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

Draft – Not for Implementation

Characterization of Metallic Coatings and/or Calcium Phosphate Coatings on Orthopedic Devices

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on January 23, 2024

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments 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 listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact OHT6: Office of Orthopedics/DHT6A: Division of Joint Arthroplasty Devices at 301-796-5650.

When final, this document will supersede 510(k) Information Needed for Hydroxyapatite Coated Orthopedic Implants, dated March 10, 1995 (revised February 20, 1997); and Guidance for Industry on the Testing of Metallic Plasma Sprayed Coatings on Orthopedic Implants to Support Reconsideration of Postmarket Surveillance Requirements dated February 2, 2000.



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

GRZAN DRAFT

Preface

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 use the document number GUI00020051 and complete title of the guidance in the request.

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Characterization of Metallic Coatings and/or Calcium Phosphate Coatings on Orthopedic Devices

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent 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 draft guidance document provides recommendations for premarket submissions for orthopedic devices that contain metallic coatings and/or calcium phosphate coatings on the surface. The recommendations reflect current review practices and are intended to promote consistency and facilitate efficient review of these submissions. In this document, the terms "you" and "your" refer to members of industry, sometimes referred to as sponsors, submitters, or applicants; and the terms "we," "us," and "our" refer to FDA.

For the current edition of the FDA-recognized standards referenced in this document, see the FDA Recognized Consensus Standards Database.[1] 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."[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

[1] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

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

use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Scope

The recommendations in this document are applicable to class II and class III devices that contain metallic and/or calcium phosphate coatings, intended for orthopedic applications. Specifically, this guidance addresses the characterization of the following coatings on orthopedic devices:

1. a metallic coating, which can be manufactured using thermal spray (e.g., plasma spray), sintering (e.g., sintering of powders, beads, or fiber mesh pad), chemical vapor deposition/infiltration, physical vapor deposition (e.g., ionic plasma deposition), additive manufacturing[3] (e.g., electron beam manufacturing, selective laser sintering) or other methods;[4]

2. a calcium phosphate coating, which can be manufactured by plasma spray, solution precipitation, electrochemical deposition or other methods[4]; and

3. a metallic and calcium phosphate dual coating, which can be manufactured using one or more of the above methods.

Other types of coatings (e.g., other calcium-based coatings, other ceramic coatings) or surface modifications (e.g., surface etching, surface anodizing) are not within the scope of this guidance document. For a coating containing a drug or a biologic, this guidance does not discuss drug or biologic characterization recommendations.

This guidance does not address device-specific functional testing, such as system component fatigue testing. For additional information on device-specific performance testing, refer to the recommendations in any applicable device-specific guidance document, if available, or contact the appropriate review division.

Some of the recommendations in this guidance may assist in complying with some of the special controls for devices within the scope of this guidance. For information regarding special controls, refer to the appropriate classification regulation and the following special controls documents, as applicable:

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[3] Please refer to FDA's guidance document entitled "Technical Considerations for Additive Manufactured Medical Devices," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-additive-manufactured-medical-devices for additional information on this topic.

[4] See ISO 17327-1 *Non-active surgical implants — Implant coating — Part 1: General requirements*.

- Class II Special Controls Guidance Document: Knee Joint Patellofemorotibial and Femorotibial Metal/Polymer Porous-Coated Uncemented Prostheses; Guidance for Industry and FDA[5]
- Class II Special Controls Guidance: Shoulder Joint Metal/Polymer/Metal Nonconstrained or Semi-Constrained Porous-Coated Uncemented Prosthesis - Guidance for Industry and FDA Staff[6]
- Class II Special Controls Guidance Document: Hip Joint Metal/Polymer Constrained Cemented or Uncemented Prosthesis[7]

Where consensus standards are included in a special control for devices within the scope of this guidance, FDA believes conformance to the currently FDA-recognized version of the standard would provide the same level of or improved protection of the public health and safety as conformance to other versions of these standards included in a special control, and that conformance to the currently FDA-recognized standard would meet any such consensus standards included in a special control. Therefore, firms may choose to submit a declaration of conformity to the currently FDA-recognized standard.[8]

III. Premarket Submission Recommendations

A. Coating Description

We recommend that you provide the following information in your submission to describe a metallic and/or calcium phosphate coating on orthopedic devices.

1. Name of the coating including the coating type (e.g., titanium coating, hydroxyapatite coating, titanium/hydroxyapatite dual coating). If a coating is applied by a third party (i.e., a coating vendor), you can reference the third party's master file (MAF) for specific information regarding the coating. In your premarket submission, you should include a letter of authorization (LOA) from the MAF holder, which specifies the location of the information relevant to your submission within the master file. The LOA allows the Agency to reference information included within the MAF and to discuss concerns applicable to your submission with the MAF holder. For additional information on master files, see FDA's website on Master Files.[9]

2. Coating method including a description of the process, and pre- and post-processing.

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[5] https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/knee-joint-patellofemorotibial-and-femorotibial-metalpolymer-porous-coated-uncemented-prostheses

[6] https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/shoulder-joint-metalpolymermetal-nonconstrained-or-semi-constrained-porous-coated-uncemented

[7] https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/hip-joint-metalpolymer-constrained-cemented-or-uncemented-prosthesis-class-ii-special-controls

[8] See section 514(c) of the Federal Food, Drug and Cosmetic Act (FD&C Act).

