatomy.

h. Rotational Speed

Significance: Inappropriate or non-stable rotational speed could lead to device failure or vessel damage.

Recommendation: We recommend specifying how the device achieves its labeled speed(s) (e.g., rotational speed ramps up until the desired level is reached or rotational speed is achieved instantaneously) in your test report and device description. We also recommend evaluating the rotational speed specified in your labeling and the speed stability over the proposed treatment time. It is beneficial to include the rotational speed of the predicate device for comparison. If the rotational speed is higher than that of the predicate and other FDA-cleared atherectomy devices, a discussion should be included to confirm that the proposed speed is not a safety concern. This speed should be supported with an animal study and/or clinical data (i.e., clinical study or cadavers).

i. Plaque Removal Efficiency

Significance: Inadequate plaque removal may lead to increased procedural time. This test is intended to characterize the debulking capability under simulated conditions.

Recommendation: We recommend characterizing the plaque removal efficiency in terms of percentage of plaque removed, luminal gain, or mass of tissue removed per pass. This test can be conducted either in a simulated-use model or cadaver model. For devices with multiple models or settings (e.g., speeds), we recommend evaluating the plaque removal efficiency at the minimum and maximum specified settings.

j. Infusion Flow Rate

Significance: Inability to achieve acceptable flow rates could lead to user error, increased procedural time, device overheating, and/or tissue damage.

Recommendation: For atherectomy devices intended to infuse saline or contrast agents, the appropriate flow-rate range should be established to ensure that the flow rate is consistent and safe. Thus, we recommend validating the device flow rate and providing a clinical/scientific rationale for why the flow rate is acceptable.

k. Aspiration Rate

Significance: Inadequate aspiration rate could lead to vessel damage or build-up of debris, resulting in device failure and/or debris embolization.

Recommendation: If applicable, we recommend evaluating both the infusion and aspiration/suction rate and confirming that the selected rate is adequate to remove emboli but not excessive enough to cause vessel collapse or injury. This acceptance criterion should be supported by a clinical rationale. The test should be conducted in a simulated-use model and supported with animal study data.

l. Debris Removal and Collection

Significance: Inadequate debris removal could lead to build-up of debris, resulting in device failure and/or debris embolization.

Recommendation: If applicable, we recommend evaluating the effectiveness of the removal mechanism in a diseased model (i.e., benchtop model, animal model, or cadaver model) via quantitative and qualitative methodologies.

m. Embolization Analysis

Significance: Distal embolization is an inherent risk with treatment of peripheral artery disease with atherectomy. Migration of large emboli could result in patient injury.

Recommendation: We recommend capturing and evaluating downstream emboli content post-atherectomy and quantifying the particulates using a bench and/or animal model. Your analysis should determine whether the type, size, and quantity of emboli are clinically acceptable. If a downstream filter is used during this test, the type, size, and quantity of the embolic contents present in the filter should be evaluated.

n. Life Cycle/Fatigue

Significance: Atherectomy systems are operated through multiple cycles (or passes) during one procedure. Failure of the atherectomy device to withstand multiple cycles could lead to device failure or vessel damage.

Recommendation: We recommend that you evaluate your device under the worst-case expected number of insertions and runtime. We recommend that you provide clinical rationales to support the number of insertions and runtime tested. Any changes or deformations to the atherectomy device after testing should be reported.

If your device contains an inflatable balloon that assists with cutter or tip apposition, we recommend evaluating balloon fatigue, rated burst pressure, balloon compliance, and inflation and deflation time. Please refer to the PTCA Catheters Guidance or Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems Guidance[23] for details.

If your device has an automated handle, we recommend that you verify that device operation under user control can withstand the maximum number of cycles expected during clinical use. Please also refer to the Automated Handle Functionality Section below for additional testing considerations.

o. Orbit Testing

Significance: For an orbital atherectomy system, the maximum orbital diameter is dependent on plaque rigidity, diameter of the rotating component, rotational speed (rpm), and the number of passes through the lesion. Inadequate speeds may lead to device failure, increased treatment times, and/or vessel damage.

