Characterization of Ultrahigh Molecular Weight Polyethylene (UHMWPE) Used in Orthopedic Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on April 26, 2019.

The draft of this document was issued on February 12, 2016.

For questions regarding this document, contact the Division of Orthopedic Devices (DOD) at 301-796-5650.



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

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Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to https://www.regulations.gov . Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2016-D-0363. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Characterization of Ultrahigh Molecular Weight Polyethylene (UHMWPE) Used in Orthopedic Devices

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

FDA has developed this guidance document for members of industry who submit and FDA staff who review testing of orthopedic devices using ultrahigh molecular weight polyethylene (UHMWPE) material. In this document, the terms "you" and "your" refer to members of industry, also known as sponsors, submitters, or applicants; and the terms "we," "us," and "our" refer to FDA. This guidance is intended to assist you in determining the appropriate information and testing to submit in Premarket Notifications (510(k)s), De Novo requests, Premarket Approval (PMA) applications, Humanitarian Device Exemptions (HDEs), and Investigational Device Exemptions (IDEs) for orthopedic devices that contain UHMWPE.

This guidance addresses the characterization and testing of UHMWPE materials used in orthopedic devices. These materials include conventional UHMWPE, highly crosslinked UHMWPE, highly crosslinked UHMWPE containing antioxidants (e.g., α-tocopherol (an isomer of vitamin E)), and non-conventional UHMWPE. This document outlines the information we recommend you include in a submission to FDA to characterize the UHMWPE material (e.g., material description, sterility, biocompatibility, mechanical properties, and chemical properties).

Many standards are referenced in this document. For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus

Standards Database.[1] A table of referenced FDA-recognized standards applicable to UHMWPE is provided in Appendix 1.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances 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 intended for orthopedic applications, including spinal devices, which contain UHMWPE. If you intend to submit an original IDE for an investigational device containing UHMWPE, we recommend you submit a Pre-Submission to the appropriate review division to determine what level of characterization is needed for the UHMWPE material. For more information on Pre-Submissions, see the FDA guidance document entitled, "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff."[2]

This guidance document does not address nor discuss device-specific functional testing, such as impingement testing, wear testing, or interconnection strength testing. If you have any questions on these topics, refer to the recommendations in any applicable device-specific guidance, when available, or contact the appropriate review division.

III. Types of UHMWPE Materials Used in Implantable Orthopedic Devices

The UHMWPE materials used in implantable orthopedic devices may be organized into four general categories: 1) conventional UHMWPE; 2) highly crosslinked UHMWPE; 3) antioxidant highly crosslinked UHMWPE; and 4) non-conventional UHMWPE.

A. Conventional UHMWPE

Conventional UHMWPE originates from virgin resin powders or consolidated forms conforming to international consensus standard ASTM F648: *Standard Specification for Ultra-High-Molecular-Weight Polyethylene Powder and Fabricated Form for Surgical Implants*. According to section 5.1 of ASTM F2759: *Standard Guide for Assessment of the Ultra High Molecular Weight Polyethylene (UHMWPE) Used in Orthopedic and Spinal Devices*, fabricated forms of conventional UHMWPE are "manufactured by

[1] Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.
[2] Available at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.

compression molding or ram extrusion and [have] not been intentionally cross-linked before terminal sterilization."[3]

B. Highly Crosslinked UHMWPE (HXLPE)

HXLPE originates from virgin resin powders or consolidated forms conforming to ASTM F648. This material type includes UHMWPE that has been highly crosslinked by various methods. According to section 5.2 of ASTM F2759, fabricated forms of extensively radiation-crosslinked UHMWPE, a subset of HXLPE, are "manufactured by compression molding or extrusion and irradiated with a dosage higher than 40 kGy of gamma or e-beam radiation for improved wear resistance."[4]

This material type may also include HXLPE that has been extensively crosslinked by methods other than ionizing radiation (e.g., peroxides, silane, high temperature exposure).