[9] https://www.fda.gov/medical-devices/premarket-approval-pma/master-files

3. Starting materials (e.g., a description of the materials and their chemical compositions) used for both the coating and the substrate and any standards to which they conform; note that the starting materials are not necessarily the same as the materials of the final coating (e.g., calcium and phosphate salts are generally used as the starting materials for a solution precipitated calcium phosphate coating).

4. Physical structure of the coating including number of layers with different physical or chemical properties, thickness of the coating and each layer, and whether the coating is a porous coating (see **Section F.(2).b** below for a description of "porous coating" as specified in certain device classification regulations); including interconnecting porosity, volume porosity percentage, and pore size.

5. Location of the coating and its coverage of the device (e.g., provide device engineering drawings showing the location of the coating and the total coverage area).

B. Sterility

Significance: Metallic and/or calcium phosphate coated orthopedic devices are implanted devices and should be adequately sterilized to minimize infections and related complications.

Recommendation: We recommend that manufacturers sterilize all coated orthopedic devices as it is unclear how processing (cleaning and sterilization) by the end user may affect the integrity of a coating (e.g., if the cleaning and sterilization method by the end user will affect the chemical properties of the coating), or if a porous coating can be adequately cleaned. Therefore, if you are intending to provide a coated device non-sterile, a rationale based on testing data or scientific literature should be provided to justify that the proposed reprocessing instructions will not affect the integrity of the coating and/or the cleanliness of the device. For recommendations regarding the development and validation of reprocessing instructions in your proposed device labeling, refer to the guidance "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling."[10]

For metallic and/or calcium phosphate coated orthopedic devices labeled as sterile, we recommend that you provide information outlined below:

1. For the sterilization method[11]:
   a. a comprehensive description of the sterilization method/process;
   b. a description of the sterilization chamber if not rigid and fixed (e.g., flexible bag);
   c. the sterilization site;
   d. in the case of radiation sterilization, the radiation dose;

[10] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reprocessing-medical-devices-health-care-settings-validation-methods-and-labeling

[11] Please refer to FDA's recognized standards database FDA Recognized Consensus Standards Database, available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm for applicable consensus standards depending on the type of sterilization method chosen for your device.

e. for chemical sterilants (e.g., ethylene oxide (EO), H_2O_2), the maximum levels of sterilant residuals that remain on the device, and an explanation of why those levels are acceptable for the device type and the expected duration of patient contact.

   In the case of EO sterilization, CDRH has accepted EO residuals information based on the currently recognized version of the standard, "ISO 10993-7 *Biological Evaluation of Medical Devices — Part 7: Ethylene Oxide Sterilization Residuals*."

2. For the sterilization method used, a description of the method used to validate the sterilization cycle (e.g., the half-cycle method), as well as the sterilization validation data.[12] A premarket submission should also identify all relevant consensus standards used and identify any aspects of the standards that were not met. In the absence of a recognized consensus standard, a comprehensive description of the sterilization process and the complete validation protocol should be submitted for review.

3. You should state the sterility assurance level (SAL) of 10^{-6} for devices labeled as sterile.

We recommend that all calcium phosphate coated devices be sterilized using gamma radiation based on a long history of clinical use of orthopedic devices with such coatings that have been sterilized using this method and non-clinical data demonstrating that gamma radiation does not negatively impact the coating properties. If any other sterilization method is used, supporting data or scientific rationale should be provided to demonstrate that the sterilization method will not affect the properties of calcium phosphate coatings (e.g., phase composition and chemical structure) and the resulting clinical outcomes.

C. Pyrogenicity

Significance: Pyrogenicity testing is used to help protect patients from 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, metallic and/or calcium phosphate coated orthopedic devices should meet applicable pyrogen limit specifications.[13] You should also follow the recommendations in FDA's guidance

[12] Submission of validation protocols and data is only recommended for certain premarket submission types and sterilization methods. For additional information regarding submission recommendations for sterility information in 510(k), please see "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-and-review-sterility-information-premarket-notification-510k-submissions-devices-labeled

[13] For devices subject to 510(k) requirements, please also see "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-and-review-sterility-information-premarket-notification-510k-submissions-devices-labeled

"Pyrogen and Endotoxins Testing: Questions and Answers."[14] To address the risks associated with material-mediated pyrogens, you should follow the recommendations in FDA's guidance "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.'"[15]

For devices intended to be labeled as "non-pyrogenic," we recommend that both bacterial endotoxins and material-mediated pyrogens be addressed.

