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Standard Guide for Coating Characterization of Drug-Coated Balloons¹

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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 Recom-*

mendations 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.

² For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at www.astm.org/contact. 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>.

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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 nonuniform 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.

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× to 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 (0.22 µm 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., ≥10 µm, ≥25 µm).

6.4.5 If applicable, collection vessel.

6.4.6 If applicable, particulate filter with appropriate pore size (e.g., 10 µm) 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., ≥10 µm, ≥25 µm).

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 7.7.6 for more information.

6.4.11 Analytical instrumentation for crystallinity characterization of particulates. See 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, blood flow) by

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 pre-specified level prior to test article evaluation. It is recommended that recovered particulates meet $\geq 90\%$ recovery in the $\geq 10\ \mu\text{m}$ and $\geq 25\ \mu\text{m}$ size ranges. The largest particulate size that is quantified should be based on the size for which the recovery study yields $\geq 75\%$. The largest size is suggested to be, at a minimum, $\geq 50\ \mu\text{m}$.

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); and 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 counting