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.

Contains Nonbinding Recommendations

Peripheral Percutaneous Transluminal Angioplasty (PTA) and Specialty Catheters - Premarket Notification (510(k)) Submissions

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Guidance for Industry and Food and Drug Administration Staff

Document issued on April 14, 2023.

The draft of this document was issued on January 13, 2020.

For questions regarding this document, contact the Plaque Modification Devices Team in OHT2: Office of Cardiovascular Devices/DHT2C: Division of Health Technology 2C at (301) 796-6075.

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

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-2019-D-5422. 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 GUI00016018 and complete title of the guidance in the request.

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Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) 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, including bench testing and coating characterizations for 510(k) submissions for peripheral percutaneous transluminal angioplasty (PTA) balloon and specialty catheters (e.g., infusion catheters, PTA balloon catheters for in-stent restenosis (ISR), scoring/cutting balloons). These devices are catheter-based devices intended to treat lesions in the peripheral vasculature. This document provides anatomy-specific testing recommendations and expands on FDA's current thinking for testing of these devices. FDA is issuing this guidance to clarify FDA's premarket submission recommendations for PTA catheters and specialty catheters and to promote consistency across submissions.

For the current edition of the FDA-recognized consensus standards referenced in this document, see the FDA Recognized Consensus Standards database 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 the FDA guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices."[1]

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

This document supplements other FDA documents regarding the specific content requirements of premarket submissions. You should also refer to 21 CFR 807.87 and FDA's guidance, "Format for Traditional and Abbreviated 510(k)s."[2]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Scope

The scope of this document is limited to class II PTA balloon catheters regulated under 21 CFR 870.1250 and class II specialty catheters regulated under 21 CFR 870.1210 and 21 CFR 870.1250 with product codes listed in the table below.

Table 1: Device Types within the Scope of This Guidance.

Regulation Number	Product Code	Device
870.1210	KRA	Continuous Flush Catheter
870.1250	DQY	Percutaneous Catheter
870.1250	LIT	Peripheral Transluminal Angioplasty Catheter
870.1250	PNO	Percutaneous Cutting/Scoring Catheter

In this guidance, PTA balloon catheters refer to standard peripheral angioplasty balloon catheters. Specialty catheters can include but are not limited to the following 510(k) devices: infusion catheters, balloon catheters with unique design characteristics (e.g., cutting/scoring), and balloon catheters intended for specific indications (e.g., ISR, post-dilatation of stents). Class III drug-coated balloons have additional risks and considerations and are not addressed in this guidance document.

III. Premarket Submission Recommendations

A. Device Description

We recommend you identify your device by the applicable regulation number and product code indicated in Section II above and include the information described below.

- **Device components and mode of operation:** FDA recommends that you identify all components and accessories included in the premarket submission, including packaging, with a clear description of how the device is utilized to achieve the intended use in the intended anatomy.

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

- **Photograph and engineering drawing(s) of the device:** FDA recommends that you provide a photograph, as well as an engineering drawing with relevant dimensions, tolerances, and components labeled, of the device. FDA recommends that you include this for each device, accessory, or component included in the premarket submission.

- **Technological characteristics:** FDA recommends that you describe the technical and performance specifications and include a brief description of the device design requirements in the device description section of the premarket submission. The specifications may include performance-related product measurement tolerances, operating limitations, and any other functional, physical, and environmental specifications of the device. We also recommend that you describe ranges and/or accuracy of the specifications.

- **Materials:** FDA recommends that you provide a list of all components, their respective material(s) of composition, and their patient-contacting classification (e.g., non-contacting, indirect-contacting, or direct-contacting). For each component, you should identify the generic material of construction and the unique material identifier (e.g., Chemical Abstract Services (CAS) number).

B. Predicate 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 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 below for an example of how this information may be organized. This table is not intended to represent an exhaustive list of comparative parameters; ensure you provide all relevant device descriptive characteristics as outlined in the "Device Description" section, above.

Table 2: Sample predicate comparison table to outline differences and similarities between the subject and predicate devices.

Description	Subject Device	Predicate Device (Kxxxxxx)
Intended Use		
Indications for Use		
Guidewire Compatibility		
Sheath Compatibility		
Catheter length		
Catheter Shaft Outer Diameter		
Balloon Lengths (if applicable)		
Balloon Diameters (if applicable)		
Nominal Pressure (if applicable)		

Description	Subject Device	Predicate Device (Kxxxxxx)
Rated Burst Pressure (if applicable)		
Component Materials (list individually)		
Coating Material (if applicable)		
Coating Length (if applicable)		
Packaging Configuration		
Sterilization Method		

C. Biocompatibility

Significance: PTA balloon catheters and specialty catheters contain patient-contacting materials, which, when used for their intended purpose (i.e., contact type and duration), 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, manufacturing, and processing methods to any PTA balloon catheters or specialty catheters with a history of safe use, you may reference previous testing experience or the literature, if appropriate. For some device materials, it may be appropriate to provide either a reference to an FDA-recognized consensus standard or 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 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 and potential mitigation strategies as well as identify knowledge gaps that remain. You should then identify any biocompatibility testing or other evaluations that have been conducted to mitigate 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'"[3], which identifies the types of biocompatibility assessments that should be considered and recommendations regarding how to conduct related tests.

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, PTA balloon catheters and specialty catheters 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, either through testing or scientific rationale for why additional testing is not needed:

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

- cytotoxicity;
- sensitization;
- irritation or intracutaneous reactivity;
- acute systemic toxicity;
- material-mediated pyrogenicity;
- hemocompatibility;
    - direct and indirect hemolysis;
    - SC5b-9 complement activation; and
    - thrombogenicity.

Please note that a genotoxicity assessment may be requested if PTA balloon catheters or specialty catheters contain novel patient-contacting materials that have not been previously evaluated for use in contact with circulating blood in legally marketed medical devices.

For biocompatibility testing, we recommend that your subject device test article be the final finished device, including exposure to all manufacturing processes, such as packaging and sterilization. If differences exist between the final subject device and the biocompatibility test article, additional information describing all differences and why they do not impact leveragability of the testing should be provided for each relevant biocompatibility endpoint as identified above. FDA recommends including only and all applicable patient contacting components in the test articles.

