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Standard Guide for Coating Characterization of Drug Coated Balloons[1]

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1. Scope

1.1 This guide describes recommended acute in-vitro characterization methods for drug coated balloon (DCB) coatings. These methods include: coating integrity, coating thickness, drug coating uniformity, and released particulates. Specifically, this guide details:

1.1.1 Characterization of integrity by inspection of the coated balloon surface.

1.1.2 Measurement of coating thickness.

1.1.3 Quantitation of drug coating uniformity (uniformity of drug distribution over the balloon surface) longitudinally and circumferentially.

1.1.4 Quantitation of the number of particulates released, in various size ranges, during simulated use testing (insertion, tracking, deployment, retraction, and withdrawal) along with chemical and crystallinity characterization of particulates.

1.2 This document does not address:

1.2.1 Mechanical testing of drug coated balloons (DCBs).

1.2.2 Drug substance evaluation (e.g., assay, related substances, uniformity of dosage units) of DCBs.

1.2.3 Production release and stability testing, although some sections may be applicable in whole or in part.

1.2.4 Standard analytical testing (e.g., drug content, drug related substances, drug uniformity of dosage).

1.3 The values stated in SI units are to be regarded as standard. No other units of measurement are included in this standard.

1.4 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.5 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

F2743 Guide for Coating Inspection and Acute Particulate Characterization of Coated Drug-Eluting Vascular Stent Systems

2.2 *AAMI Standard:*[3]

AAMI TIR 42 Evaluation of Particulates Associated with Vascular Medical Devices

2.3 *USP Standards:*[4]

USP <788> Particulate Matter in Injections

USP <905> Uniformity of Dosage Units

3. Terminology

3.1 *Definitions:*

3.1.1 *tracking, n*—navigation of a guide wire, guide catheter or introducer sheath, and/or balloon system through actual or simulated vascular anatomy.

3.1.2 *vascular model, n*—a model that simulates or replicates the geometry of a clinically relevant, sufficiently challenging anatomical vasculature for the intended anatomy through which the system will be placed. There should be a deployment site within the model or mock vessel attached to the model for balloon deployment.

3.2 *Definitions of Terms Specific to This Standard:*

3.2.1 *acute, n*—the timeframe including accessory and balloon delivery, deployment, and withdrawal.

3.2.2 *background assessment, n*—a test measuring the number/size of particulates within the Particulate test system without accessories or test articles.

3.2.3 *drug coated balloon (DCB), n*—medical device comprised of a drug coating over the surface of vascular dilatation balloon.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] Available from Association for the Advancement of Medical Instrumentation (AAMI), 4301 N. Fairfax Dr., Suite 301, Arlington, VA 22203-1633, http://www.aami.org.

[4] Available from U.S. Pharmacopeial Convention (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.

3.2.4 *drug coating uniformity, n*—a measure of drug distribution over the surface of the balloon intended to be coated. This evaluation is separate from uniformity of dosage units as described in USP<905>.

3.2.5 *expected segment content, n*—the sum of the Measured Content from all segments divided by the number of segments, yielding a calculated expected segment content (typically measured in mass), assuming all segments are the same size.

3.2.6 *longitudinal axis, n*—major axis of the balloon, parallel to the effective length.

3.2.7 *measured content, n*—the amount (typically measured in mass) of the Active Pharmaceutical Ingredient (drug) determined for each DCB test article segment during the coating uniformity assessment.

3.2.8 *mock vessel, n*—simulation of the vasculature that replicates the geometry, mechanical properties, and/or chemical properties at the intended clinical deployment site.

3.2.9 *particulate test system, n*—a combination of the vascular model, containing a deployment site or mock vessel, and an in-line particle counter or collection in a beaker or on a filter with an off-line particle counter, microscope, or other particle-counting means.

3.2.10 *simulated use, n*—a simulation of DCB clinical use in accordance with the instructions for use (IFU), including insertion, tracking, deployment, and withdrawal in a controlled aqueous environment through a vascular model using clinical accessories.

