J Therm Spray Tech (2018) 27:1280–1290
https://doi.org/10.1007/s11666-018-0759-2

PEER REVIEWED

Thermal Spray Coatings on Orthopedic Devices: When and How the FDA Reviews Your Coatings

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Submitted: 13 July 2018 / in revised form: 22 August 2018 / Published online: 20 September 2018

Abstract Thermal spray coatings have been commonly applied on medical devices for various reasons, e.g., surface roughening, biological fixation, and similarity of chemical composition to bone minerals. Generally, to introduce a thermal spray-coated device to the US market, a premarket review of the coated device is necessary by the US Food and Drug Administration (FDA). This article aims to improve understanding regarding FDA review of thermal spray coatings in orthopedic medical device marketing applications and expectations for information to be submitted as part of this process. While different thermal spray technologies and materials have been used for coatings on medical devices, thermal spray coatings often seen by the FDA on orthopedic devices include plasma-sprayed titanium (Ti) coatings and hydroxyapatite (HA) coatings as well as Ti/HA dual coatings. The coated devices are mostly metals (e.g., Ti alloy, cobalt-chromium alloy, stainless steel alloys) and some polymers (e.g., polyetheretherketone). The FDA does not clear or approve individual coatings or materials; rather, coatings and materials are evaluated as part of the final, finished medical device in the context of the specific device technological characteristics and intended use. The FDA has two current guidance documents for orthopedic implants with modified metallic surfaces and hydroxyapatite coatings, which outline the FDA's recommendations for full characterization and testing of these two types of coatings, respectively. Additionally, the standards organizations (e.g., ISO and ASTM) have developed many materials and testing standards for these coatings, some of which are recognized by the FDA. It is helpful that the coating companies reference these standards for appropriate material/coating specifications, testing methods, and acceptance criteria. Depending on the intended use of the coated device, it is important that coating properties also address some items specific to that device type. Additionally, the impact of cleaning, sterilization, and packaging/shelf-life processes on the coating properties is also considered to ensure that the coated device is safe for its intended use.

Keywords hydroxyapatite (HA) coating · ISO and ASTM standard · medical device · plasma spray · premarket review · titanium (Ti) coating · US Food and Drug Administration (FDA) guidance

Neither Dr. Sun nor a member of Dr. Sun's immediate family has received anything of value from or owns stock in a commercial company or institution related directly or indirectly to the subject of this article.

No official support or endorsement of this article by the US Food and Drug Administration (FDA) is intended or should be inferred. The views presented in this article do not necessarily reflect those of the FDA. The findings and conclusions in this article should not be construed to represent any FDA determination, guidance, or policy.

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Introduction

Coatings have been applied on the surface of numerous medical devices to achieve various physical, chemical, microstructural, and mechanical properties, and as a result, anticipated clinical effects (Ref 1). In the USA, to

introduce certain new medical devices to the market, a marketing application to the US Food and Drug Administration (FDA) is required to demonstrate that the device is as safe and effective as a predicate device or has a reasonable assurance safety and effectiveness for its intended use. Depending on the classification of the medical device, different types of marketing applications will be required (Ref 2). For a medical device containing a surface coating, inadequate coating integrity could lead to device failure and clinical complications such as poor fixation and particulate generation. Therefore, materials characterization, some manufacturing details, and testing data regarding the coating are important to include as part of the marketing application and will be reviewed by the FDA to support the substantial equivalence or safety and effectiveness of the coated medical device.

Among various coating technologies (Ref 1), thermal spraying is one of the most commonly used and well-established techniques for coating medical devices and its major applications are within orthopedic and dental devices (Ref 3-5). This article aims to help the thermal spray community to have a better understanding of the FDA premarket review process of thermal spray coatings on orthopedic medical devices, and the information that is important to submit in a marketing application as part of this process. As most thermal spray-coated orthopedic devices are cleared through a Premarket Notification (510(k)) process or approved through a Premarket Approval (PMA) process, this article will focus on the review of these two types of marketing applications. The important information generally includes a description of the thermal spray process and full characterization of the thermal spray coatings including their physicochemical, microstructure, and mechanical properties, as well as their effect on the substrate (i.e., implant) materials. The information can be provided as a part of a marketing application, or can be provided in a Medical Device Master File (MAF) from the coating company, which can be referenced by multiple device manufacturers to support their marketing applications. The article is not intended to address the clinical concerns of thermal spray coatings on medical devices or to discuss all thermal spray coatings using various technologies and/or applied on different medical devices. Instead, it will focus on plasma spray coatings on orthopedic devices as these are the most commonly seen thermal spray coatings by the FDA, and therefore will be used as an example to illustrate the FDA review process of these coatings in a marketing application. It should be noted that this article is intended to illustrate FDA review processes for the thermal spray community, and has no intent to be used in place of FDA guidance documents.