C. Antioxidant Highly Crosslinked UHMWPE (AO-HXLPE)

AO-HXLPE material originates from virgin resin powders or consolidated forms conforming to ASTM F648 and/or ASTM F2695: *Standard Specification for Ultra-High Molecular Weight Polyethylene Powder Blended with Alpha-Tocopherol (Vitamin E) and Fabricated Forms for Surgical Implant Applications*. According to section 5.3 of ASTM F2759, "Two stabilizing methods for the antioxidant UHMWPE form (Vitamin E-stabilized or alpha-tocopherol) are blending or diffusing. The blending method has the Vitamin E mixed (blended) into the UHMWPE powder before consolidation and radiation cross-linking. The diffusing method has the Vitamin E diffusing into a consolidated UHMWPE form before or after radiation cross-linking. Also, antioxidant UHMWPE could potentially be used without any radiation cross-linking."[5]

D. Non-Conventional UHMWPE

Non-conventional UHMWPE is a polyethylene material other than the three material types discussed above. Examples may include, but are not limited to, materials that are made from lower molecular weight polyethylenes that may or may not be extensively crosslinked, porous polyethylenes, functionalized UHMWPE such as hyaluronic acid-modified UHMWPE, or polyethylenes whose surfaces have been modified. These may or may not be stabilized with an antioxidant.

[3] ASTM Standard F2759, 2011, "Standard Guide for Assessment of the Ultra High Molecular Weight Polyethylene (UHMWPE) Used in Orthopedic and Spinal Devices," ASTM International, West Conshohocken, PA, 2011, DOI: 10.1520/F2759-11, www.astm.org.
[4] Ibid.
[5] Ibid.

IV. Material Processing and Characterization

For all material types and submission types (510(k), De Novo, PMA, HDE, or IDE), FDA recommends that you provide the following general technical information regarding the UHMWPE material to establish the type of UHMWPE in use:

- Starting resin (e.g., GUR 1020, GUR 1050);
- Resin consolidation method (e.g., ram extrusion, compression molding); and
- Terminal sterilization method.[6] If radiation, type (e.g., gamma irradiation, electron beam) and delivered dose or equivalent measure should be provided, along with a description of the packaging and the environment in which it was packaged (e.g., barrier film, inert gas, vacuum).

Depending on the type of UHMWPE, different mechanical and chemical characterization should be provided, as discussed in more detail below. This characterization information is summarized in Appendix 2. For information on recommended content and format of complete test reports for non-clinical bench performance testing in premarket submissions, refer to FDA's guidance, "Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions."[7] In cases where you believe the information or testing described in this document do not apply to your device, you should provide a rationale explaining why you believe the recommended information or testing are not applicable.

A. Conventional UHMWPE

Material characteristics of conventional UHMWPE should conform to the specifications of ASTM F648 for both powder and fabricated forms, and we recommend that you include a declaration of conformity to ASTM F648, as appropriate, in your premarket submission.[8] For orthopedic implants we recommend you consider the information summarized in Table 2 of ASTM F648, which identifies the material property specifications for conventional UHMWPE in fabricated form. Standard test methods typically used to assess these properties are also referenced in ASTM F648. You should provide the following material properties of your conventional UHMWPE in your regulatory submission to FDA:

- Tensile properties (e.g., yield strength, ultimate tensile strength, and elongation at break);

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[6] "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile," available at http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm109897.pdf.

[7] Available at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM606051.

[8] For more information on the use of standards in premarket submissions, see "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices" (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM077295).

- Impact resistance (e.g., Izod); and
- Density.

If the material meets the specifications in ASTM F648, no additional information will typically be requested. However, if the material's properties are not within the specification range in the standard, then additional information should be provided to demonstrate that the device can perform as intended for its indicated use.