3.2.11 *spike & recovery, n*—an evaluation of particle capture efficiency of the vascular model. Particle standards representative of the sizes being investigated should be evaluated using the same collection and counting technique to be used during testing. Recovery should meet pre-specified levels.

4. Summary of Guide

4.1 *Test Samples*—Drug coating integrity, drug coating thickness, drug coating uniformity and particulate testing should be performed as separate tests with independent samples, unless an adequate rationale is provided explaining why this is not necessary. Additionally, the samples of particulates used for chemical identification and percent crystallinity determination might need to be separate samples.

4.2 *Drug Coating Integrity*—The coating integrity characterization is a qualitative assessment of the DCB drug coating appearance over the surface intended to be coated. Coating integrity visually characterizes coating attributes and coverage anomalies at various magnifications. Representative images of the drug coating (e.g., light microscope, electron microscope, profilometer and/or spectroscope) allow for evaluation of the coating attributes which may not be detectable during other quantitative evaluations or macroscopic inspection.

4.3 *Drug Coating Thickness*—Coating thickness is a quantitative characterization meant to describe the local drug coating thickness at multiple, representative points along the DCB surface. The representative areas should include local attributes, e.g., scoring/cutting features or drug wells, if applicable. Thickness measurements may be obtained by cross-sectioning of the DCB, measuring the thickness, and reporting the range and average thicknesses. Other means of measurement may be used if appropriately justified.

4.4 *Drug Coating Uniformity*—The quantitative characterization of drug coating uniformity is intended to compare actual regional drug content to the expected segment content. The drug content on specified segments along the effective length and around the circumference of the device is analytically determined and reported relative to the expected segment content.

4.5 *Particulate Testing*—Particulate characterization is intended to determine the number of particulates released from the device and accessories in pre-specified size ranges during insertion, tracking, deployment, retraction, and withdrawal through a vascular model. Particulates released might include material from the balloon drug coating, balloon catheter system, other device coatings, accessory devices used during the procedure, and trace environmental contaminants. The chemical identity and probable source of particulate material should be determined by chemical characterization of representative samples of particulates. The scope of the chemical identification is based on multiple considerations that are device-specific. The percent crystallinity of the particulate samples should also be assessed and reported.

4.5.1 *Remaining Drug (optional)*—The amount of drug remaining on the balloon surface after simulated use may be determined analytically.

4.6 When establishing the drug coating integrity, drug coating thickness, drug coating uniformity, and particulate characterization testing conditions, the current clinical usage/practice and the instructions for use should be considered and incorporated.

4.7 Alternative means for evaluating the DCB attributes covered in this guide should be appropriately justified.

4.8 See also ASTM F2743-11 and AAMI TIR 42:2010.

5. Significance and Use

5.1 The methods described herein allow for in-vitro characterization of DCB drug coating attributes that, along with pre-clinical and clinical safety and effectiveness data, establish that the DCBs, with the characterized coating attributes, are safe and effective. Clinical safety and therapeutic benefit may be affected by non-uniform distribution of the active pharmaceutical ingredient, coating anomalies on the device, and particulate release. Variability in drug coating may result in insufficient or excessive drug availability and inconsistent device performance.

5.2 Individual characterization tests may not have direct clinical relevance, although bench-based characterization results can be combined with other data to provide insight to characteristics that influence clinical safety and effectiveness. Bench testing is performed under repeatable and controlled conditions, providing information about drug coating integrity, thickness, uniformity, particulate shedding, particulate identity, and particulate crystallinity.

5.3 Distribution of the drug coating is characterized by coating integrity, thickness, and uniformity. Particulate counts can provide a measure of manufacturing repeatability, and may provide an indication of *in vivo* safety if simulated use particulates and *in vivo* particulates are shown to be similar, or if particulate testing results are correlated to *in vivo* safety. Chemical identity of particulates and crystallinity may further advise the kinetics related to the potential for particulate persistence, dissolution or other characteristics which may relate to *in vivo* safety. Conducting this testing and gathering the data further allows for the potential comparison of devices (e.g., demonstrating equivalence between pre-clinical and clinical devices for these coating attributes).