If an animal study is being conducted in order to evaluate the safety and/or performance of your device, you can consider evaluating your device for thrombogenicity in this study in lieu of a separate thrombogenicity study (e.g., the 4-hour non-anticoagulated venous implant (NAVI) model described in ISO 10993-4 *Biological evaluation of medical devices – Part 4: Selection of tests for interactions with blood*). If assessing thrombogenicity in a large animal study, you should consider incorporating relevant thrombogenicity-related attributes into your study design (e.g., clinically relevant anticoagulation regimen and activated clotting time (ACT), worst-case device dwell time, providing high-resolution images of the device post-removal from the animal to assess for thrombus, and downstream thromboembolism assessment). In addition, a dynamic *in vitro* flow loop or material-mediated thrombogenicity approach with surface assessment (e.g., SEM or optical imaging with a 40X magnification) may be appropriate for some device types/designs based on device geometry, materials, patient blood contact duration, and anticoagulation status. To determine the thrombogenicity test strategy for your specific device, FDA recommends discussing your approach with the Agency using the Q-Submission Program prior to test initiation. 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."[4]

D. Sterility

Significance: PTA balloon catheters and specialty catheters come in contact with blood and should be adequately sterilized to minimize infections and related complications.

Recommendation: For PTA balloon catheters and specialty catheters labeled as sterile, we recommend that you provide information for the finished device in accordance with the FDA guidance, "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile."[5]

E. Pyrogenicity

Significance: Pyrogenicity testing is used to assess the risk of febrile reaction due to gram-negative bacterial endotoxins and/or 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, PTA balloon catheters and specialty catheters should meet pyrogen limit specifications by following the recommendations outlined in the FDA's guidance, "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile"[6] (510(k) Sterility Guidance). You should also follow the recommendations in "Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers."[7]

To address the risks associated with material-mediated endotoxins, you should follow the recommendations in 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'." [8]

Devices in contact with the cardiovascular system should meet pyrogen limit specifications discussed in the 510(k) Sterility Guidance and should be labeled non-pyrogenic. For devices intended to be labeled as "non-pyrogenic," we recommend that both bacterial endotoxin and material-mediated pyrogens be addressed.

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

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

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

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

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

F. 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 the device performance to ensure adequate functionality.

Recommendation: With respect to package integrity for maintaining device sterility for PTA balloon catheters and specialty catheters, you should provide a description of the packaging, including how it will maintain the device's sterility, a description of the package integrity test methods, and a summary of the package integrity test data, including the test, acceptance criteria, results, and any deviations noted. The following conditioning and testing should be conducted:

Simulated Shipping and Climatic Conditioning: The full packaging configuration should be subjected to simulated shipping (per ASTM D4169*: Standard Practice for Performance Testing of Shipping Containers and Systems*) and climatic conditioning (per ASTM D4332*: Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing*) prior to packaging testing.

Aging: With respect to evaluating the effects of aging on device performance or functionality, shelf-life studies should evaluate the critical physical and mechanical properties of the device that are required to ensure it will perform adequately and consistently during the entire proposed shelf life. To evaluate device functionality after aging, we recommend that you assess each of the bench tests described in Section III.G and repeat all tests that evaluate design components or characteristics that may be affected by aging. A rationale should be provided for changes in the methods used for the aged testing as compared to the methods used for the baseline testing (e.g., smaller sample size, different device sizes assessed, omitted testing).

For PTA balloon catheters and specialty catheters that are provided sterile and/or have a proposed expiration date, 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 subject to accelerated aging for shelf life testing, we recommend that you specify the way in which the devices were aged. We recommend that you age your devices as per the currently FDA-recognized version of ASTM F1980: *Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices* and specify the environmental parameters (i.e., test temperature, humidity, cycle, ambient temperature) established to attain the expiration date. For devices or components 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 device's design history file in accordance with the provisions of 21 CFR 820.30 (i.e., the test reports do not need to be submitted to FDA).

Packaging Testing: We recommend that you assess the packaging integrity and strength of both the materials and seal of the sterile barrier. The integrity of the packaging materials can be assessed using test methods such as the bubble leak test (per ASTM F2096*: Standard Test Method for Detecting Gross Leaks in Packaging by Internal Pressurization (Bubble Test)*) and/or burst testing (per ASTM F2054/F2054M*: Standard Test Method for Burst Testing of Flexible Package Seals Using Internal Air Pressurization Within Restraining Plates*). The integrity of the

seals can also be assessed using numerous test methods, including a visual assessment (per ASTM F1886/F1886M*: Standard Test Method for Determining Integrity of Seals for Flexible Packaging by Visual Inspection*), the bubble leak test (per ASTM F2096*: Standard Test Method for Detecting Gross Leaks in Packaging by Internal Pressurization (Bubble Test)*), and/or the dye penetration test (per ASTM F1929*: Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration*). A seal strength assessment (per ASTM F88/F88M*: Standard Test Method for Seal Strength of Flexible Barrier Materials*) should also be conducted at baseline and after aging (accelerated with real-time confirmatory testing) in order to ensure that the seals will not be compromised due to any force exerted on the seal.

G. Non-Clinical Performance Testing

(1) Standard Performance Testing for PTA and Specialty Catheters

Non-clinical performance testing is recommended for PTA and specialty catheters in order to fully characterize the device and also ensure that the devices can perform as intended under clinically-relevant conditions. The testing recommended below should be conducted on the finished product that was subjected to all manufacturing processes, including sterilization. Otherwise, a discussion of the differences between the test article and finished product should be discussed and justified.

For information on recommended content and format of test reports for the testing described in this section, refer to FDA's guidance, "Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions."[9] As noted in this document, FDA recommends that you provide a scientific or statistical justification for the sample sizes used for each test.