Recommendation: We recommend orbit testing at speeds specified in your labeling in a simulated-use model containing a plaque model. We also recommend that you provide a clinical/scientific rationale for your acceptance criteria and confirm that the orbits created at your pre-determined speeds during your specified intended run time of the device are not expected to impart vessel damage. We also recommend that you include orbit performance data in your device instructions for use (IFU) (e.g., reference graphs depicting typical orbit diameter versus duration of operation (as measured in simulated lesions) for each device size and speed).

p. Automated Handle Functionality

Significance: Devices may contain an automated handle component with control buttons (e.g., for rotational direction), rather than a handle that is physically maneuvered by hand. The automated handle should function as intended. Inadequate control of the atherectomy system by the automated handle could lead to device failure, increased treatment time, and patient injury.

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[23] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/non-clinical-engineering-tests-and-recommended-labeling-intravascular-stents-and-associated-delivery.

Recommendation: If your device contains an automated handle, you should evaluate its functionality as part of bench or animal testing. We recommend verifying that the catheter distal end (e.g., distal tip, cutter) orientation/torque capability operates as expected in worst-case simulated anatomy. Additionally, evaluate the rotational response of the atherectomy system upon activation by the automated handle and verify that the device does not rotate unexpectedly upon activation.

q. Coating Integrity

Significance: Coating separation (i.e., peeling, flaking, shedding, delamination and/or sloughing off) or degradation may result in embolized particulates that could cause clinical complications.

Recommendation: If a coating is present on your device, you should provide the following:

- Name of the coating.
- A description of the physical structure of the coating.
- Location of the coating.
- Length of the coating.
- Representative images using scanning electron microscopy (SEM) and/or optical microscopy of the coated surface before and after simulated-use testing at baseline (time zero) and post-aging. Images should be of sufficient magnification to fully characterize the coating coverage and potential defects. If your coating is clear, it may be beneficial to dye the coating before simulated use to allow for proper visualization. Apart from standard visual inspection (e.g., 2.5x), please also conduct coating inspection at higher magnifications (e.g., 40-500x)) to clearly identify and characterize any defects in the coating.
- A summary of your results should be provided. If coating delamination or defects are observed, the coating reduction or particulates should be quantified, and a clinical rationale for why the results are clinically acceptable should be provided.

r. Particulate Evaluation

Significance: Particulate generation from the device during clinical use may result in serious adverse events. If your coating integrity evaluation identified coating defects that may raise additional clinical concerns, particulate evaluation may be needed to address potential safety concerns.

Recommendation: If your device has a coating, to accurately account for particulates generated during the use of your device, the particles should be characterized and data should be interpreted after simulated use.

Test Samples

You should conduct all testing on the finished product subject to all manufacturing processes including sterilization. You should provide a scientific or statistical justification for the sample size you plan to test. We recommend that you implement a sampling plan to examine multiple lots of product (≥3) to assess both inter- and intra-lot variability. You should perform testing on the extremes and an appropriate intermediate size for the entire product matrix proposed.

Test Methods

We recommend that you evaluate particulate generated by the entire atherectomy system, including accessory devices expected to be used during a clinical procedure. Catheters should be tracked through a tortuous path fixture (as described above in Sections J(4) Simulated Use Model and J(5)b Simulated-Use Testing). When delivered to the site of interest, the device should be in direct contact with the simulated vessel without the use of other coatings, lubricants, sheaths, or protective wraps between the device and the simulated vessel. To ensure measurement of the total number of particles that could be potentially introduced into the bloodstream, the catheter should be inserted into the test fixture to the extent at which it would be inserted in clinical use.

We recommend that the number of particulates generated at each evaluation be quantified and characterized by size and count using a validated method (e.g., light obscuration, light refraction) under continuous flow conditions to simulate blood flow. Specifically, we recommend that the total number of particulates be reported in the following size ranges: ≥ 10µm, ≥25µm, and at the largest size for which validation yields ≥ 75% recovery. At a minimum, the largest size should be ≥ 50µm.