5.4 The methods described in this guide are for characterization purposes and are not intended for production release testing of drug coated balloon catheters. However, some content may be applicable to generating release data. The general guidelines presented here may be used for product control at various stages of the product development process.

6. Suggested Reagents and Materials

6.1 *Coating Integrity*—Equipment for visual assessment of the DCB drug coating appearance, capable of 25× - 200× magnification. Depending on the coating surface, higher magnification may be needed in order to fully characterize the coating integrity. Instruments such as scanning electron microscopes (SEM), optical (light) microscopes, profilometers, fluorescence microscopes, or Raman spectroscopes can be used if appropriate.

6.2 *Coating Thickness:*

6.2.1 Instruments for cross-sectioning the DCB or the DCB coating (e.g., cryostat, ion mill, scalpel) if applicable.

6.2.2 Means (e.g. material) to keep the coating in place while cutting, if applicable.

6.2.3 System for measuring DCB drug coating thickness orthogonal to the balloon surface (e.g., SEM or optical microscopy with measurement capability or in conjunction with quantitative image analysis software, quantitative micro or nano computed tomography (CT) machine, or profilometer).

6.3 *Drug Coating Uniformity:*

6.3.1 Means for dividing the DCB into circumferential and longitudinal segments. When selecting the instrument and/or means of DCB or DCB drug coating segmentation, consideration should be given to minimizing drug coating loss.

6.3.2 Analytical instrumentation for quantitative determination of drug content per segment.

6.3.3 Equipment for measuring segment size characteristics (e.g., dimensions, surface area, or mass), if applicable.

6.4 *Simulated Use and Particulates:*

6.4.1 Particle-free (0.22µm filtered) water, in general accordance with USP<788>. Other solutions may be used if justified.

6.4.2 Apparatus for facilitating flow and vascular model (see 3.1.2 and 7.7.1).

6.4.3 Heating system, capable of maintaining fluid temperature at 37 ± 2°C.

6.4.4 If applicable, a continuous flow particulate counting system:

6.4.4.1 Pump for controlling fluid flow.

6.4.4.2 Continuous flow particle counter capable of detecting and counting particles in appropriate size ranges (e.g., ≥10µm, ≥25µm).

6.4.5 If applicable, collection vessel.

6.4.6 If applicable, particulate filter with appropriate pore size (e.g., 10µm) to capture pre-specified particulate sizes.

6.4.7 Particulate analyzer or microscope system capable of detecting and counting particles in appropriate size ranges (e.g., ≥10µm, ≥25µm).

6.4.8 Reference standards for particulate sizing and counting.

6.4.9 Accessory devices per Instructions for Use (IFU).

6.4.10 Analytical instrumentation for chemical identification of particulates. See section 7.7.6 for more information.

6.4.11 Analytical instrumentation for crystallinity characterization of particulates. See section 7.7.6 for more information.

6.4.12 Analytical instrumentation for determining the remaining drug content after simulated use (optional).

6.4.13 *Test Articles*—Unless otherwise justified, all samples selected for testing should be representative of final, sterile clinical products. A sufficient number of specimens should be tested to adequately characterize the device. Testing of devices from multiple lots should be considered. If the DCB is offered in multiple sizes, appropriate sizes should be selected to ensure that the DCB size matrix is adequately characterized for the attributes covered in this guide.

7. Test Method Considerations

7.1 *Environment*—Environmental conditions may affect the balloon system and should be considered when assessing DCB characteristics. It is important that all procedures be performed in an environment (e.g., room with filtered air) that does not impact the integrity of the study. Contamination on the balloon surface may be misinterpreted as coating anomalies or may mask actual defects.

7.2 *Handling*—DCBs are to be handled appropriately so that the integrity of the study is not compromised. Poor experimental techniques and handling may be significant sources of artifacts or non-representative results. Excessive manipulation can result in loss of material resulting in changes in drug coating uniformity, local effects to coating integrity, thickness variability, and variation in particulate count.