Please note that the recommendations provided in ISO 10555-1: *Intravascular Catheters – Sterile and Single-Use Intravascular Catheters – Part 1: General Requirements* and ISO 10555-4: *Sterile and Single-Use Intravascular Catheters – Part 4: Balloon Dilatation Catheters* are directly applicable to PTA catheters and many specialty catheters. Therefore, the testing and methods recommended in these standards should be followed, or a rationale for deviating from these methods should be provided. However, these standards may not include all testing recommended by FDA or may not be specific enough regarding the methods or criteria for recommended testing. Therefore, the recommendations described below, which augment these consensus standards, should also be followed.

Before conducting the testing described below, FDA recommends that you precondition catheters by tracking through a tortuous path fixture (as described in Section III.G(1)b below). This is recommended for all testing, as clinically-relevant tracking, using physiological conditions, may impact testing outcomes. If preconditioning is not performed prior to a certain test, a scientific rationale should be provided indicating why the attribute would not be affected by this conditioning.

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

a. Dimensional Verification

Significance: Accurate device dimensions help the physician to select the proper product and accessory device sizes. They may also affect the operator's ability to track the catheter to and across lesions.

Recommendation: We recommend that you provide dimensional specifications and tolerances as well as data to verify that these specifications are met for your device as manufactured. At a minimum, we recommend that you measure and report catheter effective length, shaft inner and outer diameter, and crossing profile. For balloon catheters, the balloon outer diameter and length should also be characterized, as described in ISO 10555-4.

The crossing profile, typically defined as the maximum diameter found between the proximal end of the balloon (if applicable) and the distal tip of the catheter, should be quantitatively measured. This can include the proximal balloon bond and, in some cases, other parts of the catheter for unique devices where the maximum outer diameter may not be related to a balloon. The measurement should address potential differences in crossing profile that may exist in the circumferential direction. For these situations, we recommend that you evaluate the crossing profile of your catheter along different longitudinal paths (e.g., rotating the test sample 90° for measurements). We recommend that you report the crossing profile in either the instructions for use, the outside package labeling, or both. Various methods can be utilized, such as contact and non-contact methods, as deemed appropriate. If pass/fail testing is employed, (e.g., "go/no go" gauges), a rationale should be provided to support the methods and the sizes of these aids, along with details regarding the methods.

The quantitative crossing profile data should be used to support the labeled introducer sheath compatibility. Since the size of commercially-available introducer sheaths vary, pass/fail introducer sheath compatibility testing alone is not sufficient to support a labeled sheath compatibility. If you are labeling your device with an introducer sheath compatibility that is smaller than your measured crossing profile, a scientific rationale should be provided.

Shaft inner diameter measurement, or pass/fail guidewire compatibility testing, should be provided to support the labeled guide wire compatibility.

b. Simulated Use

Significance: The recommended instructions for use and techniques for preparation, insertion, tracking, deployment (if applicable), retraction, and removal, if properly followed, should safely and reliably deliver the catheter to the intended location without adversely affecting the device.

Recommendation: We recommend that you conduct testing to demonstrate that the catheter can be safely and reliably prepared, inserted, tracked, deployed (if applicable), retracted, and removed using the recommended techniques, accessory devices, and instructions for use, without damage to the device. We recommend that this simulated use testing be performed by tracking the device through an *in vitro* fixture that mimics typical *in vivo* physiologic conditions and appropriately challenging anatomic characteristics (e.g., a tortuous path in a 37 ?C aqueous

environment) to the length that would enter a patient in clinical use. The fluid used in the simulated use model should closely mimic the properties of human blood (e.g., water, saline) and should not include components to reduce frictional forces (e.g., lubricants, soap). The clinical basis and rationale for the model used should be provided. In general, FDA recommends a three-dimensional model, including a clinically-relevant access site (e.g., appropriately challenging entry angle and entry path curves), with a sufficient number of curves. The length, diameters, number of curves, and radii of curvatures should be sufficient to appropriately challenge the device to simulate clinical use in anatomy for which the device is intended. An engineering drawing, with relevant dimensions labeled (e.g., lengths, diameters, angles), and images of the model should be provided.

We recommend that you conduct testing with accessory devices that would be used in a typical clinical procedure (e.g., introducer, guidewire) using worst-case sizes (e.g., smallest inner-diameter introducer sheath per labeled compatibility). You should report any abnormality or difficulty observed during the simulated procedure as well as any damage observed to the catheter or any of the accessory devices.

For PTA catheters, it may be informative to measure and report the diameter and axial location of the largest deflated balloon profile, including the inner member or wire. This information may assist in determining the extreme dimensions of compatible accessory devices (i.e., minimum internal diameter). Determining the insertion/retraction forces may also be informative as this may assist in supporting the specifications used for device tensile testing.

It may be possible to combine the simulated use testing with coating integrity testing (see Section III.G(1)l) and/or particulate evaluation (see Section III.G(1)m), but you should take care to ensure that only minimal additional handling of the sample is required for the coating integrity evaluation such that particulates are neither lost nor generated.

c. Balloon Rated Burst Pressure

Significance: The rated burst pressure (RBP) is the pressure at which 99.9% of balloons can survive with 95% confidence. Failure of a balloon to maintain integrity at the RBP could result in device failure or vessel damage.

Recommendation: We recommend that you follow ISO 10555-4, Annex A, when conducting this testing. In addition to what is described in this standard, the following should be taken into consideration.

We recommend that you conduct testing on the longest length of every balloon diameter and the shortest length of both the smallest diameter and largest diameter. **Table 3** illustrates the recommended test matrix.

Table 3: Balloon Sizes Recommended for RBP Testing (Example).

Balloon Diameter (mm)	Balloon Length (mm)				
	40	60	80	100	120
4.0	X				X
4.5					X
5.0					X
5.5					X
6.0	X				X

We recommend that you test balloons that are not constrained by any test fixture, such as tubing, and that you inflate the balloons, at a rate similar to clinical use, until failure. We recommend that you record as test failures any loss of:

- integrity of the balloon, such as a rupture or leak; or
- pressure due to failure of the balloon, shaft, or seals.