Plasma Spray Coatings on Orthopedic Devices

Plasma spray coatings have been applied on the surface of orthopedic devices for several reasons, such as surface roughening, biological fixation and similarity of chemical composition to bone minerals (Ref 5, 6). Most of these coatings are applied on the bone-contacting surface of the devices (or "implants"; these terms will be used interchangeably hereafter in this article), and this article will discuss the plasma spray coatings that are intended for bone contacting only. Table 1 summarizes the most commonly seen plasma spray coatings on orthopedic devices in terms of coating types and materials, plasma spray techniques, device type and substrate material, and whether the device is labeled as porous coated for biological fixation.

Design of coatings: The plasma spray coating can be designed to have different physical layers (e.g., a Ti coating with a dense base layer and a porous surface layer), surface roughness, and microstructure (e.g., thickness, porosity, pore size, and interconnecting pores). Depending on the microstructure of the coating, some of the Ti coatings and Ti/HA coatings are designed to be porous for biological fixation and therefore need to address additional items outlined by FDA guidance, which will be further discussed in "How to Prepare Your Coating Information for FDA Review" section, below.

Application of coatings on orthopedic devices: As noted in the Table 1, some of the listed devices (e.g., joint arthroplasties) are a system of multiple components and the coating can be applied on one or more components in the system. For example, a typical total hip system consists of an acetabular shell, acetabular liner, a femoral head, a femoral stem, and sometimes optional accessories. The same or different coatings can be applied on the surface of the femoral stem, the acetabular shell or both. Additionally, the coating can be applied on different portions of the implants, such as the proximal portion of a hip stem or both the proximal and distal portions of a hip stem. The coatings on some specific devices require additional information for that device type, which will be further discussed in "How to Prepare Your Coating Information for FDA Review" section. Some photographs of these coated devices are shown in Fig. 1 for illustration only.

Marketing Applications for Medical Devices

To introduce certain new medical devices to the US market, a marketing application demonstrating substantial equivalence to a predicate (a legally marketed device to which substantial equivalence is drawn in a 510(k)) or a reasonable assurance of safety and effectiveness of the

Table 1 Summary of plasma spray coatings on orthopedic devices

Types of coatings	Commercial pure (CP) titanium (Ti) coating
	Hydroxyapatite (HA) coating
	Ti/HA dual coating (a double-layer coating with a HA layer on top of an underlying Ti coating)
Plasma spray techniques	Atmospheric plasma spraying (APS)
	Vacuum plasma spraying (VPS)
	Controlled atmosphere plasma spraying in a closed chamber filled with inert gas (CAPS)
Types of coated devices	Components in joint arthroplasties, e.g., hip femoral stems, hip acetabular cups, knee tibia component and shoulder glenoid components
	Spinal devices, e.g., cages and spacers
	Fracture fixation and/or bone fusion device, e.g., external fixation pins and sacroiliac (SI) joint screws
Substrate material of coated devices	Metals, e.g., Titanium alloy (Ti6Al4 V, Ti6Al7Nb), Cobalt-Chromium (CoCr) alloy, stainless steel alloys (Ref 7)
	Polymers, e.g., Polyetheretherketone (PEEK) or PEEK based composites (Ref 6, 8)
Coated device—labeling	Labeled as porous coated for biological fixation
	Not labeled as porous coated