7.3 *Sterilization*—Unless otherwise justified, all samples selected for testing should be representative of final, sterile clinical products. If characterization test articles are not subject to the number of sterilization cycles to be used for marketed product, a rationale should be provided to support this condition being worst case for all assessments. Additional sterilization cycles should not automatically be considered worst case.

7.4 *Coating Integrity*—Evaluation of coating integrity should be performed over areas representative of the entire coated balloon surface to allow for complete visualization of the coated surface of the device, unless otherwise justified. The device should not be in the folded state, but may be in the

inflated, partially inflated, or non-inflated state with a rationale provided for the configuration evaluated. Simulated physiological conditions (e.g., body temperature, mock vessel) may be used during balloon inflation. If applicable, both regions of high stress/strain and low stress/strain should be evaluated.

7.5 *Coating Thickness*—Measurement of the drug coating thickness should be performed at appropriate locations to adequately determine the thickness of the drug coating over the entire coated balloon surface, with a justification for the number and type of sampled areas. A rationale for the configuration used for measurement (e.g., inflated, partially inflated, or non-inflated state) should be provided. Assessment at or near any specific characteristics or landmarks of the balloon (folds, metallic structures, etc.) should be included. Simulated physiological conditions (e.g., body temperature, mock vessel) may be used during balloon inflation. Thickness values and variation should be explained to support performance based on device design. Regulatory bodies have a preference for thickness determined by direct measurement, but may accept alternative methods with appropriate justification.

7.6 *Drug Coating Uniformity*—Testing may be performed on the inflated, partially-inflated, or non-inflated device, with appropriate justification. The inflation state of the balloon should not impact drug evaluation. The amount of drug measured per balloon segment using analytical techniques (measured amount) should be compared to the expected segment amount, which is the fractional percentage of the total assay based on length, surface area, or mass. The drug per segment may be compared to the average balloon segment drug content. This can be reported in per length, per surface area, per mass, or equivalent units. The size (length, area or mass) of each segment and the number of segments for each balloon tested should be justified. Certain regulatory bodies recommend an acceptance criterion for drug coating uniformity. If needed, scientifically valid rationale describing the established acceptance criteria adopted should be provided. If the device design (e.g., balloon fold) impacts drug uniformity, a rationale for uniformity including these features should be provided. It is up to the manufacturer to determine the validation requirements for any test method with acceptance criteria.

7.7 *Particulate Characterization:*

7.7.1 An appropriate spiking and recovery study should be performed on the test system. Spiking and recovery should be performed in the test system, including the vascular model, mock vessel (if applicable) and particulate collection beaker (if applicable) without the presence of a DCB. Unless otherwise justified, accessories should not be in the test system during spike and recovery testing. The same procedural steps (e.g., flow rate, particle collection method, sample transfer, particulate counting method) used during the spiking and recovery study should be used for subsequent particulate testing.

7.7.2 Particulate standards representative of the sizes to be investigated should be used for spike and recovery studies. The number and size of particulates standards should be certified by the manufacturer or verified with a different method. One or more injections at the location where the DCB would be introduced into the test fixture should be performed because this represents the worst case for particle capture efficiency. Uniform distribution of particles within the standard used for spiking as well as accurate volume for injection are critical to the success of the spiking and recovery study. The amount of particulates recovered during this test should meet a prespecified level prior to test article evaluation. It is recommended that recovered particulates meet ≥90% recovery in the ≥10μm and ≥25μm size ranges. The largest particulate size that is quantified should be based on the size for which the recovery study yields ≥75%. The largest size is suggested to be, at a minimum, ≥50μm.