We recommend that you record the pressure at which the device failed and the failure mode (e.g., longitudinal tear, circumferential tear, pinhole). A discussion and rationale should be provided for the failure mode observed. We also recommend that you calculate RBP as the pressure at which 99.9% of the balloons will survive with 95% confidence based on statistical analysis of the test data. The lower tolerance limit determined from this analysis should be reported and be used to support the RBP specified in the device labeling.

d. Balloon Fatigue (Repeat Balloon Inflations)

Significance: Balloons on PTA catheters are often inflated multiple times during clinical use. Failure of the balloon to withstand multiple inflations could lead to device failure or vessel damage.

Recommendation: We recommend that you follow ISO 10555-4, Annex B, when conducting this testing, unless otherwise specified below. In addition to what is described in this standard, the following should be taken into consideration.

We recommend that you determine the repeatability, to 10 inflations, of successful balloon inflation to the RBP. We recommend that you test device sizes according to the "four corners" paradigm:

- largest diameter/longest length;
- largest diameter/shortest length;
- smallest diameter/longest length; and
- smallest diameter/shortest length.

Table 4 illustrates the recommended test matrix.

Table 4: Example of "Four Corners" Test Matrix.

Balloon Diameter (mm)	Balloon Length (mm)				
	40	60	80	100	120
4.0	X				X
4.5					
5.0					
5.5					
6.0	X				X

We recommend that you test balloons that are not constrained by any test fixture, such as tubing, and that you inflate the balloons incrementally until they reach the RBP. For each sample, we recommend that you hold the RBP for a typical clinical inflation time (e.g., 30 seconds), or the time specified in the instructions for use, deflate the balloon, and inflate it again to the RBP, for a total of 10 cycles. We recommend that you report loss of pressure, whether due to failure of the balloon, shaft, or proximal or distal seals, as a test failure. We recommend that you record all failure modes and that your results demonstrate that 90% of the balloons will survive the test with at least 95% confidence.

e. Balloon Compliance (Diameter vs. Pressure)

Significance: The diameter of a deployed PTA balloon varies with inflation pressure. A compliance chart in the labeling that relates balloon diameter to balloon pressure guides proper selection of catheter size to fit the target vasculature site. Incorrect selection of catheter size may lead to device failure or vessel damage.

Recommendation: We recommend that you follow ISO 10555-4, Annex D, when conducting this testing. In addition to what is described in this standard, the following should be taken into consideration.

We recommend that you test balloon sizes, as illustrated previously in **Table 3**, and that you test multiple product lots. We recommend that you include data showing inflation pressure versus balloon diameter over the full range of recommended inflation diameters and report the results in either the instructions for use, the outside package labeling, or both. A graphical or tabular presentation (i.e., a compliance chart) should be included in the labeling. We recommend that you identify the nominal inflation pressure and RBP. The compliance chart can include pressures up to (but not exceeding) 25% above the RBP, if you provide data and statistics demonstrating that 99% of the balloons will not fail at the listed pressure with 95% confidence. We also recommend that you describe if and how you performed any data rounding and show all instances, if applicable. Compliance charts should not be normalized (i.e., modified in any way in order to ensure that the nominal diameter is exactly achieved at the labeled nominal pressure) or calculated based on limited testing. **Table 5** shows an example of compliance chart for a balloon with 4.0 mm to 6.0 mm diameters, with a nominal pressure of 9 atm and varying RBPs.

Table 5: Balloon Compliance Chart Example.

Pressure (atm)	Balloon Nominal Diameter (mm) (X = balloon diameter at the given pressure)				
	4.0	**4.5**	**5.0**	**5.5**	**6.0**
9.0*	X	X	X	X	X
10.0	X	X	X	X	X
11.0	X	X	X	X	X
12.0	X	X	X	X	X
13.0	X	X	X	X	X
14.0	X	X	X	X**	X**
15.0	X	X	X**	X	X
16.0	X**	X**	X	X	X

*Nominal; **RBP

f. Balloon Inflation and Deflation Time

Significance: Balloons occlude the target vessel and obstruct blood flow while inflated. Inflation and deflation times affect occlusion time. Excessively slow inflation or deflation of a balloon could lead to prolonged lack of blood flow and damage to downstream tissues. Both inflation and deflation time are pertinent to evaluate, as both of these attributes may affect device performance and may result in prolonged lack of blood flow and damage to downstream tissues.

Recommendation: We recommend that you follow ISO 10555-4, Annex C, for deflation time testing. In addition to what is described in this standard, the following should be taken into consideration when conducting balloon inflation and deflation time testing.

We recommend that you demonstrate, using techniques recommended in your instruction manual, that the balloon inflates and deflates within acceptable times and provide the clinical basis for your acceptance criteria. We recommend that you test the largest diameter at the longest balloon length and evaluate which other sizes may warrant testing based on your risk analysis.

g. Catheter Bond Strength

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

Recommendation: We recommend that you test the bond strength at all locations where adhesives, thermal fusion, or other joining methods are used for bonding components of the catheter. Multiple bonds/joints that are located in close proximity should be tested separately, if possible. We recommend that the testing demonstrate that all joints/bonds can withstand tensile forces greater than those that may be experienced during clinical use. As such, we also recommend that you provide the clinical basis (e.g., literature, retraction forces) for your bond strength acceptance criteria. As discussed above, insertion and retraction force assessments during simulated use testing may also be used to support your bond strength acceptance criteria. Comparative testing involving a legally marketed predicate device that has a history of safe use

is also appropriate. Please note that the values identified in ISO 10555-1: *Intravascular Catheters – Sterile and Single-Use Intravascular Catheters – Part 1: General Requirements* alone should not be used to rationalize your acceptance criteria, as the clinical relevance of these criteria have not been established for peripheral interventional applications. The test method/protocol for this testing should clearly describe the methods utilized, including the portions of the device that were fixed into each clamp and the pull rate.

h. Tip Pull Test

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

Recommendation: For devices with one or more joints in the distal tip (e.g., spring or nose-cone tips), we recommend evaluating the tensile force that will separate the distal tip from the catheter. We recommend that the testing demonstrate that the joints/bonds can withstand tensile forces greater than those that may be experienced during clinical use.