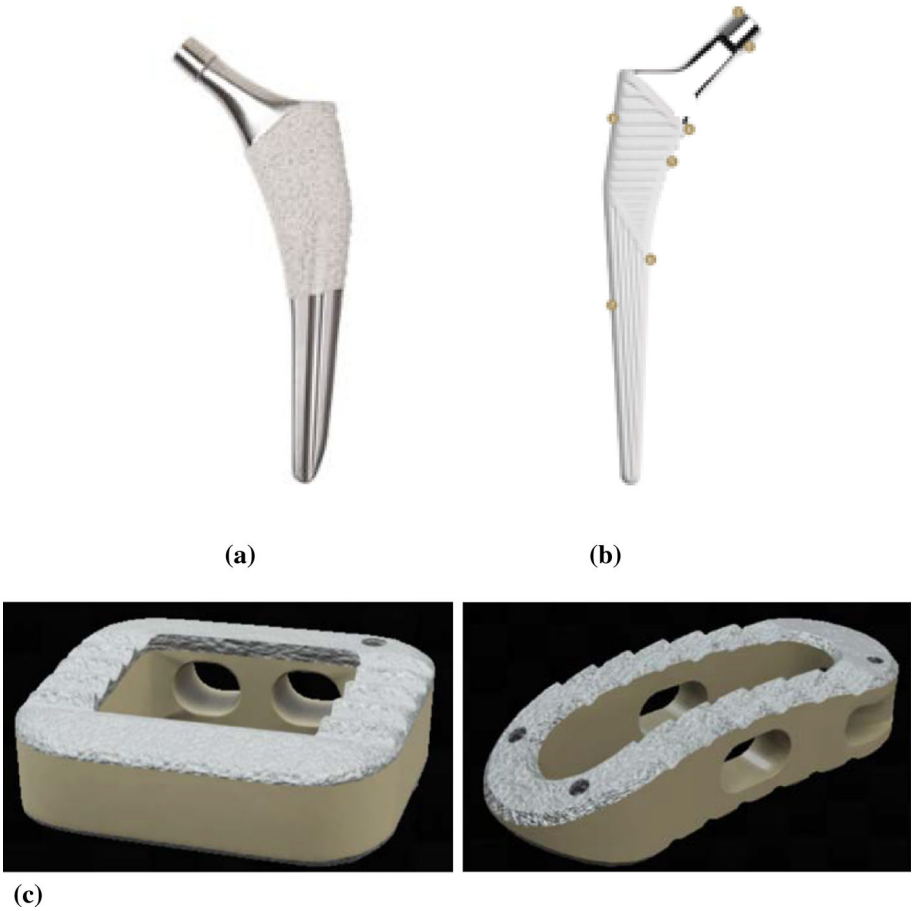

Fig. 1 Photographs of plasma spray-coated orthopedic devices (for illustration only). (a) Accolade II femoral stem with a proximal plasma spray Ti and HA dual coating (Stryker Orthopaedics, Mahwah, NJ) (Ref 9), (b) Corail® hip stem with a plasma spray HA coating at both proximal and distal portions (DePuy Sythses, Inc. Warsaw, IN) (Ref 10), (c) Discovery™ PEEK cervical interbody fusion case and EOS™ TLIF interbody fusion cage (Aurora Spine, Carlsbad, CA) with a plasma spray titanium coating (Ref 11). Image reprinted with permission from Stryker Corporation, © 2018 Stryker Corporation. All rights reserved

medical device should be submitted to the FDA for review. Medical devices are categorized into one of three classes, based on the degree of risk they present, including (Ref 2):

- Class I—lowest risk: Class I devices are subject to general controls.
- Class II—moderate risk: Class II devices are subject to general controls and special controls.

- Class III—highest risk: Class III devices are subject to general controls and premarket approval.

Once the device classification is determined, a marketing application should be selected for that device. Table 2 summarizes the common types of marketing applications (Ref 2).

Depending on the type of marketing application, the device will be reviewed accordingly to ensure that the device is safe and effective for its intended use before it can be marketed and sold in the USA. Note that from a regulatory perspective, the terms "cleared" (for 510(k)s), "approved" (for PMAs and HDEs), and "granted" (for De Novos) have different regulatory implications.

Please see the following FDA website for a detailed description of the general controls, special controls, classification, and the four types of marketing applications: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/ucm2005378.htm (Ref 12).

The plasma spray-coated orthopedic devices listed in Table 1 are Class II or Class III devices and are primarily submitted to the FDA as 510(k)s or PMAs. Note that the device classification is based on the degree of risk they present as discussed in the beginning of this section, and addition of a surface coating on a device does not necessarily increase or decrease the degree of risk for the device. As indicated in "Plasma Spray Coatings on Orthopedic Devices" section above, some of the coated devices (e.g., joint arthroplasties) are a system of multiple components, and the device classification is based on the level of risk of the system, not on a single component or feature (e.g., surface coating). For additional information about the orthopedic joint device regulation, please see Foy J.R. and Buch B.D.'s 2008 article (Ref 13), which illustrates the FDA regulatory process with a focus on the orthopedic joint device examples.

Depending on the intended use and technology of the device, a plasma spray-coated orthopedic device can also be submitted as an Evaluation of Automatic Class III Designation (De Novo) or Humanitarian Device Exemption (HDE) (see Table 2 above). In addition, a thermal spray-coated orthopedic device can be submitted as an Investigational Device Exemption (IDE) device, which allows the device to be used in a clinical study to collect safety and effectiveness data (Ref 13).