We recommend that manufacturers refer to ASTM F2759 which provides general guidelines for physical, chemical, biocompatibility, mechanical, and preclinical assessments of UHMWPE in implantable orthopedic and spinal devices intended to replace a musculoskeletal joint.

B. Highly Crosslinked UHMWPE (HXLPE)

HXLPE primarily differs from conventional UHMWPE in that extensively radiation-crosslinked UHMWPE absorbs a relatively larger radiation dose and is then thermally processed. These differences alter the mechanical, physical, and chemical properties of the material, and these properties should be characterized. In addition to the information that is requested for conventional UHMWPE in Section IV.A, you should provide the following information in your regulatory submission to FDA:

- Radiation type (e.g., gamma irradiation, electron beam) and delivered dose, inclusive of terminal sterilization, as measured by dosimeters or equivalent measures;
- Percent crystallinity;
- Melting temperature;
- *Trans*-vinylene index throughout the sample;
- Post-accelerated aging testing (e.g., oxidation index throughout the sample to compare pre- and post-aging properties and/or mechanical properties that demonstrate no adverse effect on performance);
- Crosslink density;
- Fatigue resistance crack propagation testing ($\Delta K_{inception}$, Paris exponent, Paris coefficient);
- Free radical concentration;
- Time, temperature, and rationale for all post-crosslinking thermal processing steps such as heating above the melt temperature of UHMWPE or annealing below the melt temperature (e.g., to reduce/eliminate free radicals, relieve internal stresses); and
- Compression ratio of mechanical thermal processing steps.

We recommend that characterization tests listed above be performed per the current FDA-recognized standards, ASTM F2759 and ASTM F2565: *Standard Guide for Extensively Irradiation-Crosslinked Ultra-High Molecular Weight Polyethylene Fabricated Forms for Surgical Implant Applications*, which reference standard test methods recommended to assess this information.

If the measured values lie within an acceptable range, as determined by comparison to either another legally marketed device with the same intended use or literature, no additional information will typically be requested. However, if the material's properties lie outside the previously accepted range, then additional information should be provided to demonstrate that the device can perform as intended for its indicated use.

For the characterization of properties that are also recommended for conventional UHMWPE, such as tensile properties, impact resistance, and density, we consider the minimum specifications set forth in ASTM F648 to be acceptable for highly crosslinked polyethylenes, which are outside the scope of that standard. If the material meets the specifications of ASTM F648, no additional information will typically be requested to characterize these properties. However, if the material's properties do not meet these acceptance criteria, then additional information should be provided as recommended in the preceding paragraph.

During the radiation crosslinking process, free radicals are produced, and the free radical concentration directly influences the oxidative stability of the material. As a result, post irradiation thermal treatment of the polymer is performed to reduce or eliminate the free radical concentration and to ensure the long term oxidative stability of the polyethylene. For materials thermally processed above or below the melt temperature, the free radical concentration should be determined. There currently is no standard test method for determining free radical concentration. Free radical concentration is typically assessed using electron paramagnetic resonance (EPR) spectroscopy, also known as electron spin resonance (ESR) spectroscopy. The test method you choose should be fully described and justified in your submission and the limit-of-detection of EPR/ESR measurements should be included in the test reports. We recommend that, in addition to supplying the measured concentration of free radicals, spectrographs showing the free radical spectra should also be provided.

Some properties, such as wear, fatigue crack propagation resistance, and morphology of the fabricated form (i.e., consolidation quality, per Annex 2.1 of ASTM F648-14), are comparative in nature. No acceptance criteria are specified. These properties should be evaluated in a manner that demonstrates that the device can perform as intended for its indicated use.

Finally, device-specific impingement and/or fatigue studies should also be carried out on HXLPE in its final component design form factor to test locking mechanisms, posts, and other design features that may be sensitive to fatigue crack propagation. Refer to the recommendations in any applicable device-specific guidance document, when available, or contact the appropriate review division for comments on proposed testing.