Please note that this testing should be conducted on all tips that are joined or bonded to the catheter by any means, regardless of tip length. If the tip is not long enough to be gripped for tensile testing, modifications to the test methods (e.g., longer tip joined by same method for the test article, alternate or modified grip) should be employed. Tips that are not separate components (e.g., extension of inner tubing) do not need to be tested as they are not bonded.

i. Flexibility and Kink Test

Significance: Catheters may be subjected to tight angulations in tortuous vasculature during use. Inability to withstand flexural forces that are typical of clinical use could lead to device failure or vessel damage.

Recommendation: We recommend that you conduct testing which demonstrates that the catheter will not kink at a bend radius that is appropriate for the intended anatomy. For example, we recommend that you consider wrapping the catheter around a series of mandrels with successively smaller radii until the catheter kinks, the lumen collapses, or the device shows no kinking at a radius smaller than what could be considered appropriately challenging for the intended anatomy. This testing should be conducted along the full length, or representative portions, of the catheter without the use of a guidewire as this would indicate a worst-case scenario (or a rationale should be provided if a guidewire is used). We also recommend you provide the clinical basis for your acceptance criterion. This could include literature or testing demonstrating the proposed criterion is appropriate in representative angulations for the intended anatomy. Assessment of the kink resistance of your device during simulated use alone is not considered an appropriately challenging assessment as it does not challenge the device to failure. This should be considered supporting information.

j. Torque Strength

Significance: Catheters may be subjected to torsional forces during use. Even non-fixed wire catheters could be subject to torsional forces if the tip is inadvertently caught on a stent, calcified

lesion, etc. Inability to withstand torsional forces that are typical of clinical use could lead to device failure or vessel damage.

Recommendation: We recommend that you assess the ability of the catheter to withstand torsional forces when the distal tip is not free to rotate by rotating the proximal end of the catheter until failure. We also recommend that you test the torque strength of the catheter in the simulated-use fixture by tracking through the fixture and then clamping the distal end and rotating the proximal end. We recommend that you report the number of rotations to failure and the failure mode for each sample tested. Alternatively, it may be possible to test the device to a specific number of turns (i.e., not to failure) if the pre-determined acceptance criterion is established as appropriately challenging compared to clinical use.

k. Radiopacity

Significance: Insufficient radiopacity may impede safe and reliable delivery of the balloon to the intended location as it will not be clearly visible during use.

Recommendation: We recommend that you demonstrate that the radiopaque markers/materials on the balloon catheter can be seen under typical fluoroscopic methods. We recommend that you provide a qualitative or quantitative measure of radiopacity, wherein the balloon catheter is visible using real-time and plain film x-ray. It is acceptable to provide images from animal studies, *in vitro* phantoms, or equivalent models in order to support the visibility/radiopacity of your device. If these data are leveraged from animal or bench testing, please provide a reference in the submission to where the images can be located. The methods described in ASTM F640: *Standard Test Methods for Determining Radiopacity for Medical Use* are generally considered acceptable.

l. Coating Integrity

Significance: Coatings are intended to improve the performance of the device. Delamination or degradation of a coating may lessen its benefit or otherwise negatively impact its clinical performance and patient safety (e.g., causing embolization downstream).

Recommendation: Coating integrity testing should be conducted if your device has any coating along the length of the catheter and/or on the balloon portion of the device. We recommend that you address the aspects described below for any coatings applied to the surfaces of your product.

Coating Description

We recommend that you describe the clinical purpose and intended function of the coating, such as enhanced radiopacity, thromboresistance, or lubricity. We also recommend that you describe the physical structure of the coating, such as coating thickness, and indicate its chemical identification.

Test Samples

You should conduct testing on the finished product that was subjected to all manufacturing processes, including sterilization. Otherwise, discussion of, and justification for, the differences

between the test article and finished product should be provided. You should provide a scientific or statistical justification for the sample size for each test. We recommend that you implement a sampling plan to examine multiple lots of product (≥3) to assess both inter- and intra-lot variability. Because coating integrity may be impacted by balloon size, you should perform testing on the extremes (i.e., "four corners") and an appropriate intermediate size for the entire product matrix proposed, as depicted in **Table 6**.

Table 6: Example of "Four Corners Plus Intermediate" Test Matrix.

Balloon Diameter (mm)	Balloon Length (mm)				
	40	60	80	100	120
4.0	X				X
4.5					
5.0			X		
5.5					
6.0	X				X

It may be possible to combine coating integrity testing and particulate evaluation (Section III.G(1)m) with simulated use testing (Section III.G(1)b), but you should take care to ensure that only minimal additional handling of the sample is required for the coating integrity evaluation such that particulates are neither lost nor generated.

Interpretation of Data

Coating integrity is considered a characterization test. While acceptance criteria do not need to be included in the premarket submission, descriptions of visualization criteria for the assessment (e.g., no voids, no cracks) should be provided. Furthermore, you should provide an interpretation of the analysis.

Test reports should include a detailed discussion of the morphology of the coated surfaces. If numerous defects are observed, quantifying defects using microscopy may be helpful. This may include counting the number of total defects per unit area or measuring the total representative defect area. You should support your discussion with representative color images, including any areas with observed defects, at a sufficient magnification to characterize the defects. Multiple magnifications may be warranted to visualize and adequately characterize the product. If the coating is difficult to visualize (e.g., clear hydrophilic coating), measures should be taken in order to ensure proper visualization (e.g., dyeing). The discussion of acceptable coating integrity should include a justification that the number, size, and/or total area of defects observed will not impact clinical performance or safety. Side-by-side testing with a predicate device may be helpful to support substantial equivalence for 510(k) devices.

We recommend that you address the aspects described below for any coatings applied to the surfaces of your product.

Baseline Coating Integrity

We recommend that you conduct a visual assessment of the coating integrity on all appropriate surfaces of the final catheter to establish a baseline for comparison to coating characteristics after testing performed after simulated use. If the coating is present on the balloon surface, unfolding or partially inflating the device may be necessary to characterize coating at different locations. We recommend that you appropriately quantify characteristics such as continuity and voids in the coating, as described above.