In this article, a submitter or an applicant of a marketing application will also be referred to as "sponsor," as generally referred to by the FDA in their guidance documents. A sponsor of a coated device can apply a plasma spray coating to their own devices (in this case, the sponsor is also the coating company for their device) or contract a third-party coating company to apply the coating. A third-party coating company, or a supplier of a thermal spray coating, will be referred to as a "coating vendor."

When FDA Review Your Coatings

For an orthopedic device that contains a plasma spray coating, it is important to include the information on the coating materials, manufacturing details, and properties as well as their effects on the final coated device in a marketing application.

If you are a sponsor of a marketing application, and you apply coatings on your device yourself, you can include manufacturing details and testing data of the coating in your marketing application. Alternatively, you can submit this information to the FDA in a Medical Device Master File (MAF). On the other hand, if your coating is applied

Table 2 Summary of the common types of marketing applications

Types of marketing applications	Description of marketing applications
510(k) (premarket notification)	Some Class I and most Class II devices require a 510(k). In a 510(k), the sponsor must demonstrate that the new device is "substantially equivalent" to a predicate device in terms of intended use, technological characteristics, and performance
PMA (premarket approval)	Most Class III devices require a PMA. A PMA is the most stringent type of marketing application. Before the FDA approves a PMA, the sponsor must provide valid scientific evidence demonstrating a reasonable assurance of safety and effectiveness for the device's intended use
De novo (evaluation of automatic class III designation)	De Novo provides a means for a new device, without a valid predicate, to be classified in Class I or Class II if general controls or general and special controls provide a reasonable assurance of safety and effectiveness
HDE (humanitarian device exemption)	HDE provides a regulatory path for devices that are intended to benefit patients with rare diseases or conditions. In order for a device to be eligible for an HDE, a sponsor must obtain designation as a Humanitarian Use Device (HUD), which is granted through application to FDA's Office of Orphan Products Development (OOPD)

by a third-party coating company (i.e., a "coating vendor"), for proprietary reasons, the coating vendor may wish to submit their manufacturing details and testing data for the coating in a master file. In this case, the master file may be referenced by more than one sponsor to support multiple submission types.

It should be noted again that the FDA does not clear or approve individual coatings or materials, i.e., a master file on a specific coating will not be reviewed unless it is referenced by a marketing application. Also, coatings and materials are evaluated as part of the final, finished device in the context of the specific device technological characteristics and intended use. If a sponsor of a marketing application is referencing a third party's master file for specific coating information, it is important that the sponsor includes a letter of authorization (LOA) from the coating vendor, which specifies the location of the information relevant to the submission within the master file. The LOA allows the FDA to reference information included within the master file and to discuss concerns applicable to a marketing application with the coating vendor directly as needed. For additional information on master files, please see the FDA website: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm (Ref 14).

Once the FDA receives a marketing application that contains a surface coating, the FDA will review the coating information provided in the submission and/or the referenced master file (if applicable) as part of the review process.

How to Prepare Your Coating Information for FDA Review

To support the addition of a plasma spray coating to your device, it is important to include the following coating-related information in a marketing application or a master file for FDA review including:

- Coating description
- Coating manufacturing details
- Coating properties and characterization data
- Effects of coating on coated substrates (implants)
- Sterilization and labeling considerations for the coated orthopedic devices

Each of the above items will be further discussed below. As indicated in "When FDA Review Your Coatings" section, one option is for coating vendors to provide their proprietary information in a master file.

Coating Description

As a coating is part of the final device, it is important to include an appropriate description of the coating on the device as part of the device description in a marketing application, including, but not necessarily limited to, the following:

1. Coating type and method (e.g., plasma-sprayed Ti coating).
2. Coating thickness (or thickness of each layer if the coating contains multiple layers) and location on the device; e.g., device engineering drawings showing coating thickness and coated portion of the implant.
3. Name of the coating company, master file number, and letter of authorization for the FDA to assess this master file if applicable.

Coating Manufacturing Details

There are some differences in the manufacturing details needed for the different types of marketing applications. Information common to several marketing applications includes a detailed description of raw powder, coating method (e.g., APS), equipment, process steps including any pre- and post-coating processes (e.g., sand blasting and cleaning). The facility information is required in a PMA per 21 Code of Federal Regulations (CFR) §814.20 (Ref 15) but may be beneficial if provided to the FDA in other marketing applications in order to understand how the coating is applied on the device and how the manufacturing process could affect the final coating properties and the coated device.

Coating Properties and Characterization Data

It is important to provide a full characterization of the coating properties including metallurgical (for a Ti coating) or physicochemical (for a HA coating), microstructural, and mechanical properties should be provided. The following sections outline the major resources and general issues for you to consider to appropriately characterize your coating in your marketing application.