Appropriate precautions should also be implemented to ensure that the particles are suspended during particle counting and sizing to minimize aggregation and other artifacts from the test system. We recommend that you measure the total quantity and size of the particulates generated during the simulated use of your device. We recommend you perform particulate evaluation under the worst-case conditions of use. For example, for devices intended for in-stent restenosis (ISR), we recommend that you evaluate the quantity and sizes of particulate generated from tracking the device through the tortuous path fixture and placement within a stent which has been deployed in the mock vessel.

Method Validation

You should describe and validate particle counting and sizing methods. We recommend that you introduce a known amount of various particle sizes into the test setup and quantify the amount of particles recovered. The number of particles recovered should closely approximate the number you artificially introduced into the system. For a system to be considered validated, ≥90% recovery should be demonstrated for the ≥10µm and ≥25µm size ranges.

You should provide a clinical discussion explaining why the results of the particulate evaluation and the associated coating integrity assessments do not raise any safety concerns. If the particulate evaluation raises safety concerns, then chemical characterization may be appropriate to identify the particulate source(s).

(6) Additional Engineering Testing for Devices Intended to Treat In-stent Restenosis

If your atherectomy device is also intended for treatment of in-stent restenosis (ISR), we recommend conducting the bench tests specified below in addition to conducting a thorough risk analysis to evaluate the risks caused by stent and atherectomy device interaction. If applicable,

the risk analysis should include an evaluation of the stent interaction with the atherectomy device (e.g., metal exposure, stent fatigue, post-fatigue corrosion). If you decide to omit any of the tests specified below, we recommend providing a rationale based on your risk analysis.

a. Simulated-Use of Atherectomy Device in a Stent

Significance: Interaction with the stent could lead to device failure, stent fracture, and vessel damage.

Recommendation: We recommend evaluating the atherectomy system in an *in vitro* or *in vivo* model containing both a stent and plaque analog (e.g., using a diseased model or overstretch model). Visual inspection should be conducted with the naked eye and under SEM of both the stent and atherectomy device pre- and post-testing. The vessel should be assessed for damage. See Section IV.K for additional information regarding animal testing.

b. Heat Generation

Significance: High heat generation caused by interaction between the atherectomy system and stent could lead to device failure and tissue damage.

Recommendation: We recommend evaluating heat generation under *in vitro* simulated-use conditions. The acceptable limit of heat generation, if any, should be supported by literature and/or clinical data. The acceptance criterion should include the upper heat limit (considering both the heat generated by the atherectomy device and heat generated from the interaction of the atherectomy device and stent), which could influence vessel safety.

c. Embolization Analysis

Significance: For ISR treatment, migration of metallic particles downstream as a result of stent and atherectomy device interaction could also result in patient injury.

Recommendation: For atherectomy devices intended for ISR treatment, the quantity, identity, and size of metallic particulates should also be evaluated. Your analysis should determine whether the type and quantity of emboli are clinically acceptable. If a downstream filter is used during this test, the quantity, identity, and size of the embolic contents present in the filter should be evaluated.

K. Animal Testing

Significance: Animal testing is generally recommended to evaluate the *in vivo* safety of peripheral vascular atherectomy devices, particularly for new designs, significant device modifications, new indications (e.g., ISR), and/or specific anatomies.

Recommendation: Animal testing of atherectomy devices should address factors that cannot be evaluated through bench tests or in a clinical study. The study design and endpoints should be based upon the mechanism of action of the device and mitigation of associated risks.