For UHMWPE that has been extensively crosslinked by methods other than ionizing radiation (e.g., peroxides, silane, high temperature exposure), additional tests may be requested depending on the crosslinking procedures, such as assessment of residual peroxide concentration and reaction by-products. If a different crosslinking method is used, we recommend discussing your proposed procedures and any additional

characterization assessments with the Agency prior to submission of a marketing application. Please refer to the guidance "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff"[9] for more information on meetings with FDA staff.

C. Antioxidant Highly Crosslinked UHMWPE (AO-HXLPE)

AO-HXLPE primarily differs from HXLPE in that an antioxidant (e.g., α-tocopherol) is added either before or after exposure to radiation and the material is not thermally processed above its melting temperature. In addition to the information that is requested for conventional UHMWPE in Section IV.A, and HXLPE in Section IV.B., the following additional characterization information should be provided to address specific concerns raised by the addition of antioxidants:

1. Concentration and identification of antioxidant or other additives (in weight percent (wt. %) and parts per million (ppm) or as a Vitamin E index or equivalent).[10]

2. Stability of antioxidant in the material. It is possible that the added antioxidant may leach out over time due to loading and/or *in vivo* fluids that act as a solvent for the antioxidant. The loss of the antioxidant may undermine the material's oxidation resistance. This concern can be addressed by demonstrating adequate oxidation resistance following wear testing where the material is exposed to clinically relevant loads and solvents.

3. Effect of antioxidant on the wear mechanism. An antioxidant may affect the mechanism by which the material wears. FDA recommends that you assess if the wear mechanism has been altered due to the addition of the antioxidant by characterizing the wear debris from wear testing of the new device per ASTM F1877: *Standard Practice for Characterization of Particles*. In addition, wear testing under normal and abrasive wear conditions should be performed. An analysis of the wear rates and wear surfaces in terms of type and extent of damage modes should also be provided. The anticipated, or known, impact of the wear test results on device performance should be thoroughly discussed and supported with available literature and scientific rationale (e.g., comparison to the control, animal studies[11]). Alternatively, it may be possible to address this concern by supplying a scientific rationale comparing the antioxidant type, concentration, radiation dose, and radiation type (i.e., gamma or electron beam) to a legally-marketed, antioxidant-containing device with a similar intended use.

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[9] Available at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.

[10] Oral E, Neils A, Muratoglu OK. 2014. High vitamin E content, impact resistant UHMWPE blend without loss of wear resistance. J Biomed Mater Res Part B 2015:103B:790–797.

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

We recommend contacting the appropriate review division for questions regarding device-specific wear testing.

The following FDA-recognized standards may be helpful when performing wear testing:

- ASTM F732: *Standard Test Method for Wear Testing of Polymeric Materials Used in Total Joint Prostheses*
- ASTM F1714: *Standard Guide for Gravimetric Wear Assessment of Prosthetic Hip Designs in Simulator Devices*
- ASTM F2423: *Standard Guide for Functional, Kinematic, and Wear Assessment of Total Disc Prostheses*
- ISO 14242-1: *Implants for surgery – Wear of total hip-joint prostheses- Part 1: Loading and displacement parameters for wear-testing machines and corresponding environmental conditions for test*
- ISO 14242-2: *Implants for surgery – Wear of total hip-joint prostheses – Part 2: Methods of measurement*
- ISO 14242-3: *Implants for surgery – Wear of total hip-joint prostheses – Part 3: Loading and displacement parameters for orbital bearing type wear testing machines and corresponding environmental conditions for test*
- ISO 14243-1*: Implants for surgery – Wear of total knee-joint prostheses – Part 1: Loading and displacement parameters for wear-testing machines with load control and corresponding environmental conditions for test*
- ISO 14243-2: *Implants for surgery – Wear of total knee-joint prostheses – Part 2: Methods of measurement*
- ISO 14243-3: *Implants for surgery – Wear of total knee-joint prostheses – Part 3: Loading and displacement parameters for wear-testing machines with displacement control and corresponding environmental conditions for test*
- ISO 18192-1: *Implants for surgery – Wear of total intervertebral spinal disc prostheses- Part 1: Loading and displacement parameters for wear testing and corresponding environmental conditions for test*
- ISO 18192-2: *Implants for surgery – Wear of total intervertebral spinal disc prostheses – Part 2: Nucleus replacements*