D. Shelf Life and Packaging

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

Recommendation: With respect to package integrity for maintaining device sterility, you should provide a description of the packaging, including how it will maintain the device's sterility, and a description of the package integrity test methods. Depending on submission type, you should also provide the protocol(s) used for your package integrity testing, the results of the testing, and the conclusions drawn from your results. We recommend that a package validation study include simulated distribution and associated package integrity testing, as well as an aging process (accelerated and/or real-time) and associated seal strength testing, to validate package integrity and shelf-life claims. We recommend you follow the methods described in the FDA-recognized series of consensus standards ISO 11607-1 *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging* and ISO 11607-2 *Packaging for terminally sterilized medical devices — Part 2: Validation requirements for forming, sealing and assembly processes.*

With respect to evaluating the effects of aging on performance or functionality of a metallic and/or calcium phosphate coated device, shelf-life studies should evaluate the critical physical, chemical and mechanical properties of the metallic and/or calcium phosphate coating to ensure the coated device will perform adequately and consistently during the entire proposed shelf life. To evaluate coating performance, we recommend that you assess each of the bench tests described in **Section F.(2).** for metallic coatings and **Section F.(3).** for calcium phosphate coatings and repeat all tests that evaluate critical coating characteristics that are potentially affected by aging using aged devices.

We recommend that you provide the protocol(s) used for your shelf-life testing, results, and the conclusions drawn from your results. If you use coated devices or specific test samples (coupons) subject to accelerated aging for shelf-life testing, we recommend that you specify the way in which the devices or coupons were aged and provide a rationale to explain how

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

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

the results of shelf-life testing based on accelerated aging are representative of the results if the device were aged in real time. We recommend that you age your devices 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 established to attain the expiration date. For resorbable calcium phosphate coatings, you should conduct testing on real-time aged samples to confirm the results of the accelerated aging study. This testing should be conducted in parallel with submission review, with results documented to file in the design history file (i.e., complete test reports do not need to be submitted to FDA).

E. Biocompatibility

Significance: Both the metallic coatings and calcium phosphate coatings on orthopedic devices are patient-contacting, 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, including both the device substrate as well as the coating. If your coating is identical in composition and processing methods to a coating on a legally marketed device with a history of successful use, you can reference previous testing experience or literature, if appropriate. For some device materials, it may be appropriate to provide a reference to either a recognized consensus standard, or to a LOA for a device MAF.

If you are unable to identify a legally marketed device with similar location/duration of contact and intended use that uses the same coating (i.e., materials and manufacturing process) as used on your device, we recommend you conduct and provide a biocompatibility evaluation as recommended in FDA's guidance "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.'"[16] The evaluation should explain the relationship between the identified biocompatibility risks, the information available to mitigate the identified risks, and any knowledge gaps that remain. You should then identify any biocompatibility testing or other evaluations that were conducted to mitigate any remaining risks. We recommend that you consider the recommendations in this guidance, 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, orthopedic implants are considered implant devices in contact with tissue/bone for a long-term contact duration. Therefore, the following endpoints should be addressed in your biocompatibility evaluation:

[16] 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;
- subchronic toxicity (sub-acute toxicity);
- genotoxicity;
- implantation;
- chronic toxicity; and
- carcinogenicity.

We recommend consideration of the following for metallic and/or calcium phosphate coatings:

- Your biocompatibility assessment should consider not only the starting materials used for the coating and the device, but also the subsequent processing of the materials, the manufacturing methods (including coating process and pre- and post-coating processes), cleaning, and sterilization steps, and any residuals from manufacturing aids used during the process to ensure the biocompatibility assessment reflects the final sterilized device.

- Differences in formulation, processing, sterilization, device surface properties (e.g., a coating containing "nano" characteristics) compared to legally marketed devices that could affect biocompatibility of the final device may warrant additional biocompatibility testing.

- For new formulations of degradable or resorbable calcium phosphate coatings, in addition to the testing described above, we recommend you address the biocompatibility of the coating over the life of the device and discuss the starting, intermediate, and final degradation products present over the course of degradation.

F. Non-Clinical Bench Testing

(1) General Recommendations

This section identifies general recommendations to consider when conducting non-clinical tests to characterize coatings. **Section F.(2)** and **Section F.(3)** below list recommended non-clinical tests for evaluating the integrity of metallic coatings and calcium phosphate coatings, respectively. Inadequate coating integrity could cause device failure and clinical complications such as poor fixation.

For information on the 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."[17]

Unless a coupon is described in the consensus standard used, we recommend that you use final sterilized devices from multiple lots for testing and characterization. Alternatively, a rationale should be provided to justify that the test sample is equivalent to the final device in terms of manufacturing process including variability between lots, geometry (e.g., radius of curvature), cleaning and sterilization. Also, whenever applicable, you should include a description of the test sample, such as the test sample is a coating with substrate, a coating peeled off from a substrate, or powder that has been pulverized from a coating. A minimum sample size has been recommended for each test below unless it is specified in the associated material/testing consensus standards. Unexpected test results (e.g., a large variability in results) or device design may suggest a larger sample size should be utilized.

The specifications (a range of values to be achieved) for a specific coating property, if applicable, must meet the established acceptance criteria from required special controls, if any, and should follow any other applicable recommendations arising out of guidance documents, or consensus standards, or be supported by clinical justifications. The range of the specifications defined for each coating property should be assessed and justified both individually and as an aggregate with the other properties to demonstrate that the worst-case scenario is acceptable. For example, a coating with a thickness (or porosity or pore size) at the highest end of the specifications should demonstrate acceptable mechanical properties. The test results should be expressed quantitatively including average, standard deviation, and range whenever applicable. You should provide a discussion of the conclusions drawn from your test results.

