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Evidentiary Expectations for 510(k) Implant Devices

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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Preface

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

As part of FDA's Medical Device Safety Action Plan: Protecting Patients, Promoting Public Health (herein referred to as the "Safety Action Plan"),[1] FDA committed to strengthen and modernize the premarket notification [510(k)] Program. To enhance the predictability, consistency, and transparency of the 510(k) Program, FDA is issuing this guidance to provide our current thinking on 510(k) submissions for implant devices. This guidance is intended to serve as a primary resource on general recommendations for all implant devices for which a 510(k) is required (510(k) Implants), while device-specific guidances may provide further specificity for a given device type. This document is intended to clarify our evidentiary expectations for 510(k) Implants. By "evidentiary expectations," we mean that this document is intended to assist industry in design and execution of appropriate performance testing that may be necessary to support 510(k) submissions for implants. It also provides general recommendations for other content, including proposed labeling, to include in these submissions. In addition, some of the recommendations in the guidance, such as those related to identification and mitigation of certain risks associated with implants, may be relevant beyond the context of preparing a 510(k) submission and helpful to consider throughout the total product lifecycle. For purposes of this guidance, a "submitter" is the entity that submits the 510(k) to FDA for review.

For the current edition of the FDA-recognized consensus standards referenced in this document, see the FDA Recognized Consensus Standards Database.[2] For more information regarding use of consensus standards in regulatory submissions, refer to the FDA guidance titled "Appropriate

[1] Available at https://www.fda.gov/about-fda/cdrh-reports/medical-device-safety-action-plan-protecting-patients-promoting-public-health.

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

Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices"[3] and "Standards Development and the Use of Standards in Regulatory Submissions Reviewed in the Center for Biologics Evaluation and Research."[4]

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

II. Background

In April 2018, CDRH issued the Safety Action Plan to communicate CDRH's vision for modernizing measures to improve the safety of medical devices while continuing to create more efficient pathways to bring critical devices to patients. The Safety Action Plan describes efforts underway to modernize the 510(k) Program.

In November 2018, FDA announced transformative new steps to modernize FDA's 510(k) Program to advance the review of the safety and effectiveness of medical devices.[5] In connection with this announcement, FDA also requested public feedback on these steps to continue to modernize the framework for 510(k) review while promoting innovation and patient safety, and posed other questions that could inform regulatory policy development.[6] One area identified by the public comments where additional clarity and transparency would be helpful related to recommendations specific to 510(k) submissions for implants.

Under section 510(k) of the Federal Food, Drug, and Cosmetic (FD&C) Act, a premarket notification submission (often referred to as a 510(k)) must be submitted to FDA at least 90 days before introducing, or delivering for introduction, a device into interstate commerce for commercial distribution.[7] A 510(k) is required for devices intended for human use, for which a premarket approval application (PMA) is not required, unless the device is exempt from the 510(k) requirements of the FD&C Act and does not exceed the relevant limitations of exemptions in the device classification regulations. Through review of the 510(k), FDA

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

[4] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/standards-development-and-use-standards-regulatory-submissions-reviewed-center-biologics-evaluation.

[5] Please see the Statement from then FDA Commissioner Scott Gottlieb, M.D., and Jeff Shuren, M.D., Director of the Center for Devices and Radiological Health, on November 26, 2018, available at https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-jeff-shuren-md-director-center-devices-and.

[6] Please see "Modernizing FDA's 510(k) Program; Establishment of a Public Docket; Request for Comments," Docket Number FDA-2018-N-4751, available at https://www.regulations.gov/docket/FDA-2018-N-4751.

[7] See sections 510(k) and (n) of the FD&C Act (21 U.S.C. §§ 360(k) & (n)).

determines whether the "new device"[8] is substantially equivalent[9] (SE) to a predicate device.[10] For additional information on how FDA evaluates SE in the 510(k) premarket review process, please see the FDA guidance entitled "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]," [11] hereafter called the "510(k) Program Guidance."

For FDA to find a new device SE to a predicate device, FDA must first find that the new device and predicate device have the same intended use. FDA must then find that the new device and predicate device have the same technological characteristics, or if they do not, that the different technological characteristics[12] of the new device do not raise different questions of safety and effectiveness and that the new device is as safe and effective as a predicate device.