1. FDA Guidance Documents:

The FDA has two current guidance documents for Orthopedic implants with surface coatings, which are intended to assist you in determining the appropriate information and testing to submit in your marketing applications for orthopedic devices that include metallic coatings and/or hydroxyapatite coatings, and are available at the following FDA websites:

- Guidance Document for Testing Orthopedic Implants with Modified Metallic Surfaces Apposing Bone or Bone Cement, dated April 28, 1994 (http://www.fda.gov/downloads/MedicalDevices/…/ucm081247.pdf) (Ref 16).
- 510(k) Information Needed for Hydroxyapatite Coated Orthopedic Implants, dated March 10, 1995 (revised February 20, 1997) (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080224.htm) (Ref 17).

FDA's guidance documents do not establish legally enforceable responsibilities. Instead, a guidance document describes the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. For most current version of related guidance documents, please check the following FDA website: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ (Ref 18).

2. Consensus Standards

The standards organizations (e.g., ISO and ASTM) have developed many materials and testing standards for metallic and HA coatings, some of which are recognized by the FDA. It is recommended that you reference these standards for appropriate testing methods and acceptance criteria (see Subsection 3, below).

As the standards are under continuous revision, for the current edition of the FDA-recognized standards, see the FDA-Recognized Consensus Standards Database website at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm (Ref 19).

3. General Recommendations

Tables 3 and 4 summarize the general considerations for characterizing a plasma spray Ti coating and a plasma spray HA coating, respectively, which include the recommended material/coating properties per the current FDA guidance documents, and the associated ISO/ASTM standards for the material/coating specifications and testing methods, as well as special considerations to be noted for porous Ti coatings.

For a Ti/HA dual coating, in addition to the full characterization of the Ti coating in Table 3 and the physiochemical analysis of the HA coating in Table 4, it is also important to perform additional microstructural characterization and mechanical testing of the Ti/HA dual coating. If the underlying Ti coating is porous and the coated device is intended to be labeled as porous coated for biological fixation, it is important that a microstructural characterization of the dual coating be conducted to determine if the Ti/HA dual coating still meets the definition of a "porous coating" (see Table 3).

For each test, it is important to include a complete test report, including a description of the test setup and methods or standards used, a description of the test specimens, a worst-case rationale for the test specimens (e.g., the thickest coating is generally considered the worst case for the mechanical strength testing), pre-specified acceptance criteria, test results including raw data, and test conclusions. Unless a specific test sample (also called a coupon) is described in the test standard, it is important that all characterizations are performed with the final sterilized device from multiple lots, or you may provide a rationale 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.

As the thermal spray-coated orthopedic devices are implanted devices, additional cleaning and sterilization are generally needed to minimize infections and related complications. It is also important to evaluate the impact of cleaning, sterilization, and packaging/shelf-life processes on the coating properties to ensure that the coated device is safe for its intended use.

Effects of Coating on Coated Substrates (Implants)

A coating process may affect the physical, chemical (e.g., changes in dimension, color, and chemical structure/stability) or fatigue properties of the coated device; for example, (1) when a coating is significantly thicker than coatings of the same type on legally marketed devices; (2) when a coating process is novel; or (3) when a device material (e.g., polymer) or geometry (e.g., very thin) could be impacted by the coating process. In these situations, it is important that additional tests or a scientific rationale be provided to evaluate the effect of the coating process on properties of the coated device.

Additionally, the Ti and HA coatings on orthopedic devices are patient contacting, which, when used for their intended purpose (i.e., in contact with tissue/bone for a permanent contact duration), may induce a harmful biological response. Therefore, a biocompatibility risk assessment should be conducted and provided per FDA's guidance—Use of International Standard ISO10993-1, "Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management process" (http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf) (Ref 21). It is important that the biocompatibility assessment evaluates not only the starting materials used for the coating, but also the subsequent processing of the materials including the coating process and pre- and