If you believe some of the recommended tests described below are not applicable to your coating, or if you are using an alternative testing standard/method, you should describe your approach (e.g., providing a scientific rationale to explain the tests that you have conducted and decided not to conduct).

Note that the tests specified in **Section F.(2)** and **Section F.(3)** are not all inclusive. Thus, it is important to ensure that unique attributes specific to your coating or your device are adequately evaluated. Also note that some orthopedic devices have device-specific recommendations for certain coating properties and/or testing methods, and some devices are subject to special controls. Refer to FDA's website regarding Guidance Documents (Medical Devices and Radiation-Emitting Products)[18] for additional guidance documents or class II special controls documents[19] that may pertain to your device type.

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

[18] https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/guidance-documents-medical-devices-and-radiation-emitting-products

[19] https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/class-ii-special-controls-documents

For feedback regarding your specific coating, we recommend submitting a Pre-Submission to obtain Agency feedback. For further information regarding the Q-Submission Program, refer to the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[20]

(2) Testing of Metallic Coatings

This section lists recommended bench tests for characterizing metallic coatings. Three types of metallic coatings with significant clinical experience may be sufficiently evaluated with a subset of these tests (see **Section F.(2).d** below).

a. Coating Chemical Analysis

Significance: Chemical composition of a metallic coating affects the stability and the patient's biological response to the coated device.

Recommendation: We recommend providing a chemical composition analysis of the metallic coating on the final device with a minimum sample size of three. The test results should be expressed quantitatively and compared to specifications identified in relevant consensus standards (e.g., for plasma-sprayed coatings derived from unalloyed titanium and TiAl6V4 powders, see ISO 13179-1 *Implants for surgery — Coating on metallic surgical implants — Part 1: Plasma-sprayed coatings derived from titanium and titanium-6 aluminum-4 vanadium alloy powders*).

b. Coating Microstructural Characterization

Significance: The microstructure of a metallic coating affects the implant fixation since the coating directly interfaces the bone/tissue. These tests provide elementary quantifications of the microstructural characteristics of the coating on the device. For a porous-coated device, the characteristics of the porous coating are indicators of the ability of the coating to allow for biological fixation.

Recommendation: You should specify in your premarket submission if you intend to label your device as porous coated for biological fixation. Per 21 CFR 888.3358(a) and 21 CFR 888.3670(a), the porous coating of a hip joint metal/polymer/metal semi-constrained porous-coated uncemented prosthesis and a shoulder joint metal/polymer/metal nonconstrained or semi-constrained porous-coated uncemented prosthesis "has a volume porosity between 30 and 70 percent, an average pore size between 100 and 1,000 microns, interconnecting porosity, and a porous coating thickness between 500 and 1,500 microns." Such devices are designed "to achieve biological fixation to bone without the use of bone cement" (21 CFR 888.3358(a) and 21 CFR 888.3670(a)). While the description is included in the aforementioned regulations only, FDA recommends that other orthopedic device types that include porous coatings for biological fixation that are discussed in this guidance generally have those characteristics as well.

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

Regardless of whether the device is labeled for biological fixation, we recommend providing the following microstructural evaluation of the coating on the final device with a minimum sample size of three.

1) Surface and cross-sectional photomicrographs of the coating should be provided to show all microstructural features of the coating such as physically or chemically distinct layers, interconnecting porosity, and coating-substrate interface. The magnification should be identified on each image.

2) Thickness, average pore size, and overall porosity of the coating and/or each layer should be reported.

- We recommend using ASTM F1854 *Standard test method for stereological evaluation of porous coatings on medical implants* to evaluate the mean coating thickness, average pore size (mean void intercept length), and porosity (volume percent void) of the coating and each distinct layer, if applicable.
- For some device types (e.g., knee femoral and tibial components; anatomic shoulder glenoid components), the Tissue Interface Gradients method per ASTM F1854-15 sections on Tissue Interface Gradients and Tissue Interface Gradient Method should be used to evaluate the porous coating. In this case, the volume percent void and the mean void intercept length should be evaluated in three 200-µm-thick zones below the tissue interface. The results should demonstrate that the mean void content and intercept length in all three zones generally align with the porous coating description in 21 CFR 888.3358(a) and 21 CFR 888.3670(a).
- For some devices, coatings with a higher volume porosity (i.e., > 70%), larger average pore size (>1000 µm) or greater thickness (i.e., > 1500 µm) than those described in 21 CFR 888.3358 and 21 CFR 888.3670 may be desired. These coatings may have low rigidity; therefore, we recommend additional mechanical testing pertaining to their application, e.g., a test on plastic deformation of porosity (see **Section F.(2).c**, below*)*.

c. Coating Mechanical Testing

Significance: Mechanical properties of a metallic coating impact the integrity (e.g., coating delamination, spallation, abrasion) of the coated device. These tests evaluate the mechanical strength and abrasion resistance of a metallic coating due to the implantation of the device during surgery or micromotion/fatigue loading of the implant over time.

Recommendation: All mechanical tests should be performed with a minimum sample size of six, using the worst-case sample, which is usually the thickest coating to be marketed.

The following should be evaluated for any metallic coating:

1) Static tensile strength per ASTM F1147 *Standard test method for tension testing of calcium phosphate and metallic coatings.* The static tensile strength should exceed 22 MPa (per ISO 13179-1).