7.7.3 *Simulated Use Tracking Within Anatomical Model*—Tracking for particulate testing should be through a vascular model that simulates a sufficiently challenging, tortuous anatomical path geometry, including vascular access, through which the balloon catheter will be passed during clinical use. The vascular model should include the portion of the anatomy in which the DCB would be passed through the guide catheter or introducer sheath and the portion through which it would be passed after exit from the guide catheter or introducer sheath, if applicable. The appropriate geometry may be different for different intended deployment sites (e.g., carotid, coronary, or femoral arteries) or for different access points (e.g., femoral or radial arteries). Vascular access angulation should be considered. Critical features for selection of the appropriate vascular model include lumen diameter, bend radii, bend reversals, rigidity, ability to clean, ability to recover particles, and coefficient of friction of the tracking material (e.g., polyurethane, silicone, Teflon, glass, latex, and native vessel). The vascular model may be constructed of glass or other durable materials which minimize background particulate counts.

7.7.4 *Simulated Use Deployment Within Anatomical Model*—Simulated use deployment should be into an appropriately justified vascular model that reasonably represents the intended clinical deployment site. Critical features to be considered for the integral deployment site or mock vessel include geometry (e.g., reference vessel internal diameter (ID), radius of curvature (if applicable), taper (if applicable)), mechanical properties (e.g., radial compliance, flexibility, coefficient of friction), chemical properties (e.g., presence of lubricant, other manufacturing aids, material, interaction with the drug coating). The DCB should be inflated to the rated burst pressure (RBP) within a suitably sized lumen, resulting in complete wall apposition. The inflation duration, within the mock vessel or model (as appropriate), should be in accordance with the IFU. If used, any effect of the mock vessel on particulates (coating adhesion to the mock vessel, particulate release from the mock vessel) will impact the total cumulative count and should be discussed in the report.

7.7.5 *Particulate Collection and Analysis:*

7.7.5.1 *Particulate Collection*—Particulate matter should be captured for later analysis or continuously monitored and analyzed. Unless otherwise justified, particulates released from accessories and the DCB, beginning when the first accessory is introduced into the vascular model and ending when the DCB and accessories are completely withdrawn, should be counted and sized. Since particulates released can be considered a

single bolus, they may be collected and analyzed as a single sample. However, there may be advantages to collecting separate samples at different phases of the test or to continuously monitor particulates. In the event that coating components are water-soluble (e.g., excipient), a constant particulate test time that is no longer than necessary is recommended. The collection method and materials used (e.g., filter effective pore size, diameter, material, solvent compatibility, crystallinity, color, flatness, and roughness) should be appropriate for subsequent imaging and analysis steps.

7.7.5.2 *Sizing and Counting*—The sizing and counting of particulates can be accomplished by light obscuration or by filtration and microscopic analysis. Each method has its advantages and disadvantages. A brief summary of methods is provided in Annex A1. Additional information on particulate sizing and counting may be found in USP<788> and AAMI TIR 42. The user is encouraged to consider all options prior to testing.

7.7.6 *Analytical Methods*—Chemical characterization of captured particulates for identity and crystallinity can be accomplished through a variety of methods including energy-dispersive x-ray spectroscopy (EDX), Fourier transform infrared (FTIR) spectroscopy, Raman spectroscopy, mass spectroscopy, differential scanning calorimetry (DSC), or diffraction techniques. A combination of two or more methods might be needed to fully characterize the crystallinity. Analytical methods are a vast field that continues to evolve. The user is encouraged to evaluate possible methods that support the data required. A brief summary of possible analytical method advantages and disadvantages is provided in Annex A2.