FDA supports the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. You should consider the best practices for the development, conduct, and presentation of these animal studies while incorporating modern animal care and use strategies. In addition, we encourage you to consult with FDA if you wish to use a non-animal testing method that you believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

We encourage manufacturers to take advantage of the Q-Submission Program to ensure that the animal study protocol addresses safety concerns and contains elements which are appropriate for a regulatory submission (i.e., the study should be performed under Good Laboratory Practice (GLP) regulations as stated in 21 CFR part 58 at an animal study facility with appropriate licensure and accreditations). In addition, if you are proposing to use a non-animal testing method that you believe is suitable, adequate, validated, and feasible, we recommend that you discuss the proposal using the Q-Submission Program. We will consider if such an alternative method could be assessed for equivalency to an animal test method. For details on the Q-Submission Program, please refer to the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[24]

(1) Animal Model

An ideal animal model should be representative of the human atherosclerotic disease. Unfortunately, there are currently no animal models that completely mimic the human pathology.[25,26] Despite this limitation, animal models can provide safety information that cannot be obtained through other assessments. Therefore, we recommend the use of a porcine or ovine large animal model because of the similarities in cardiovascular system size and anatomy, which have demonstrated suitability for translation to humans. For details on animal study recommendations, please refer the FDA guidance, "General Considerations for Animal Studies for Cardiovascular Devices."[27]

Although experimental animal models of atherosclerosis do exist (i.e., swine diet-induced atherosclerotic model or simulated plaque), the cost and time involved with developing the test systems with intravascular lesions often make these models prohibitive to yield robust data for regulatory safety studies. Healthy native vessel models are therefore typically employed and represent the worst-case scenario caused by direct contact of the debulking portion of the device with the intima versus a hard-atherosclerotic lesion, as is intended for clinical use. This factor and species-related differences are taken into consideration when interpreting the data for the premarket submission. Additional animal models may be applicable to evaluate specific intended

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[24] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

[25] Kapourchali, Fatemeh Ramezani, Gangadaran Surendiran, Li Chen, Elisabeth Uitz, Babak Bahadori, and Mohammed H. Moghadasian. "Animal Models of Atherosclerosis." *World Journal of Clinical Cases*, vol. 2, no. 5, 2014, pp. 126-132.

[26] Li, Xiangdong, Yuanwu Liu, Hua Zhang, Liming Ren, Qiuyan Li, and Ning Li. "Animal Models for the Atherosclerosis Research: A Review." *Protein & Cell*, vol. 2, no. 3, 2011, pp. 189-201.

[27] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-considerations-animal-studies-cardiovascular-devices-guidance-industry-and-fda-staff.

uses or anatomies. For example, as noted above, an overstretch model may be employed to generate stenosis in a stent for evaluating atherectomy systems in ISR. [28,29]

(2) Study Endpoint Considerations

When defining your study endpoint, we recommend that animal safety studies for atherectomy devices should contain both acute and chronic testing elements that use the specified predicate device(s) as the control article. The elements we generally recommend evaluating in animal studies for atherectomy devices are as follows:

a. Acute Testing (Day 0)

Acute testing should capture:

- user data (as rated by qualified independent interventionalists), including:
  - ease of use/usability;
  - catheter trackability in vascular anatomy;
  - visibility on standard imaging; and
  - compatibility with accessory devices;
- major adverse events;
- acute procedural vascular safety via angiography for overall vessel integrity, including:
- dissection;
- filling defects;
- stenosis;
- thrombosis; and/or
- other abnormalities;
- acute procedural evaluation, including hemolysis and downstream emboli (size and type); and
- examination of device for thrombus-acute thrombogenicity.

b. Chronic Study Data (Days 28+)

Duration of testing and evaluation timepoints should be based upon mechanism of action, identified risks, expected resolution of the inflammatory response, and vascular healing. We generally recommend a 28- to 30-day observation period following treatment. However, longer studies may be warranted if healing is not observed at 30 days. In your submission, we recommend providing a justification for the chosen timepoints based upon device design and mechanism of action. If unsure, we recommend using the Q-Submission Program to obtain feedback on your study protocol; please refer to the Q-Submission Guidance. The chronic study endpoints should include:

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[28] Schwartz, Robert S., Joseph G. Murphy, William D. Edwards, Allan R. Camrud, Ronald E. Vlietstra, and David R. Holmes. "Restenosis after Balloon Angioplasty. A Practical Proliferative Model in Porcine Coronary Arteries." *Circulation*, vol. 82, 1990, pp. 2190-2200.