2) Shear fatigue strength per ASTM F1160 *Standard test method for shear and bending fatigue testing of calcium phosphate and metallic medical and composite calcium phosphate/metallic coatings.* Results from shear fatigue testing to 10^7 fatigue cycles should be provided with the inclusion of the photomicrographs of the test samples before and after each test. The coating should withstand at least 10^7 cycles with a shear fatigue maximum stress of at least 10 MPa without any failure (per ISO 13179-1).

3) Taber abrasion resistance test per ASTM F1978 *Standard test method for measuring abrasion resistance of metallic thermal spray coatings by using the Taber Abraser.* Results should include the cumulative mass loss for each specimen and the mean cumulative mass loss and standard deviations for 2, 5, 10, and 100 cycles. The coatings should lose less than a total of 65 mg (by weight) when abraded for 100 cycles (per ISO 13179-1).

The following test should be conducted for metallic coatings with low rigidity (which may include, but is not limited to, a coating with a higher volume porosity (i.e., > 70%), larger average pore size (i.e., >1,000 μm) or greater thickness (i.e., > 1,500 μm)). See **Section F.(2).b**, above.

Test for plastic deformation of the coating porosity. We recommend reporting the amount of plastic deformation of the porosity with a minimum sample size of six. The device should be loaded by a flat surface under the worst case loading anticipated to occur during and after implantation. The test method and test sample used should be defined and appropriately justified given the device type. Test results including an evaluation of post-testing pore structure of the coating should be provided and justified.

d. Testing recommendations for three specific types of metallic coatings

Three types of metallic coatings with a long history of clinical use, specifically:

a) beaded, sintered cobalt-chrome coatings on a cobalt-chrome substrate,
b) beaded, vacuum-sintered titanium coatings on a titanium substrate, and
c) vacuum-sintered titanium fiber mesh pads on a titanium substrate,

may be sufficiently evaluated with the descriptive information and testing outlined in items 1-3) below:

1) Identify the materials used for both the metallic coating and the substrate and any consensus standards to which they conform.

2) Evaluate the static shear strength of the coating to the substrate per ASTM F1044 *Standard test method for shear testing of calcium phosphate coatings and metallic coatings*.

3) Provide the average bead size and number of bead layers for beaded coatings; and evaluate average pore size, overall pore volume, and thickness of the coating per ASTM F1854.

   i. If you intend to label the device as porous coated for biological fixation, the coating characteristics generally should align with the porous coating description referenced in **Section F.(2).b**.

   ii. The Tissue Interface Gradients method per ASTM F1854-15 sections on Tissue Interface Gradients and Tissue Interface Gradient Method should be used for certain orthopedic devices (see **Section F.(2).b**, above).

(3) Testing of Calcium Phosphate Coatings

This section lists recommended bench tests for characterizing a calcium phosphate coating.

a. Coating Physicochemical Analysis

Significance: The physicochemical properties of a calcium phosphate coating affect the stability, dissolution and resorption *in vivo*, and other biological response of the coated device. These tests evaluate if the calcium phosphate coating has appropriate physicochemical properties to ensure the safe use of the coated device in the human body.

Recommendation: For any plasma-sprayed calcium phosphate (also known as hydroxyapatite or HA) coating, we recommend providing the following physicochemical properties with a minimum sample size of three (see "**Additional Information"** at the end of this section for the recommended physicochemical analysis for other types of calcium phosphate coatings). Unless there are other types of control samples for a specific test, we recommend a control sample, e.g., National Institute of Standards & Technology (NIST) Standard Reference Material (SRM) 2910B[21] or a historical control be tested as a comparison for the analyses.

We recommend that the starting material for plasma-sprayed HA coatings be HA powder that conforms to one of the following two consensus standards in terms of trace elements, phase composition /crystallinity, and Ca/P ratio:

- ASTM F1185 *Standard specification for composition of hydroxylapatite for surgical implants* or

[21] https://shop.nist.gov/ccrz__ProductDetails?sku=2910b&cclcl=en_US

- ISO 13779-6 *Implants for surgery — Hydroxyapatite — Part 6: Powders.*

List of recommended physicochemical analyses:

1) Elemental analysis including calcium and phosphorous, intentional additions, and manufacturing impurities per ASTM F1609 *Standard specification for calcium phosphate coatings for implantable materials* or ISO 13779-2 *Implants for surgery — Hydroxyapatite — Part 2: Thermally sprayed coatings of hydroxyapatite*.

2) Phase analysis per X-ray diffraction – X-ray diffraction patterns with crystallographic interpretations, including the identification and quantitative analysis of each crystalline phase (i.e., HA, α-tricalcium phosphate or α-TCP, β-tricalcium phosphate or β-TCP, tetracalcium phosphate or TTCP, calcium oxide or CaO) and amorphous calcium phosphate (ACP), as well as crystallinity ratio. The X-ray diffraction determination and phase analysis should be performed with a copper radiation and scanned from 4° to 60° and utilize one of the following two standards. The worst-case coating for this test, which is usually the thinnest coating, as a thinner coating generally contains more amorphous phase compared to a thicker coating, should be used.