7.7.6.1 *Particulate Chemical Identification*—Chemical identification of representative particulate material >10µm from each of multiple test articles should be performed. A justification for the sample size (number of devices) and sample quantity (percent of total particulates analyzed per device) should be provided. The analysis sample quantity should be sufficiently large in order to ensure that the particulates assessed are representative of all of the >10µm particulates that were released during the simulated use procedure. If necessary to obtain a sufficient sample, particulates smaller than 10µm may be included in the sample. The total particulate sample quantity analyzed, as compared to the total amount of particulates shed during the simulated use procedure, should be reported and justified. The method used should be capable and sufficient for chemical identification of particulates. Ability to identify trace levels of materials may not be necessary if an appropriate scientific rationale is provided for omitted or minimally identified materials. There are certain instances when providing additional supporting analyses along with the particulate chemical identification may allow for reduced testing requirements and support a justification for the thresholds of chemical reporting. Some examples of reduced testing requirements include: evaluating smaller sample sizes (fewer devices), reducing the sample quantity (smaller amount of particulate matter analyzed per device), and omitting the evaluation of certain particulate types. Additional supporting analyses leading to reduced testing requirements could include: particulate quantitation of the uncoated balloon catheter platform, discussions regarding potential interactions of the drug coating components with the balloon catheter components (e.g. materials), representative colored images of the particulates captured on the filter with tabular description of the particulate appearance to help classify and identify particles, performing a risk assessment related to potential contaminants and the coating chemical compositions, and discussions regarding any available animal and/or clinical data related to downstream or embolic events. This approach may not be practical if: the device is made of novel materials, there is a hydrophilic coating present, high amounts of particulates are observed in the quantification studies, there are concerning events in animal/clinical data, etc. Various regulatory agencies may have different recommendations for this analysis and should be consulted prior to commencing testing. Unless otherwise justified, results should be reported as a percentage of total material analyzed.

7.7.6.2 *Particulate Crystalline Characterization*—The percent crystallinity of the particulate samples should be reported. Peaks not associated with the active pharmaceutical ingredient (API) should be reported and discussed or their omission appropriate justified. A justification for the samples analyzed should be provided. If necessary and justified, samples from multiple devices can be combined to conduct this analysis or particles smaller than 10 µm may be included in the analysis.

7.7.7 *Retained Material Content (optional)*—If desired, drug content analysis of the drug coating remaining on the DCB following simulated use may be performed.

8. Suggested Generic Test Methods

8.1 The following sections outline the suggested basic elements for coating integrity, coating thickness, coating uniformity, and simulated use particulate testing.

8.2 For each of the tests, quantitative data and/or representative images should be provided to support results as appropriate.

8.3 *Coating Integrity*—The as-manufactured surface appearance of the DCB coating should be characterized. Qualitatively document the condition of the overall coating using a sufficient number of representative images over the entire coated balloon surface such that an assessment of the complete coating consistency can be made. Coarse visual inspection (25× - 50× magnification) may be performed to inspect surfaces of the coated portion of the balloon; documenting the appearance and location of any coating attributes, anomalies, or artifacts. Attributes or surface anomalies observed under coarse inspection should be further examined under high (100× – 200×) magnification. Higher magnification may be helpful to estimate the size and depth of the attribute using appropriate means (e.g., image analysis software). Coating integrity characterization may be performed by visualization methods adequate to fully depict the surface appearance of the coating. Methods such as scanning electron microscopy (SEM), optical (light) microscopy, profilometry, fluorescence microscopy, or spectroscopy can be used with appropriate resolution.

8.4 *Coating Thickness*—The thickness of the as-manufactured drug coating should be characterized in order to

determine the range of the coating thickness throughout the device. Methods to determine the coating thickness include cross-section imaging with direct measurement or profilometry. Imaging methods such as scanning electron microscopy (SEM), optical (light) microscopy, interferometry, micro/nano computed tomography (CT), or fluorescence microscopy can be utilized as long as the method provides an acceptable resolution and the thickness can be accurately measured. The evaluation method used should be justified. Test articles may be embedded (e.g., with resin) before cross-sectioning, so as to avoid compromising the coating during the sectioning process. The number and location of measurements, both around the circumference and along the effective length of the balloon, should be recorded. A sufficient number of sections should be analyzed to fully characterize the coating. Coating integrity and coating uniformity results may be used to support the number of sections analyzed for coating thickness. Measurements every 10mm - 40mm are generally suggested, depending on length and distribution of coating. A minimum of two points around the circumference per cross-section should be made, preferably opposite one another. If the coating is irregular due to the manufacturing process, such as pooling of coating material at certain spots, and/or the design of the device (e.g., scoring or other specialty balloons) additional measurements should be made at or near these features.