Simulated Use Coating Integrity

We recommend that you evaluate the coating integrity via visual assessment after simulated use. Catheters should be tracked through an aqueous, tortuous path fixture (as described in Section III.G(1)b) and then expanded in the aqueous medium to the maximum labeled diameter described in the instructions for use prior to visual inspection.

We recommend you test coating integrity under appropriately challenging conditions of use. For example, for balloons intended for ISR or post-deployment stent expansion, we recommend that you evaluate the coating integrity after tracking the device through a tortuous path fixture and inflating to the largest labeled diameter within a stent which has been deployed in the mock vessel.

Functional Testing

We recommend you demonstrate that the coating can achieve its intended function. For example, if a coating is intended to provide lubricity to the catheter, it may be helpful to demonstrate that the frictional forces are decreased or at least equivalent to similar products with similar coatings. For this type of assessment, we recommend that you characterize the drag force of the coating (e.g., pinch test, force characterization during simulated use) after the samples are prepared per the instructions for use.

m. Particulate Evaluation (Coated Devices Only)

Significance: Particulate matter can be generated by the manufacturing process, environment, or from the breakdown of any coating (e.g., hydrophilic coating) on the catheter or from the device packaging. If particles are introduced in the bloodstream during an angioplasty procedure, they may present an embolic risk to the patient. Measurement of the total quantity and size of particulates a device may generate is an indication of embolic risk. Due to lower embolic risks of peripheral devices as compared to other vasculatures, if the coating and substrate are not novel and coating integrity testing has been conducted with acceptable results, a particulate evaluation may not be needed. However, this testing should be conducted if these factors have not been met, or to further support the coating integrity of your device.

Recommendation: We recommend that you measure the total quantity and size of the particulates generated during the simulated use of your device, addressing the aspects described below.

Test Samples

We recommend conducting testing on the finished product that was subjected to all manufacturing processes, including sterilization. Otherwise, discussion of, and justification for, the differences between the test article and finished product should be provided. A scientific or statistical justification for the sample size should be provided. 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 (i.e., "four corners" and intermediate size matrix; see **Table 6**.)

It may be possible to combine the particulate evaluation and simulated use coating integrity testing (Section III.G(1)l) with simulated use testing (Section III.G(1)b), but you should take care to ensure that only minimal additional handling of the sample is required for the coating integrity evaluation such that particulates are neither lost nor generated.

Interpretation of Data

Particulate testing, if warranted, should be conducted as part of your design verification testing and should include acceptance criteria (i.e., not be for characterization only). A rationale for the criteria used as well as a discussion of the results should also be provided. The discussion of acceptable particulate evaluation and limits should include a justification that the number and size of particulates is not expected to impact safety or clinical performance. This may include a reference to any applicable standards, the use of side-by-side testing with a legally marketed device (e.g., predicate device) demonstrating equivalent results, or references to animal testing or other available safety information. Because acceptable number and size of particulates for devices such as catheters have not been standardized, a clinically relevant scientific rationale for the particulate acceptance criteria, which should consider the device indication, the procedure in which the device is used, and the tissues or organs that may be affected, should be provided.

Test Methods

We recommend that you evaluate particulate generated by the entire PTA system, including accessory devices expected to be used during a clinical procedure. Catheters should be tracked through an aqueous, tortuous path fixture (as described in Section III.G(1)b) and then expanded in an aqueous medium to the maximum labeled diameter described in the instructions for use prior to visual inspection. When deployed, the balloon should be in direct contact with the simulated vessel without the use of other coatings, lubricants, sheaths, or protective wraps between the balloon and the simulated vessel. To ensure measurement of the total number of particulates 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. The total number of particulates, including those from the catheter and accessory devices, should be reported in each of three 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 be taken to ensure that the particles are suspended during sampling for particle counting and sizing to minimize artifacts from the test system.

We recommend that you perform particulate evaluation under appropriately challenging conditions of use. For example, for balloons intended for ISR or post-deployment stent expansion, we recommend that you evaluate the quantity and sizes of particulates generated from tracking the device through the tortuous path fixture (as described in Section III.G(1)b) and inflating to the largest labeled diameter within a stent which has been deployed in the mock vessel.

Method Validation

You should describe and validate particle counting and sizing methods. Validation should be conducted using particulate standards of known quantity and size. Particles should be introduced into your model and counting apparatus in a similar manner as the device would be introduced clinically. The percent recovery, or accuracy, should be determined and meet the criteria described above. For a system to be considered validated, ≥90% recovery should be demonstrated for the ≥10µm and ≥25µm size ranges. Please note that recovery rates well above 100% would not be considered valid.

Acceptance Criteria

Particulate testing should include acceptance criteria (i.e., not be for characterization only). Specific criteria should be established, justified, and met. If large amounts of particulates are shed, it may be important to demonstrate comparability to a legally-marketed predicate device used in the same target vasculature or provide evidence of safety through your animal studies (with appropriate downstream assessments). A scientific rationale should be provided to support the particulate acceptance criteria that are used. Note that safety issues related to particulates may go undetected in patients or may be attributed to the disease or other comorbidities and, therefore, a rationale based only on history of safe clinical use of the device, or other similar catheters, is often not sufficient to justify particulate acceptance criteria.

Particulate Chemical Identification

Particulate matter can be generated from numerous sources, including the manufacturing process and/or environment contamination, from the breakdown of any coating on the catheter, or from the device packaging. It is important to establish that a significant number of particulates are not being introduced from other unintended sources, as described above, which may present an embolic risk. Therefore, if a large amount of particulates are shed from your device, it may be pertinent to conduct additional analysis, such as a chemical characterization of the particulates, in order to determine their source. For this testing, FDA recommends that you perform chemical identification of representative particulate populations and report the results in relative amounts (percentages). Chemical characterization of captured particulates for identity can be accomplished through a variety of methods including energy-dispersive x-ray spectroscopy (EDX), Fourier transform infrared (FTIR) spectroscopy, Raman spectroscopy, mass spectroscopy, or diffraction techniques.