   - ASTM F2024 *Standard practice for X-ray diffraction determination of phase content of plasma-sprayed hydroxyapatite coatings.*

   - ISO 13779-3 *Implants for surgery — Hydroxyapatite — Part 3: Chemical analysis and characterization of crystallinity ratio and phase purity.*

   If the phase composition determined per each standard is out of the specified range in that standard, supporting data or scientific rationales should be provided to justify that the coating is acceptable for the intended clinical use.

3) Ca/P ratio analysis using one of the following two methods:

   - X-ray method per ISO 13779-3: If the calculated Ca/P ratio is outside the range established in ISO 13779-2 Third Edition 2018-12 Clause 5.2 “Calcium to phosphorus ratio (Ca:P)” (i.e., 1.61 to 1.76), supporting data or a scientific rationale should be provided to justify the Ca/P ratio, or

   - A general wet chemistry method such as inductively coupled plasma mass spectroscopy (ICP-MS) or inductively coupled plasma atomic or optical emission spectroscopy (ICP-AES or ICP-OES).

4) Structural analysis per infrared analysis – Infrared spectra with detailed molecular interpretations, including band assignments for all phosphate (HPO_4^{2-}, PO_4^{3-}) and hydroxyl (OH^-) bands, crystallinity, structural water, and carbonate. The infrared

spectra allow us to understand the chemical structure of the coating, which cannot be obtained from X-ray diffraction.

5) Dissolution rate measured at 37°C in both pH 7.4 and pH 5.5 buffered solutions per ASTM F1926/F1926M *Standard test method for dissolution testing of calcium phosphate granules, fabricated forms, and coatings*. The pH changes of the solution during measurement should be recorded. In addition, we recommend the following:

    a. Ratio of initial material mass (mg) to total dissolution media volume (mL): ASTM F1926/F1926M-14 (Clause 6 "Analytical Parameters") recommends a ratio of 1 to 4 mg/ml, which is a wide range; a justification should be provided for the ratio used in your test.

Additional Considerations: If you are using a coating method other than plasma spray, or if the phase composition of your coating is different from that of a typical plasma-sprayed calcium phosphate coating, for example, your coating is intended to contain one or more other crystalline phases (e.g., dicalcium phosphate dihydrate (DCPD or Brushite), octacalcium phosphate (OCP) with or without amorphous phase, the phase composition(s) of the coating should be determined against the corresponding crystalline phase(s), respectively. If the calcium phosphate phases formed in the coating are novel, animal or clinical data may be requested to ensure safe clinical use (see **Sections G and H**, below).

b. Coating Microstructural Characterization

Significance: The microstructure of a calcium phosphate coating affects implant fixation as the coating directly interfaces the bone/tissue. These tests provide elementary quantifications of the microstructural characteristics of the coating on the device.

Recommendation: We recommend providing the following microstructural evaluation of a calcium phosphate coating on the final device with a minimum sample size of three.

1. Surface and cross-sectional photomicrographs of the coating should be provided to demonstrate all microstructural features of the coating such as physically or chemically distinct layers, interconnecting porosity, and coating-substrate interface. The magnification bar should be identified on each image.

2. Thickness, average pore size, and overall porosity of the coating and each layer should be provided.

    You may use ASTM F1854 to determine the thickness, average pore size, and porosity of the coating and each distinct layer or an alternative standard/method.

If you intend to label the calcium phosphate coating as a "nano" coating (e.g., nano-crystalline, nano-structured), you should provide additional microstructural characterization to demonstrate the "nano" characteristics (e.g., nano crystal size or other nano features) and

address concerns related to the biocompatibility of the "nano" characteristics (see **Section E. Biocompatibility***)*.

c. Coating Mechanical Testing

Significance: Mechanical properties of a calcium phosphate coating impact the integrity (e.g., coating delamination, spallation, abrasion) of the coated device itself. These tests evaluate the mechanical strength of a metallic coating following the implantation of the device during surgery or micromotion/fatigue loading of the implant over time.

Recommendation: All tests should be performed with a minimum sample size of six using the worst-case sample, which is usually the thickest coating to be marketed.

1. Static tensile strength per ASTM F1147 or ISO 13779-4: *Implants for surgery — Hydroxyapatite — Part 4: Determination of coating adhesion strength,* (see ISO 13779-2 Third Edition 2018-12 Clause 5.7 "Coating strength" for acceptance criteria, i.e., the mean tensile coating adhesion strength should not be less than 15 MPa and no individual result should be less than 10 MPa.*)*.

2. Static shear strength per ASTM F1044.

3. Fatigue strength per ASTM F1160. Results from shear fatigue testing for 10^7 cycles should be provided with inclusion of the photomicrographs of the test samples before and after each test.