4. Effect of antioxidant on material consolidation. When an antioxidant is added to the UHMWPE powder prior to consolidation, its presence may hinder powder consolidation. Therefore, FDA recommends that the morphology of the fabricated forms be assessed as described in Annex 2 of ASTM F648-14.

5. Biocompatibility should be evaluated per the recommendations in Section V, below.

If additional concerns not discussed above are identified based on the material characterization, additional information such as preclinical or clinical data may be requested to mitigate these concerns.

D. Non-Conventional UHMWPE

As non-conventional UHMWPE is not clearly defined, it is not possible to provide specific testing recommendations at this time. We encourage you to submit a Pre-Submission with specific questions to be discussed for non-conventional UHMWPE devices. For additional information regarding the Pre-Submission process, refer to the Guidance for Industry and FDA Staff, "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff."[12]

In addition to the testing discussed above, we recommend you consider the following points:

- Compression properties of the material;
- Crystal size and structure;
- Creep resistance; and
- Durability of modified surface.

If additional concerns are identified based on the material characterization, additional information such as additional preclinical or clinical data may be requested to mitigate these concerns.

V. Biocompatibility

UHMWPE materials used in implantable orthopedic devices are patient-contacting materials, which, when used for their intended purpose (i.e., contact type and duration), may induce a harmful biological response.

You should determine the biocompatibility of all patient-contacting materials present in your device. If the subject device uses the *identical* UHMWPE materials and manufacturing processes as a legally marketed device with a history of safe use, you may reference previous testing experience or literature, if appropriate.

If you are unable to identify a legally marketed device with similar location/duration of contact and intended use that uses the same materials and manufacturing processes as used in your device, we recommend you conduct and provide a biocompatibility risk assessment. The assessment should explain the relationship between the identified biocompatibility risks, 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. If your biocompatibility assessment relies on

[12] Available at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.

information regarding the raw material in a device Master File (MAF), we recommend that you include a Letter of Authorization (LOA) for the relevant Master File, and ensure that you address the subsequent processing, cleaning, and sterilization steps to address the biocompatibility of the final sterilized device. In addition, you may declare conformity to a recognized material consensus standard, if applicable.

We recommend that you follow 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'"[13] (referred to as "CDRH's 2016 Biocompatibility Guidance"), which identifies the type of biocompatibility assessments that should be considered and recommendations regarding how to conduct related tests, if applicable.

Per ISO 10993-1 and Attachment A of CDRH's 2016 Biocompatibility Guidance, most orthopedic devices that incorporate UHMWPE are considered implant devices in contact with tissue/bone for a permanent contact duration. Therefore, the following endpoints should be addressed in your biocompatibility evaluation:

- Cytotoxicity;
- Sensitization;
- Irritation or Intracutaneous Reactivity;
- Acute Systemic Toxicity;
- Material-Mediated Pyrogenicity;
- Subchronic toxicity (Sub-acute toxicity);
- Genotoxicity (We recommend that both mutagenicity and clastogenicity be assessed.);
- Implantation;
- Chronic Toxicity; and
- Carcinogenicity.

For device-specific, patient-contacting device instrumentation in contact with tissue/bone for a temporary contact duration, the following endpoints should be addressed in your biocompatibility evaluation:

- Cytotoxicity;
- Sensitization;
- Irritation or Intracutaneous Reactivity;
- Acute Systemic Toxicity; and
- Material-Mediated Pyrogenicity.