[29] Touchard, Arturo G., and Robert S. Schwartz. "Preclinical Restenosis Models: Challenges and Successes." *Toxicologic Pathology*, vol. 34, 2006, pp. 11–18.

- major adverse events;
- in-life clinical observations;
- imaging of vascular treatment site by angiography or other imaging modalities for vascular integrity/patency, filling defects, and stenosis at baseline, interim timepoints, and at sacrifice;
- clinical pathology at baseline and at time of sacrifice;
- complete necropsy with focus on vascular treatment sites, major organ systems and downstream tissue beds for thromboembolic events;
- histopathology of vascular treatment sites for injury (external elastic lamina (EEL)/internal elastic lamina (IEL) integrity), intimal thrombi, inflammation, endothelialization, hemorrhage, and mineralization; and
- histomorphometric evaluation of vascular treatment sites for stenosis, as appropriate.

L. Clinical Performance Testing

Significance: Non-clinical evaluation does not fully characterize all relevant clinical experience, outcomes, and risks needed to demonstrate substantial equivalence. As previously noted, a diseased animal model with clinically relevant challenging anatomy and lesions does not currently exist. We believe a clinical study evaluating multiple operators, patient demographics, and lesion characteristics represents the least burdensome approach to demonstrate substantial equivalence. Therefore, we recommend that you conduct *in vivo* (i.e., clinical) studies to evaluate device safety and effectiveness for new and modified peripheral vascular atherectomy devices.

Recommendation: Clinical data are typically expected for new devices, devices modified in design and/or functionality (e.g., modification to the debulking portion of the atherectomy device), and new indications for use or labeling changes associated with device benefit or improved clinical outcomes. Because of the multivariable considerations for establishing the need for clinical data, FDA recommends having a discussion via the Q-Submission Program early in device development or when modifications are proposed; please refer to the Q-Submission Guidance.

If a clinical study is needed to demonstrate substantial equivalence, i.e., conducted before obtaining 510(k) clearance of the device, the study must be conducted under the Investigational Device Exemption (IDE) regulation, 21 CFR part 812.Generally, FDA believes that atherectomy devices addressed by this guidance are significant risk devices subject to requirements set forth in 21 CFR 812. please see the FDA guidance, "Significant Risk and Nonsignificant Risk Medical Device Studies."[30] In addition to the requirements of 21 CFR part 812, sponsors of such trials must comply with the regulations governing institutional review boards (21 CFR part 56) and informed consent (21 CFR part 50).

In some cases, real-world data (RWD) may be used to support expansion of the indication for a device for which 510(k) clearance has already been obtained. Whether the collection of RWD for

[30] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/significant-risk-and-nonsignificant-risk-medical-device-studies.

a legally-marketed device requires an Investigational Drug Exemption (IDE) depends on the situation. Specifically, if a cleared device is being used in the normal course of medical practice, an IDE would likely not be required. For additional information regarding this topic, please refer to the FDA guidance, "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices."[31]

(1) Considerations for the Level of Clinical Evidence

The level of clinical evidence depends on several factors, including but not limited to the following:

a. Proposed Indications for Use

If the device is intended to be used as the primary treatment (e.g., in lieu of percutaneous transluminal angioplasty (PTA)), clinical evidence should be provided to demonstrate that the device has equivalent safety and performance compared to PTA or another atherectomy device with regards to meaningful clinical outcome measures (e.g., major adverse events, patency, target lesion revascularization measured at six months).