(4) Testing of Metallic and Calcium Phosphate Dual Coatings

For a metallic and calcium phosphate dual coating, we recommend that you provide the following information:

1) a description of any additional processing between the two coating processes in addition to the coating description recommended in **Section A** for both metallic coatings and calcium phosphate coatings;

2) testing of the metallic coating per the recommendations in **Section F.(2);**

3) physicochemical properties of the calcium phosphate coating per the recommendations in **Section F.(3).a**; and

4) microstructural characterization and mechanical testing of the dual coating per the recommendations in **Section F.(2).b and F.(2).c**. The underlying metallic coating can be porous (intended for biological fixation) or nonporous (intended for surface roughening and enhanced bonding between calcium phosphate coating and substrate). If the underlying metallic coating is porous and you intend to label the dual-coated device for biological fixation, you should characterize the dual coating to determine if

the dual coating generally aligns with the previously discussed description of "porous coating."[22]

(5) Coated Substrate/Device Testing

Significance: Some coating processes may affect the physical, chemical (e.g., changes in dimension, color, and chemical structure/ stability) or fatigue properties of the coated device. This may include but not be limited to i) when a coating is significantly thicker than coatings of the same type on legally marketed devices; ii) when a coating process is novel; or iii) when an implant material (e.g., polymer) or implant geometry (e.g., very thin) could be impacted by the coating process. These tests evaluate the effect of the coating process on performance of the coated device in these situations.

Recommendation: We recommend conducting the following tests:

1) Comparative Physical and Chemical Testing of the Coated Substrate – Examination and testing of the substrate before and after coating with a minimum sample size of three to demonstrate that the coating process will not lead to physical or chemical changes (e.g., changes in dimension, color, chemical structure/stability) of the coated substrate.

2) Comparative Fatigue Testing of the Coated Substrate – This can be evaluated using the bending fatigue testing recommendations outlined in ASTM F1160 or a similar method to assess the substrate material (i.e., axial, bending, or rotating beam test with a minimum sample size of six). Both the non-coated (i.e., substrate only) and the coated specimens should be tested to quantify any effect that the coating has on the substrate.

   Alternatively, the effect of the coating process on the fatigue property of the coated device can be assessed using a fatigue test method specific to the final device if such a method exists. You should examine and describe the coating integrity and/or failure mode after the test in the test report. If failure of the device is associated with the coating, rationales or a benefit-risk analysis should be provided to justify the addition of the coating on the device.

   For some applications (e.g., spinal devices), when performing a device-specific fatigue test, you should characterize the wear particulates generated from the metal coated device per ASTM F1877 *Standard Practice for Characterization of Particles*. Please refer to any applicable device-specific guidance documents and special controls for your device.

[22] See 21 CFR 888.3358 and 21 CFR 888.3670.

G. Non-Clinical Animal Studies

Significance: Due to limitations of bench models, animal studies are often conducted to support medical device premarket submissions for novel metallic and/or calcium phosphate coatings. The *in vivo* setting generally provides an initial assessment of how a medical device interacts with biological systems, including physiological, pathological, and toxicological effects of the device, and how the biological system may affect the device.

Recommendation: Animal testing is generally unnecessary for most metallic and calcium phosphate coated devices; however, such testing may be appropriate in situations such as novel technology (e.g., novel materials, compositions and/or phases in a calcium phosphate coating) that cannot be evaluated through bench tests or in a clinical study. The study design and endpoints should be based upon the intended use of the device and mitigation of risk.

FDA supports the principles of the "3Rs," to replace, reduce, and/or refine animal testing when feasible. We encourage sponsors to consult with us if they wish to use a non-animal testing method that they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal study.

We encourage manufacturers to take advantage of the Q-Submission Program to ensure that the animal study protocol addresses safety concerns and contains elements that are appropriate for a regulatory submission. Additionally, for information and recommendations regarding animal studies used to support medical device submissions, refer to the guidance "General Considerations for Animal Studies Intended to Evaluate Medical Devices."[23] If you are proposing to use a non-animal testing method in lieu of an animal study, 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, refer to the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[24]

H. Clinical Performance Testing

Clinical studies are generally unnecessary for metallic and calcium phosphate coated orthopedic devices; however, such testing may be appropriate in situations such as the following:

- Use of novel technology (e.g., materials, compositions and/or phases in a calcium phosphate coating) different from that used in legally marketed devices of the same type; and/or
- Cases where bench and/or animal testing raise issues that warrant further evaluation with clinical studies (e.g., devices with concerning mechanical properties compared

[23] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-considerations-animal-studies-medical-devices

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

to legally marketed devices of the same type such as lower shear fatigue strength, higher abrasion rate, or new types of wear particulates).

We will consider alternatives to clinical studies when the proposed alternatives are supported by an adequate scientific rationale. If a clinical investigation involving one or more subjects is conducted to determine the safety or effectiveness of a device, the Investigational Device Exemption (IDE) regulation, 21 CFR Part 812, applies unless the investigation is excepted from the IDE requirements (see 21 CFR 812.3(a) and (c)). Generally, we believe metallic and/or calcium phosphate coated orthopedic devices addressed by this guidance document are significant risk devices (see 21 CFR 812.3(m)) subject to all requirements of 21 CFR Part 812 (the abbreviated requirements referenced in 21 CFR 812.2(b) are generally not applicable to significant risk devices). See the FDA guidance titled, "Significant Risk and Nonsignificant Risk Medical Device Studies."[25] In addition to the requirements of 21 CFR Part 812, investigations to determine safety and effectiveness of a device may also be subject to FDA regulations governing institutional review boards (21 CFR Part 56) and the protection of human subjects (21 CFR Part 50), including informed consent (21 CFR Part 50, subpart B).