Chemical identification of representative particulate material should be performed with justification for the methods used and samples analyzed. The sample should be sufficiently large in order to ensure that the particulates assessed are representative of the particulates that would

be generated during the deployment of the device. The method used should be capable and sufficient for chemical identification. Specific details regarding the capture and analysis (e.g., how the samples were filtered, color images of the filters, how the samples were chosen, details regarding the number of particulates analyzed as compared to the total particulates filtered) of the particulates should be provided. Regarding sizes to be assessed, the four corners testing paradigm may not be needed if adequate justification is provided for why the device sizes used for testing are representative of their entire product matrix (e.g., same materials, manufacturing processes).

There are certain instances when providing additional supporting analyses may allow for reduced (e.g., smaller sample size, fewer particulates analyzed) or omitted chemical identification testing. Supporting analyses could include any or all of the following:

- particulate quantitation studies with the uncoated balloon catheter manufactured in the identical way as the coated device but including potential inclusion of a "dummy" coating process, demonstrating sufficiently low amounts of particulates;
- a discussion regarding the potential interactions of your coating, including all components, with the catheter materials and their potential to introduce some of the catheter extractables/leachables into the particulates;
- representative color images of the particulates captured on the entire filter demonstrating no concerning information (e.g., unexpected appearance);
- a risk assessment regarding potential contaminants and the coating chemical compositions;
- a discussion of the animal studies data indicating no concerning downstream or embolic events; and
- a discussion and references to any historical clinical data indicating no concerning embolic events.

(2) Additional Tests for Catheters Intended for Infusion of Contrast Media or Other Fluids

a. Catheter Body Burst Pressure

Significance: The catheter body should be designed to withstand pressures typically needed to achieve contrast media flow rates used in clinical practice. Inability to withstand pressures that are typical of clinical use could lead to device failure or vessel damage.

Recommendation: We recommend that you follow ISO 10555-1, Annex F, for burst pressure testing. In addition to what is described in this standard, the following should be taken into consideration when conducting balloon inflation and deflation time testing.

We recommend that you determine the maximum pressure that the catheter body can withstand during injection. We recommend you conduct the testing under clinical use conditions (i.e.,

including use of a syringe, automatic injector). The contrast medium or fluid should be representative of worst-case clinical conditions. We also recommend you provide the clinical basis for your acceptance criteria.

b. Infusion Flow Rate

Significance: The catheter should be designed to achieve clinically acceptable contrast media flow rates. Inability to achieve acceptable flow rates could lead to user error and adverse clinical consequences.

Recommendation: We recommend that you follow ISO 10555-1, Annex E, for flowrate testing. In addition to what is described in this standard, the following should be taken into consideration when conducting balloon inflation and deflation time testing.

We recommend that you conduct testing that demonstrates that the catheter is capable of achieving clinically acceptable contrast media flow rates. We recommend that testing be conducted at maximum catheter burst pressures (as identified in Section III.G(2)a) as well as pressures typical of clinical use. We recommend that you report the maximum flow rate in the device labeling. We also recommend you provide the clinical basis for your acceptance criteria.

(3) Additional Tests for Catheters Intended for In-Stent Restenosis (ISR) Use or for Stent Expansion following Stent Deployment

If you label a PTA catheter for ISR use or for stent expansion immediately following stent deployment (for purposes of securing the stent to the vessel wall and ensuring that the stent is completely deployed), we recommend you conduct balloon rated burst pressure and fatigue testing within an expanded stent (see Sections III.G(1)c and III.G(1)d). If the balloon has a coating on it, we also recommend conducting coating integrity and particulates testing in a simulated use model that includes an expanded stent (see Sections III.G(1)l and III.G(1)m).

(4) Additional Tests for Scoring/Cutting Balloons

Scoring and cutting balloons concentrate the dilating forces along the scoring elements or atherotomes. Due to the additional design features, scoring and cutting balloons have additional considerations beyond a standard PTA catheter.

a. Scoring/Cutting Mechanism Securement

Significance: Detachment of the scoring/cutting mechanism(s), such as wire or atherotomes, could result in device failure, vessel damage, and/or embolic risk due to device remnants within the vasculature.

Recommendations: We recommend that you determine the force (e.g., tensile, shear) at which the bonding of the scoring/cutting mechanism fails. We recommend you provide the clinical basis for your test method and acceptance criteria based on the type and level of risk.

b. Scoring/Cutting Performance

Significance: The scoring/cutting mechanism of the device introduces additional risks, such as vascular damage, as compared to a standard PTA catheter. Failure to achieve adequate scoring or cutting could lead to the device not performing as intended.

Recommendations: We recommend that you demonstrate that the device can score a lesion, as intended. Performance of your device should be evaluated in a calcified bench model, animal model with calcified lesions, cadaveric model, and/or clinical study and compared to a legally marketed predicate device. We encourage you to contact the FDA early to discuss the proposed model to evaluate the scoring/cutting performance (see FDA guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program"[10]).

c. Substantially-Equivalent Safety Outcomes (Demonstration of No Added Risks)

Significance: If a scoring/cutting balloon catheter has novel technological characteristics (i.e., scoring/cutting mechanism that is different from the standard scoring wire or cutting atherotomes of the predicate device), additional safety questions may arise, such as added risk of vessel dissection or perforation.

Recommendations: If different technological characteristics as compared to the predicate are used to achieve the intended function, we recommend that you assess whether the safety outcomes (i.e., scoring depth, perforation/dissection rate) of your device are substantially equivalent to those of the identified predicate, using the predicate device as the control in an animal model and/or clinical study.

H. Animal Safety and Performance Testing

Significance: Animal testing is generally recommended to evaluate the *in vivo* safety and performance of some specialty catheters and potentially some PTA balloon catheters, particularly for new designs, significant device modifications, and new indications for use. An example of this is for a scoring balloon with a new cutting mechanism.

Recommendation: Animal testing of PTA balloon catheters and specialty catheters 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 risk.

FDA supports the principles of the "3Rs," to replace, reduce, and/or refine animal 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.