Table 3 Characterization of a plasma-sprayed titanium (Ti) coating

Properties	ISO/ASTM standards for material/coating specification and testing methods
Ti powder specification	ASTM F1580-12 Standard Specification for Titanium and Titanium-6 Aluminum-4 Vanadium Alloy Powders for Coatings of Surgical Implants
Ti coating specification	ISO 13179-1:2014 Implants for surgery—Plasma-sprayed unalloyed titanium coatings on metallic surgical implants—Part 1: General requirements
Metallurgical analysis	Iron content shall be determined by Inductively Coupled Plasma Atomic Emission Spectrometry (ICPAES) in accordance with ASTM E2371-13 Test Method for analysis of Titanium and Titanium Alloy by Atomic Emission Plasma Spectrometry
	Nitrogen, oxygen, carbon, and hydrogen content shall be determined by combustion using a recognized validated method
Microstructural characterization	
Surface morphology and roughness	ISO 4287:1997 Geometrical Product Specifications (GPS)—Surface texture: Profile method—Terms, definitions and surface texture parameters
Cross-sectional microstructure including thickness, pore size and porosity	ASTM F1854-15 Standard test method for stereological evaluation of porous coatings on medical implants
	Note
	If the coated device is intended to be labeled as porous coated for biological fixation, the coating shall meet the definition of "porous coating" per 21 CFR 888.3358 and 21 CFR 888.3670, i.e., has a volume porosity between 30 and 70 percent, an average pore size between 100 and 1000 μm, interconnecting porosity, and a porous coating thickness between 500 and 1500 μm
	For some device types (e.g. knee femoral and tibial components and anatomic shoulder glenoid components), it is important to evaluate the porous coating using the Tissue Interface Gradients method per ASTM F1854 Clause 4.4 "Tissue Interface Gradients" and Clause 9.4 "Tissue Interface Gradient Method." In this case, the volume percent void and the mean void intercept length are evaluated in three 200-μm-thick zones below the tissue interface, and it is important that the results demonstrate that the mean void content and intercept length in all three zones meet the criteria for a "porous coating."
Mechanical testing	
Static tensile	ASTM F1147-05 (2011) Standard test method for tension testing of calcium phosphate and metallic coatings
Static shear	ASTM F1044-05 (2017) Standard test method for shear testing of calcium phosphate coatings and metallic coatings
Shear fatigue	ASTM F1160-14 Standard test method for shear and bending fatigue testing of calcium phosphate and metallic medical and composite calcium phosphate/metallic coatings
Taber abrasion	ASTM F1978-12 Standard test method for measuring abrasion resistance of metallic thermal spray coatings by using the Taber Abraser

post-coating processes, cleaning, and sterilization steps, and any residuals from manufacturing aids used during the process.

Sterilization and Labeling Considerations for Coated Devices

Plasma spray Ti and/or HA-coated orthopedic devices are implanted devices, and it is important to adopt adequate sterilization to minimize infections and related complications and label the device appropriately. The following list identifies some common sterilization and labeling issues for marketing applications that contain a plasma spray Ti and/or HA coating. This is not an exhaustive list.

- It is important that plasma spray HA-coated devices be provided sterile using gamma radiation, as other sterilization methods or reprocessing by the end user may affect the integrity of the coating.
- It is important that plasma spray HA-coated joint arthroplasty devices be implanted using a cementless method, and it is clearly specified in the "Indications for Use Statement" and labeling, as the HA coating can adversely affect the longevity of cemented fixation.
- A device with a "porous coating" (see Table 3) may be labeled for biological fixation, but no other enhanced fixation claims have been accepted in labeling for plasma spray Ti and/or HA-coated devices, as the FDA is not currently aware of valid scientific means to assess

Table 4 Characterization of a plasma-sprayed hydroxyapatite coating

Properties	ISO/ASTM standards for material/coating specification and testing methods
HA powder specification	ASTM F1185-03(2014) Standard specification for composition of hydroxylapatite for surgical implants
	ISO 13779-6:2015 Implants for surgery—Hydroxyapatite—Part 6: Powders
HA coating specification	ASTM F1609-08 (2014) Standard specification for calcium phosphate coatings for implantable materials"
	ISO 13779-2:2008 Implants for surgery—hydroxyapatite—Part 2: coatings of hydroxyapatite
Physicochemical analyses	Unless there are other types of control samples for a specific test, it is important to test a control sample, e.g., National Institute of Standards and Technology (NIST) Standard Reference Material (SRM) 2910B (https://www-s.nist.gov/srmors/view_detail.cfm?srm=2910B) (Ref 20) or a historical control as a comparison for the analyses
Phase compositions per x-ray diffraction	ASTM F2024-10 (2016) Standard practice for x-ray diffraction determination of phase content of plasma-sprayed hydroxyapatite coatings
	ISO 13779-3:2008 Implants for surgery—hydroxyapatite—Part 3: chemical analysis and characterization of crystallinity and phase purity
Ca/P ratio analysis	ISO 13779-3:2018 Implants for surgery—Hydroxyapatite—Part 3: Chemical analysis and characterization of crystallinity and phase purity
Structural analysis per infrared spectroscopy	Provide 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.
Dissolution rate	ASTM F1926-14 Standard test method for evaluation of the environmental stability of calcium phosphate granules, fabricated forms, and coatings
Microstructural characterization	
Surface Morphology and Roughness	ISO 4287:1997 Geometrical Product Specifications (GPS)—Surface texture: Profile method—Terms, definitions and surface texture parameters
Cross-sectional microstructure including thickness, pore size and porosity	ASTM F1854-15 Standard test method for stereological evaluation of porous coatings on medical implants or an alternative recognized validated method
Mechanical testing	
Static tensile	ASTM F1147-05 (2011) Standard test method for tension testing of calcium phosphate and metallic coatings
	ISO 13779-4:200 Hydroxyapatite—determination of coating adhesion strength
Static shear	ASTM F1044-05 (2017) Standard test method for shear testing of calcium phosphate coatings and metallic coatings
Shear fatigue	ASTM F1160-14 Standard test method for shear and bending fatigue testing of calcium phosphate and metallic medical and composite calcium phosphate/metallic coatings