When data from clinical investigations conducted outside the United States are submitted to FDA for metallic and/or calcium phosphate coated orthopedic devices, the requirements of 21 CFR 812.28 may apply.[26] 21 CFR 812.28(a) outlines the conditions for FDA acceptance of data from clinical investigations conducted outside the United States to support an IDE or a device marketing application or submission. For more information, see the FDA guidance "Acceptance of Clinical Data to Support Medical Device Applications and Submissions: Frequently Asked Questions."[27]

In some cases, "real-world data" (RWD) may be used in lieu of traditionally collected clinical data. 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, refer to the FDA Guidance entitled "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices."[28]

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

[26] 21 CFR 812.28 applies to relevant clinical investigations that enroll the first subject on or after February 21, 2019, and that support an IDE or a device marketing application or submission to FDA.

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

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

I. Labeling

As prescription devices, orthopedic devices with coatings are exempt from the requirement to have adequate directions for use under section 502(f)(1) of the FD&C Act as long as the conditions in 21 CFR 801.109 are met. For instance, to be so exempt, labeling that furnishes information for use of the prescription device must, among other things, contain adequate information for such use, including indications, effects, routes, methods, and frequency and duration of administration and any relevant hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to employ the device can use the device safely and for the purposes for which it is intended. (21 CFR 801.109(d)).

Specific labeling information will vary depending on the device on which the coating is used. The following should be considered for the labeling of orthopedic devices with coatings:

1. Calcium phosphate coated joint arthroplasty devices should only be implanted using a cementless method because calcium phosphate coatings can adversely affect the longevity of cemented fixation; we recommend that this information be clearly specified in the Indications for Use Statement and labeling.

2. A device with a porous coating that generally aligns with the description identified in 21 CFR 888.3358 and 21 CFR 888.3670 may be labeled for biological fixation. FDA is currently not aware of valid scientific means, including clinical, animal, or bench models, to support enhanced fixation claims such as osseointegration, bone ingrowth or bone ongrowth in a clinical setting.

3. If you intend to label a coated device as "nano" (e.g., nano-crystalline, nano-structured), characterization data to demonstrate the "nano" characteristics of the coating should be provided in the submission (see **Section F.(3).b**).

IV. Modifications (Devices subject to 510(k))

21 CFR 807.81(a)(3) provides that a device change or modification "that could significantly affect the safety or effectiveness of the device" or represents "[a] major change or modification in the intended use of the device" requires a new 510(k).[29] The changes or

[29] Section 3308 of the Food and Drug Omnibus Reform Act of 2022 (FDORA), enacted as part of the Consolidated Appropriations Act, 2023, added section 515C "Predetermined Change Control Plans for Devices" to the FD&C Act (Pub. L. No. 117-328). Section 515C provides FDA with express authority to approve or clear PCCPs for premarket notification. For example, section 515C provides that supplemental applications (section 515C(a)) and new premarket notifications (section 515C(b)) are not required for a change to a device that would otherwise require a premarket approval supplement or new premarket notification if the change is consistent with a PCCP 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 devices requiring premarket approval or as such device changes pursuant to such plan, notification requirements if the device does not function as

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). Also note this list does not address other modifications for your device but is limited to the modifications for coatings. For additional details, see FDA guidance "Deciding When to Submit a 510(k) for a Change to an Existing Device."[30]

Such changes or modifications include:

- A change to a different coating method or to a different coating vendor (different coating vendors generally have different specifications of coating process parameters, e.g., spray power, distance, and environment for a plasma spray process) that lead to final coatings with different properties – FDA generally considers these changes to be significant changes in material and chemical composition, which could significantly affect the safety and effectiveness of the coated device by adversely impacting biocompatibility or impacting coating integrity. Complete characterization of the new coating should be provided in a new 510(k) submission.

- Addition of coating layers, increasing thickness, or modifying the pore size or porosity – FDA generally considers these changes to be significant changes in design, which could significantly affect the safety and effectiveness of the coated device by introducing a new potential worst-case scenario for mechanical properties of the coating and the risks associated with device failure.

- A change to another substrate material (e.g., from one metal to either another metal or a polymer) or modifications of the surface treatment that could result in a significantly different surface roughness – FDA generally considers these changes to be significant changes in material or material processing, which could significantly affect the safety and effectiveness of the coated devices by introducing a change in the risks associated with device strength and failure modes.

FDA believes that the following changes or modifications would likely not require submission of a new 510(k):

- A change to another supplier for the starting material for a plasma-sprayed metallic coating (e.g., unalloyed titanium powder) where the material specifications such as

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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

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

chemical composition conforming with an FDA-recognized consensus standard, particle size distribution, morphology and porosity are still within the same material specifications. This change generally is not expected to impact biocompatibility or change the risks associated with device failure.

- Reduction of number of coating layers or thickness of a metallic coating on a previously cleared device while other microstructural characteristics (i.e., interconnecting porosity, pore size, volume porosity) are still within the initial specifications (in the case of a porous coating, the microstructural characteristics should still generally align with the porous coating description previously discussed[31]). Provided that the overall device dimensions still remain within the tolerance of the cleared device, these scenarios generally are not expected to introduce new or significantly modified risks or a new worst-case for mechanical properties of the coating and the failure modes of the coated devices.

[31] See 21 CFR 888.3358 and 21 CFR 888.3670.