The following additional considerations are recommended for components made from UHMWPE materials containing antioxidants:

[13] Available at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM348890.

- The addition of antioxidants raises concerns regarding the biocompatibility of the antioxidant itself and the biocompatibility of radiation-induced degradation products. The second concern generally applies to materials that contain the antioxidant and have been exposed to radiation (i.e., AO-HXLPE, or possibly Non-Conventional UHMWPE). For tissue/bone contacting, permanently implanted devices, FDA recommends that you submit a biocompatibility evaluation as per CDRH's 2016 Biocompatibility Guidance, referenced above.

- Wear debris is an important consideration for any UHMWPE-containing, articulating device component. Therefore, the body's response to any antioxidant and associated degradation products leached from the wear debris should be assessed. This may be accomplished via injecting wear particles from the wear simulator or other representative particles into an appropriate animal model. The results of the test should be compared to a control. We encourage you to submit a Pre-Submission with a testing protocol for review prior to initiating animal testing. As an alternative to the animal testing, it may be possible to demonstrate that the wear debris generated has similar size/number/shape of particles as other similar, legally marketed devices, and the antioxidant and its degradation products are not bioavailable.

VI. Shelf Life and Packaging

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

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. 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. FDA recommends that package integrity test methods include simulated distribution and associated package integrity, as well as simulated (and/or real-time) aging 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 systems,* and ISO 11607-2: *Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly processes.*

The mechanical properties of UHMWPE that contains unstable free radicals may degrade if the product is exposed to air during shelf storage. In addition, the shelf life of UHMWPE that has been irradiated and packaged in an inert environment may be limited by the integrity of the packaging material. Therefore, FDA recommends that the stability of UHMWPE materials used in implantable devices be assessed for the duration of their specified shelf life. With respect to evaluating the effects of aging on device performance or functionality, shelf life studies should evaluate the critical device properties to ensure that it will perform adequately and consistently during the entire proposed shelf life. To evaluate device

functionality, we recommend that you assess each of the relevant bench tests described in Section IV and repeat all tests that evaluate design components or characteristics that are potentially affected by aging.

If you intend to extend the shelf-life of the device after initial approval, we recommend that you provide the methods or protocol(s) to support the extension in the original submission.

We recommend devices undergo real-time aging to determine definitively the effects of aging on the maintenance of sterility and device performance. If you use devices subjected to accelerated aging, we recommend that you specify the way in which the device was aged and develop a rationale to explain how 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. Testing of real-time aged devices can 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).