osseointegration, bone ingrowth or bone on growth in a clinical setting.

How FDA Reviews Your Coating in a 510(k) Process?

As discussed in "When FDA Review Your Coatings" section, the FDA reviews a plasma spray coating as part of a marketing application and the review starts once the submission is received by the FDA. As indicated in "Marketing Applications for Medical Devices" section, most orthopedic medical devices with thermal spray coatings are cleared through the 510(k) process or approved through the PMA process by the FDA prior to commercial distribution in the USA. While these two types of applications follow different review processes and timelines (Ref 22, 23), the review of the coating information have some similarities. However, for a 510(k) application, the coated device needs to demonstrate substantial equivalence to the identified predicate device; and for a PMA application, which requires additional facilities information and Quality System review (Ref 23), the coated device needs to demonstrate a reasonable assurance of safety and effectiveness. To understand how the coating information is reviewed by the FDA, the review of a traditional 510(k) will be used to illustrate this process with a focus on the review of coating information. The timeline for a traditional 510(k) review is as follows (Fig. 2):

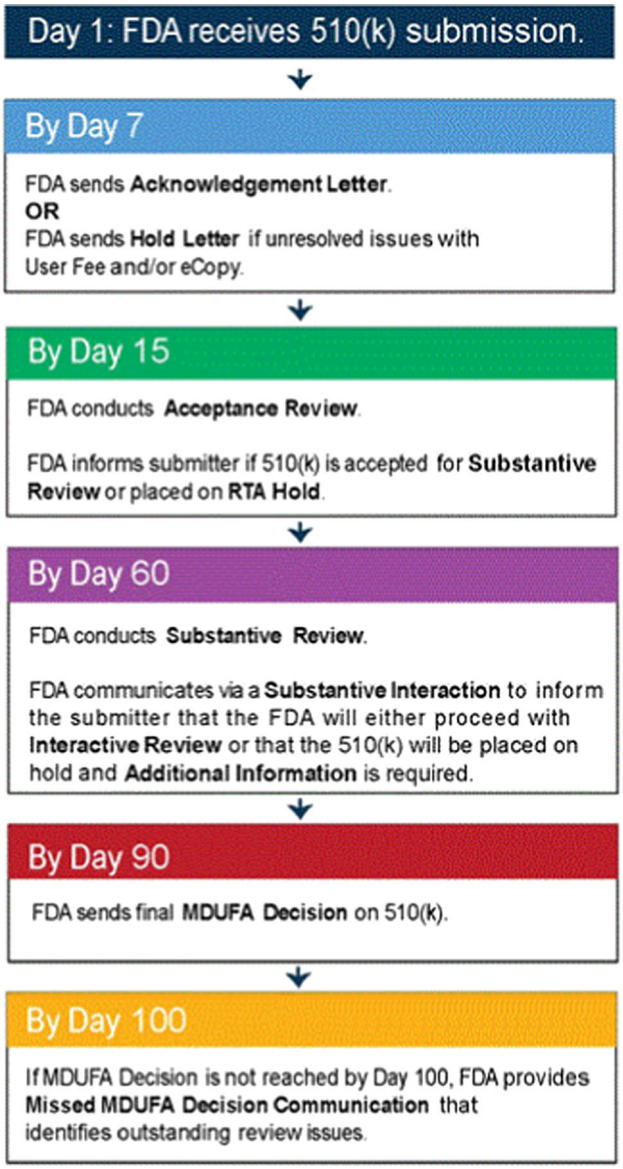

Fig. 2 Timeline of communication during 510(k) review (Ref 22)

Acceptance Review (also referred as Refuse to Accept or RTA): FDA determines whether the 510(k) submission meets the minimum threshold of acceptability and should be accepted for substantive review. A 510(k) for a coated device has rarely been placed on RTA hold due to coating issues, so long as minimum coating information is provided.