b. Use with Other Endovascular Therapies

If you propose to label the atherectomy device to be used in conjunction with PTA, stenting, or other endovascular therapies, the contribution of the atherectomy device itself should be demonstrated in a clinically meaningful way. Clinical data may be appropriate to support labeling of the devices when used in combination with other endovascular therapies. Your labeling should accurately reflect the outcome of your clinical study.

c. Novelty of Design

For new or modified designs and technologies, clinical data may be expected to be provided to support a substantial equivalence determination. FDA recommends that you assess the need for additional clinical testing based on your device operational characteristics via the Q-Submission Program; please refer to the Q-Submission Guidance.

d. Use in Specific Lesion Types

Clinical data should be provided if your device is intended to treat specific anatomies or lesion types (e.g., below-the-knee, ISR lesions, long lesions) and should be noted in your indications for use and/or labeling. For example, patients with ISR lesions should be independently studied (e.g., separate arm, separate study) given the unique characteristics of these lesions as well as the potential for interactions between devices that may impact clinical outcomes.

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[31] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices.

(2) Study Endpoint Considerations

We recommend that you conduct a multi-center, prospective study designed to collect data to support the safety and effectiveness of your device. As previously noted, a diseased animal model with clinically relevant challenging anatomy and lesions does not currently exist. Therefore, we believe a clinical study represents the least burdensome approach to demonstrate substantial equivalence while evaluating multiple operators, patient demographics, and lesion characteristics. The sample size should be determined based on sound clinical and statistical principles. The study endpoints and results should be compared to known outcomes for alternative atherectomy therapies. Patient selection should include both clinical and anatomical criteria (e.g., Rutherford categorization, lesion diameter/length, lesion location). We recommend considering the following safety and effectiveness evaluations:

a. Safety Assessment

For all planned studies, data regarding a composite of Major Adverse Events (MAEs) adjudicated by an independent Clinical Events Committee (CEC) should be captured. MAE may be defined as the composite of the occurrence through 30-day follow-up of all-cause death, unplanned major amputation, and target lesion revascularization (TLR).

b. Performance Assessment

Demonstrating performance of an atherectomy device generally includes: (1) a measure of acute technical success (e.g., residual diameter stenosis after treatment) and (2) a measure of clinical success (e.g., target lesion revascularization at six months).

We may consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale. We suggest that you contact FDA to discuss clinical study planning early in your device development process using the Q-Submission Program.

M. Labeling

The premarket notification must include proposed labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). Proposed labels and labeling, sufficient to describe the peripheral vascular atherectomy device, its intended use, and the directions for use, must be provided. As noted previously for specific non-clinical tests in Section IV.J, your labeling should include relevant attributes (e.g., rotational speed(s), duration of treatment, aspiration characteristics) of your device. Your labeling should also include a description of how long your device takes to achieve its labeled speed (e.g., ramped up to desired rotational speed or rotational speed achieved instantaneously) and orbit performance data, if applicable, for each device size and speed.

As prescription devices, peripheral vascular atherectomy devices are exempt from having adequate directions for non-prescription use under section 502(f) of the FD&C Act (21 U.S.C. 352(f)) as long as the conditions in 21 CFR 801.109 are met. For instance, labeling must include adequate information for practitioner use of the device, including indications, effects, routes, methods, frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions (21 CFR 801.109(d)).

V. Modifications

In accordance with 21 CFR 807.81(a)(3), a device change or modification "that could significantly affect the safety or effectiveness of the device" or represents "a major change or modification in the intended use of the device" requires a new 510(k). The changes or modifications listed below would likely require submission of a new 510(k). Note that the lists provided below are not exhaustive but provide examples of modifications that generally require submission of a new 510(k). For additional details, please see FDA guidances "Deciding When to Submit a 510(k) for a Change to an Existing Device"[32] and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device."[33]

Such changes or modifications that generally require a new 510(k) submission include:

- Significant change in device dimensions: FDA considers this change to be a modification in design that could alter the device performance, which in turn could impact the safety and effectiveness of the device. Thus, if dimensional changes are not in the range previously cleared, test data reports should be provided for FDA review to support the change.
- Change to the debulking component or mechanism (e.g., change from directional to orbital): FDA considers this change to be a modification in design. FDA has determined that this change could significantly affect safety and effectiveness of the device as it could change how the device operates and interacts with blood vessels. More specifically, changes in the debulking component could also impact the extent of vessel trauma, which could pose a safety risk.
- Supplier or material change to a critical component (e.g., rotation component, catheter coating): FDA considers this change to be a modification in material. FDA has determined that this change could significantly affect safety and effectiveness of the device as a change in supplier and/or material may affect performance and/or introduce different types or quantities of residual chemicals, which could result in a toxic response, corrosion, or device failure.
- Change in the laser component specifications: FDA considers this change to be a modification in design. FDA has determined that a change in the laser component specifications (e.g., laser generator type, optical fiber density, laser modes, device crossing profile, device working length) could significantly affect safety and effectiveness of the device by potentially influencing laser output parameters (e.g., pulse duration, output energy, repetition rate), which would ultimately influence how the device effectively targets and ablates lesions. To support a change in laser component specifications, new testing should be provided to demonstrate that the device does not ablate lesions outside the expected range of use such that it would pose a safety risk or affect ablation effectiveness.

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[32] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device.

[33] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-software-change-existing-device.

- Change in sterilization technique: FDA considers this change to be a significant change. FDA has determined that this change could affect the safety and effectiveness of the device as it could impact device sterility and biocompatibility. For example, changes to an ethylene oxide sterilization process may leave increased ethylene oxide residuals. Additionally, changes in sterilization may unintentionally affect device materials, which could consequently affect the safety and effectiveness of the device.
- Significantly altered user technique (e.g., change from manual to automatic feature): FDA considers this change to be a significant change. FDA has determined that this change could significantly affect safety and effectiveness of the device by altering the extent of user control, which could significantly impact how the device interacts with the patient.
- Change in power source: FDA considers this change to be a modification in energy source. FDA has determined that his change could significantly affect the safety and effectiveness of the device by introducing new risks that were not previously considered or evaluated in a prior 510(k) submission. For example, a change from AC power to DC power in the form of a rechargeable battery may alter the failure modes. For example, a battery can fail due to over-charge or over-discharge, while AC power usually does not have this failure mode. Alternately, if a non-rechargeable battery is used to power the catheter, then the capacity of the battery would limit the device use-time while AC power would allow for potentially limitless device use time. Thus, it is important for FDA to evaluate changes in the power source to ensure safe and effective use of the device.

Changes or modifications in the indications for use or labeling could significantly affect both the safety and effectiveness of the device. The following changes are examples that would require a new 510(k) submission:

- Change in specific lesion characteristics (e.g., ISR) or a change in specific vasculature (e.g., below the knee, upper extremities)
- Labeling changes to capture improvement of outcomes in combination with other technologies (e.g., pre-treatment with atherectomy improves outcomes of angioplasty or drug-coated balloon). This type of labeling change should be supported with bench and/or clinical data because utilization of atherectomy in combination with other therapies could impact patient safety when considering the extent or level of treatment the patient is expected to receive.

Conversely, FDA believes that the following changes or modifications, generally, do not require the submission of a new 510(k):

- Minor change in packaging: A minor change in packaging (e.g., removal of hardcopy Instructions for Use from the box and replacement with an electronic version, update to the expiration date) is not expected to impact device safety and performance.
- Increase in shelf-life: An increase in device shelf-life is not expected to impact device safety and performance as long as the testing protocols and acceptance criteria have been previously reviewed and accepted (e.g., in the original 510(k)). Additionally, the

test results should fall within the acceptance criteria previously found to be acceptable.

The following list provides a history of revisions to this guidance document from July 2020 to present:

- Select Updates for Peripheral Vascular Atherectomy Devices - Premarket Notification [510(k)] Submissions: Draft Guidance for Industry and Food and Drug Administration Staff issued July 13, 2020