Appendix 1. FDA-Recognized Standards Applicable to UHMWPE Evaluation

Standard Number	Standard Title
ASTM E647	Standard Test Method for Measurement of Fatigue Crack Growth Rates
ASTM F648	Standard Specification for Ultra-High-Molecular-Weight Polyethylene Powder and Fabricated Form for Surgical Implants
ASTM F732	Standard Test Method for Wear Testing of Polymeric Materials Used in Total Joint Prostheses
ASTM F1714	Standard Guide for Gravimetric Wear Assessment of Prosthetic Hip Designs in Simulator Devices
ASTM F1877	Standard Practice for Characterization of Particles
ASTM F2003	Standard Practice for Accelerated Aging of Ultra-High Molecular Weight Polyethylene after Gamma Irradiation in Air
ASTM F2102	Standard Guide for Evaluating the Extent of Oxidation in Polyethylene Fabricated Forms Intended for Surgical Implants
ASTM F2214	Standard Test Method for In Situ Determination of Network Parameters of Crosslinked Ultra High Molecular Weight Polyethylene (UHMWPE)
ASTM F2381	Standard Test Method for Evaluating Trans-Vinylene Yield in Irradiated Ultra-High Molecular-Weight Polyethylene Fabricated Forms Intended for Surgical Implants by Infrared Spectroscopy
ASTM F2423	Standard Guide for Functional, Kinematic, and Wear Assessment of Total Disc Prostheses
ASTM F2565	Standard Guide for Extensively Irradiation-Crosslinked Ultra-High Molecular Weight Polyethylene Fabricated Forms for Surgical Implant Applications
ASTM F2625	Standard Test Method for Measurement of Enthalpy of Fusion, Percent Crystallinity, and Melting Point of Ultra-High-Molecular Weight Polyethylene by Means of Differential Scanning Calorimetry
ASTM F2695	Standard Specification for Ultra-High Molecular Weight Polyethylene Powder Blended with Alpha-Tocopherol (Vitamin E) and Fabricated Forms for Surgical Implant Applications
ASTM F2759	Standard Guide for Assessment of the Ultra High Molecular Weight Polyethylene (UHMWPE) Used in Orthopedic and Spinal Devices
ISO 5834-1	Implants for surgery – Ultra-high-molecular-weight polyethylene – Part 1: Powder form
ISO 5834-3	Implants for surgery – Ultra-high-molecular-weight polyethylene – Part 3: Accelerated ageing methods
ISO 5834-4	Implants for surgery – Ultra-high-molecular-weight polyethylene – Part 4: Oxidation index measurement method
ISO-5834-5	Implants for surgery – Ultra-high-molecular-weight polyethylene – Part 5: Morphology assessment method
ISO 14242-1	Implants for surgery – Wear of total hip-joint prostheses – Part 1: Loading and displacement parameters for wear-testing machines and corresponding environmental conditions for test
ISO 14242-2	Implants for surgery – Wear of total hip-joint prostheses – Part 2: Methods of measurement
ISO 14242-3	Implants for surgery – Wear of total hip-joint prostheses – Part 3: Loading and displacement parameters for orbital bearing type wear testing machines and corresponding environmental conditions for test

ISO 14243-1	Implants for surgery – Wear of total knee-joint prostheses – Part 1: Loading and displacement parameters for wear-testing machines with load control and corresponding environmental conditions for test
ISO 14243-2	Implants for surgery – Wear of total knee-joint prostheses – Part 2: Methods of measurement
ISO 14243-3	Implants for surgery – Wear of total knee-joint prostheses – Part 3: Loading and displacement parameters for wear-testing machines with displacement control and corresponding environmental conditions for test
ISO 18192-1	Implants for surgery – Wear of total intervertebral spinal disc prostheses – Part 1: Loading and displacement parameters for wear testing and corresponding environmental conditions for test
ISO 18192-2	Implants for surgery – Wear of total intervertebral spinal disc prostheses – Part 2: Nucleus replacements
ISO 10993-1	Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process

Refer to FDA's consensus standards database (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm) to identify the most current version of the standard recognized by FDA, as well as the extent of recognition.

Appendix 2. Summary of Characterization Information for Various UHMWPE Materials[14]

Property	Conventional	HXLPE	AO-HXLPE	Non-Conventional	Relevant Standards
Tensile Properties	X	X	X	X	ASTM F648, ASTM F2759
Crystallinity, Melting Temperature		X	X	X*	ASTM F2625, ASTM F2759
Impact Resistance	X	X	X	X	ASTM F648, ASTM F2565, ASTM F2759
Trans-vinylene index		X	X	X*	ASTM F2381, ASTM F2625, ASTM F2759
Post-accelerated Aging; Maximum Oxidation Index, and/or Mechanical Properties		X	X	X*	ASTM F2003, ASTM 2102, ASTM F2759
Density	X	X	X	X	ASTM F648
Crosslink Density		X	X	X*	N/A
Fatigue Resistance		X	X	X	ASTM F2565, ASTM F2759
Free Radical Concentration		X	X	X*	N/A
Morphology Testing			X	X*	ASTM F648 (Annex 2)

* As applicable.

[14] Note that this table is not all-inclusive. Refer to the main body of this guidance document for additional information that should be provided to characterize the material.