Substantive Review (SR): FDA conducts substantive review of the 510(k) including coating information provided in both the 510(k) and the referenced master file if applicable, and communicates with submitters via a Substantial Interaction (SI). FDA may contact the 510(k) sponsor for any coating issues identified in the 510(k) and the coating vendor for any issues identified in the master file during this stage through email or telephone.

By the end of the SI stage, if FDA determines that any outstanding deficiencies may be adequately addressed within the timeframe set by the Medical Device User Fee Amendment of 2017 (MDUFA IV) performance goal for a 510(k) (90 FDA days), FDA will choose to continue with Interactive Review (IR). However, if FDA determines that an Additional Information (AI) request is needed, the submission will be placed on AI hold.

Interactive Review (IR): FDA continues interactive communications with the 510(k) sponsor or the coating vendor to resolve any outstanding coating deficiencies. The 510(k) sponsor or the coating vendor should submit any information requested by the FDA to ensure that FDA has a complete response to make the final MDUFA decision by Day 90.

Additional Information (AI): Once the 510(k) is placed on AI hold, the sponsor has 180 calendar days from the date of the AI Request to submit a complete response to the AI Request email. If the 510(k) is being placed on AI hold wholly or partially due to deficiencies identified in the coating master file, for proprietary reasons, the coating vendor will receive a separate email from the FDA listing all deficiencies with the master file. The coating vendor is encouraged to work with the 510(k) sponsor to ensure that a complete response to the master file deficiencies is submitted to the FDA at the same time or before the 510(k) sponsor's AI response and no later than Day 180. Otherwise, the sponsor's AI response will be considered incomplete, and the 510(k) will be deleted after Day 180.

Once the FDA receives the complete AI response including the response from the coating vendor, the clock will restart and the FDA will review the additional information and address any additional issues with the 510(k) sponsor and/or the coating vendor interactively until a final decision is made by Day 90.

Coating vendors can submit their response to deficiencies directly to the FDA through email; however, if they have performed additional testing in response to any major deficiencies, it is ideal if they submit all new or updated testing data as an amendment to their original master files within the requested timeframe and notify the 510(k) applicants that they have submitted the information to the FDA. In this case, all new or updated testing data in the Amendment may also be referenced by more than one sponsor to support multiple submissions as discussed in "When FDA Review Your Coatings" section. Additionally, coating vendors can amend their master file with new coating information (e.g., new or updated testing data and new manufacturing information) anytime even if there is no associated 510(k) under FDA review; however, as pointed out in "When FDA Review Your Coatings" section, the amended information and data will not be

reviewed by the FDA until they are referenced by a new marketing application received by the FDA.

Pre-Submission Program

In addition to the above information, if you are looking for technical or regulatory feedback regarding your specific coating, for example, a coating having a new intended use, applied using a new thermal spray technique, featuring new technologies (e.g., material, design), or utilizing a new characterization method, you can submit a Pre-Submission to obtain the FDA's feedback. For further information regarding the Pre-Submission Program, refer to the guidance "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf.

Glossary

510(k): Premarket Notification (see Table 2)
PMA: Premarket Approval (see Table 2)
De Novo: Evaluation of Automatic Class III Designation (see Table 2)
HDE: Humanitarian Device Exemption (see Table 2)
HUD: Humanitarian Use Device
Predicate: A legally marketed device to which substantial equivalence is drawn in a 510(k)
MDUFA: Medical Device User Fee Amendment
SE/NSE: Substantially Equivalent/Not Substantially Equivalent, which are the MDUFA Decisions for 510(k) submissions; a 510(k) that receives an SE decision is considered "cleared."
RTA: Refuse to Accept
SR: Substantive Review
SI: Substantive Interaction
IR: Interactive Review
AI: Additional Information
FDA Days: FDA days are calculated as the number of calendar days between the date the 510(k) was received and the date of a MDUFA decision, excluding the days the submission was on hold for an AI request
MAF: Medical Device Master File
LOA: Letter of Authorization
ISO: International Organization for Standardization
ASTM: ASTM International—an international standard organization
CFR: Code of Federal Regulations
Ti/HA dual coating: This refers to a double-layer coating with a HA layer on top of an underlying Ti layer
Porous Coating: Per 21 CFR 888.3358 and 21 CFR 888.3670, a porous coating has a volume porosity between 30 and 70 percent, an average pore size between 100 and 1000 µm, interconnecting porosity, and a porous coating thickness between 500 and 1500 µm. This generic type of device has a design to achieve biological fixation to bone without the use of bone cement.

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