8.5 *Drug Coating Uniformity*—Drug coated balloons should be characterized for drug coating uniformity along the effective length (longitudinal uniformity) and around the circumference (circumferential uniformity) of the balloon. Longitudinal uniformity and circumferential uniformity should be performed as separate tests with independent samples unless an adequate rationale is provided explaining why this is not necessary. The recommended method for balloon uniformity assessment is to cut the drug coated portion of the DCB into segments followed by a drug assay of each segment. Any appropriate method for segmentation can be utilized with description and justification.

8.5.1 Drug Coating Longitudinal Uniformity compares the amount of drug on balloon segments to the average amount of drug per segment. The balloon is to be divided along the effective length, making cuts orthogonal to the longitudinal axis. Segment lengths of 10mm - 30mm are generally suggested, depending on the balloon length, with a recommended minimum of three segments, or appropriate rationale. The number and length of segments per balloon length should be supported by an appropriate rationale. Content results can be normalized to a justified measured segment characteristic (e.g., length, surface area, mass).

8.5.2 Drug Coating Circumferential Uniformity compares the amount of drug on balloon segments to the average amount of drug per segment. The balloon is to be divided around the circumference, cut along the length. The number of segments should be supported by an appropriate rationale, with a suggested minimum of two segments to be analyzed. Content results can be normalized to a justified measured segment characteristic (e.g., length, surface area, mass).

8.6 *Particulate Characterization:*

8.6.1 *Vascular Model and Mock Vessel (if applicable) Background Assessment*—Perform test in an environment that does not contribute any significant amount of additional particulate matter. The particulate test system must be cleaned to the extent that any level of extraneous particles added has a negligible effect on the outcome of the test. Use cleaning procedures and test environment considerations in general accordance with appropriate sections of USP <788>. Analyze test fluid (e.g., particle-free water) passed through the cleaned test system to verify that the test system is sufficiently clean to allow an accurate assessment of particulates shed from the DCB and accessories. Unless otherwise justified, the flushing flowrate and volume used for the background assessment should be the same as that used for the spike and recovery validation and the particulation test. Background data should be recorded. It is up to the user to reduce background particulates since they will affect the reported total cumulative counts if their subtraction is not appropriately justified.

8.6.2 *Simulated Use Deployment:*

8.6.2.1 Prepare the DCB and accessories in accordance with IFU.

8.6.2.2 *Tracking*—Track the accessories and DCB through the appropriate water-filled, vascular model, in accordance with IFU. If applicable, repeat the procedure using the number of steps appropriate for the clinical indication and/or IFU. Use accessory devices as appropriate. Unless otherwise justified, the entire portion of the DCB that is intended to enter the body should be tracked through the vascular model in an aqueous environment that is thermally controlled at 37 ± 2°C.

8.6.2.3 *Deployment*—Deploy the DCB in accordance with the IFU. Unless otherwise justified, inflate to the rated burst pressure within a suitably sized lumen resulting in good wall apposition for the recommended time, and then completely deflate the DCB. Unless otherwise justified, if multiple inflations of the DCB are permitted in the IFU, repeat the inflation and deflation for the maximum number of times permitted in the IFU. Completely withdraw the DCB per IFU and/or clinical practice.

8.6.2.4 *Rinse/Flush*—Unless otherwise justified, remove the accessories per the IFU and/or clinical practice from the mock vessel, if applicable, and vascular model. Flush the vascular model and mock vessel, if applicable, with enough particle-free water to capture released particles, as was done in the spike and recovery testing. The flow rate and volume used should be identical to those used in the spike and recovery testing. Since all particulates released during the simulated use evaluation can be considered as a single bolus, it may be collected and analyzed as a single sample. There may be advantages to collecting separate samples at different phases (e.g., after insertion of accessories, after tracking but before inflation of the DCB, after each inflation of DCB).

8.6.2.5 *Particulate Accumulation*—If necessary, transfer the collection beaker contents to the container used for particulate analysis. If transfer is necessary, the particulate sample should be stirred or otherwise agitated to maintain a uniform suspension of particulates prior to transfer and during analysis in accordance with the spiking and recovery testing. Continuous particulate counting is one means to eliminate the need to transfer the sample for particulate analysis.