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

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

a regulatory submission (e.g., the study should be performed under Good Laboratory Practice (GLP) regulations as stated in 21 CFR 58 at an animal study facility with appropriate licensure and accreditations).[11] 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."[12]

For devices with notable dissimilarity from legally-marketed PTA devices (e.g., new indications, designs, technology), we recommend that you conduct animal testing to confirm safety of the device and procedure and to evaluate the performance, including functional characteristics, of the PTA or specialty catheter.

For scoring balloons, we strongly recommend animal testing to demonstrate equivalent safety outcomes for all scoring/cutting devices, as compared to their predicate, especially when the technological characteristics differ. We recommend that you evaluate these devices in an appropriate animal model and that you provide a supporting rationale for the chosen animal model in your submission. The predicate device should be used as a control in these studies. We strongly recommend that these studies be conducted in accordance with 21 CFR part 58 or explain why the noncompliance would not impact the validity of the study data provided to support a substantial equivalence determination.

I. Clinical Performance Testing

Clinical evidence is generally unnecessary for most PTA balloon and specialty catheters; however, such testing may be requested in situations such as the following:

- indications for use dissimilar from legally marketed devices of the same type (e.g., treatment of specific diseases or lesion types);
- new technology (i.e., technology different from that used in legally marketed devices of the same type); and
- cases where engineering and/or animal testing raise issues that warrant further evaluation with clinical evidence.

If a clinical study is needed to demonstrate substantial equivalence, i.e., conducted prior to obtaining 510(k) clearance of the device, the study should generally be conducted under the Investigational Device Exemptions (IDE) regulation, 21 CFR 812. Generally, we believe PTA balloon catheters and specialty catheters addressed by this guidance document are significant risk

[11] See also FDA Guidance "General Considerations for Animal Studies Intended to Evaluate Medical Devices" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-considerations-animal-studies-medical-devices).

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

devices subject to all requirements of 21 CFR part 812. Please see the FDA guidance, "Significant Risk and Nonsignificant Risk Medical Device Studies."[13] 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). When data from clinical investigations conducted outside the United States are submitted to FDA for PTA and specialty catheters, the requirements of 21 CFR 812.28 may apply.[14] 21 CFR 812.28 outlines the conditions for FDA acceptance of clinical data from investigations conducted outside the US when submitted to support premarket submissions. For more information, see the FDA guidance, "Acceptance of Clinical Data to Support Medical Device Applications and Submissions: Frequently Asked Questions."[15]

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 a legally-marketed device requires an IDE depends on the particular facts of 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 entitled "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices."[16]

J. Labeling

The regulatory submission must include proposed labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e) for premarket notifications. Labeling for PTA balloon catheters and specialty balloons should include all applicable information, including indications, contraindications, warnings, product information, a summary of the clinical data (if applicable), and directions for use.

As prescription devices, PTA balloon and specialty catheters are exempt from having adequate directions for lay use under section 502(f)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) 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 (e.g., infusion time, inflation duration), and any relevant hazards, contraindications, side effects and precautions (21 CFR 801.109(d)).

K. 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

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

[14] Applies to data from clinical investigations that began on or after February 21, 2019 and are submitted to support a premarket submission, including IDEs, PMAs, and 510(k)s.

[15] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acceptance-clinical-data-support-medical-device-applications-and-submissions-frequently-asked

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

modification in the intended use of the device" requires a new 510(k).[17] The changes or modifications listed below are examples of changes that may require submission of a new 510(k). Note that this list is not exhaustive but provides examples of modifications that are likely to require submission of a new 510(k). For additional details, please see FDA guidance "Deciding When to Submit a 510(k) for a Change to an Existing Device."[18]

Such changes or modifications include:

- Change in device dimensions: FDA considers dimensional changes to be modifications in design. This type of change could significantly affect safety and effectiveness of the device as it may alter the device performance. Thus, if dimensional changes are not within the range that was previously cleared, testing may be needed to support the change. The magnitude and criticality of the modified dimension should be considered when determining if a new 510(k) is needed.

- Change to indirect or direct blood contacting components: FDA considers these changes to be modifications in material, which could significantly affect safety and effectiveness of the device by altering engineering attributes and/or introducing different types or quantities of residual chemicals, which could result in a toxic response. Therefore, a change in the material could impact device performance and biocompatibility, which could impact patient safety.

- Change in sterilization technique: Depending on the type of change, a change in sterilization method can be significant as it could significantly affect safety and effectiveness of the device (e.g., 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/or performance of the device. The potential impact of the sterilization change on material performance and characteristics should be considered when determining the need for a new 510(k).

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[17] Section 3308 of the Food and Drug Omnibus Reform Act of 2022, Title III of Division FF of the Consolidated Appropriations Act, 2023, Pub. L. No. 117-328 ("FDORA"), enacted on December 29, 2022, added section 515C "Predetermined Change Control Plans for Devices" to the FD&C Act (section 515C). Under section 515C, FDA can approve or clear a predetermined change control plan (PCCP) for a device that describes planned changes that may be made to the device and that would otherwise require a supplemental premarket approval application or premarket notification. For example, section 515C provides that a supplemental premarket approval application (section 515C(a)) or a premarket notification (section 515C(b)) is not required for a change to a device if the change is consistent with a PCCP that is approved or cleared by FDA. Section 515C also provides that FDA may require that a PCCP include labeling for safe and effective use of a device as such device changes pursuant to such plan, notification requirements if the device does not function as intended pursuant to such plan, and performance requirements for changes made under the plan. If you are interested in proposing a PCCP in your marketing submission, we encourage you to submit a Pre-Submission to engage in further discussion with CDRH. See FDA's guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

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

Examples of changes or modifications in the indications for use of the device that would likely require a new 510(k) are:

- A change in specific lesion characteristics (e.g., chronic total occlusion, ISR).

- Claims in improvement of outcomes in other technologies (e.g., pre-treatment with scoring balloons improves outcomes of drug-coated balloons).

We believe that the following modifications will likely not require submission of a new 510(k):

- Minor changes in packaging: A minor change in packaging (e.g., replacing hardcopy instructions for use 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 protocol has been previously reviewed and accepted in a prior submission. Additionally, the test results should fall within the acceptance criteria previously found to be acceptable.