To determine the safety and effectiveness of a device, FDA weighs if there is "any probable benefit to health from the use of the device against any probable risk of injury or illness from such use,"[13] among other relevant factors. Under the 510(k) paradigm, the benefit-risk profile of the new device is determined in the context of a comparison to the benefit-risk profile of a predicate device; the benefit-risk profile of a new device with different technological characteristics does not need to be identical to that of its predicate device in order to determine if the new device is as safe and effective as a predicate device. The FDA guidance "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics"[14] describes considerations for evaluating benefit-risk profile of a device in comparison to a predicate device for purposes of SE determinations.

FDA expects that submitters will typically provide a variety of non-clinical and/or clinical data to support that an implant is "as safe and effective" as a predicate device, given the scientific and clinical considerations that implants often raise. In addition, if FDA has established special controls applicable to the device type, the information in the 510(k) submission would need to demonstrate that the proposed device meets the relevant special controls for the device to be

[8] For purposes of this guidance, a "new device" means a device within the meaning of section 201(h) of the FD&C Act that is not legally marketed. It can be either a completely new device or a modification of a legally marketed device that would require a new 510(k).

[9] The standard for a substantial equivalence determination for a 510(k) submission is set out in section 513(i) of the FD&C Act.

[10] A predicate device is a legally marketed device. For purposes of an SE determination, a predicate device is (1) a device that was legally marketed prior to May 28, 1976 (preamendments device) and for which a PMA is not required, or (2) a device that has been classified or reclassified into Class II or I, or (3) a device that has been found to be SE through the 510(k) process. See 21 CFR 807.92(a)(3) and section 513(f)(2) of the FD&C Act.

[11] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/510k-program-evaluating-substantial-equivalence-premarket-notifications-510k.

[12] For purposes of an SE determination, "'different technological characteristics' means, with respect to a device being compared to a predicate device, that there is a significant change in the materials, design, energy source, or other features of the device from those of the predicate device." See section 513(i)(1)(B) of the FD&C Act.

[13] See 21 CFR 860.7(b).

[14] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-factors-consider-when-determining-substantial-equivalence-premarket-notifications-510k.

classified into class II, which may require, among other things, submission of certain performance data for the device.[15]

As with all devices reviewed through the 510(k) process, to reach a scientifically justified determination regarding SE for an implant, FDA conducts a robust and comprehensive evaluation of information included in a submission. If necessary to reach a determination regarding SE, FDA will request additional information.[16] FDA may rely on descriptive information, non-clinical data and/or clinical data, including postmarket data, to support SE determinations for implants.

In order to enhance transparency, consistency, and predictability of the review process and to promote the development of safe and effective 510(k) Implants, this guidance discusses considerations that are generally relevant to all types of implants subject to 510(k) requirements. It is intended to serve as a primary resource, used in conjunction with other guidances, to provide clarity and facilitate discussions regarding expectations for performance data that may be necessary to establish SE for implants. However, the type and quantity of performance data needed to support an SE determination for a particular device will vary depending on the device and/or device type, and on the differences from the predicate device. As noted above, the guidance also includes recommendations, such as those related to implant labeling, that are important to consider for any 510(k) Implant.

To help guide submitters, this guidance also refers to a wide variety of guidances and voluntary consensus standards that might apply to a particular submission. While this document discusses recommendations for implants generally, device-specific guidances may provide further specificity for a given device type.[17]

III. Scope

This guidance applies to implants for which a 510(k) is required. Implants subject to premarket approval, including those that may be eligible for the De Novo classification process, and implants that are exempt from the 510(k) requirements of the FD&C Act are outside the scope of this document.[18] An implant is defined in 21 CFR 860.3(d) as "a device that is placed into a surgically or naturally formed cavity of the human body." The regulation further specifies that "[a] device is regarded as an implant for the purpose of this part only if it is intended to remain implanted continuously for a period of 30 days or more, unless the Commissioner determines

[15] See section 513(a)(1)(B) of the FD&C Act.

[16] See 21 CFR 807.87(m). For more information on FDA's policies regarding requests for additional information, please see the FDA guidance, "Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/developing-and-responding-deficiencies-accordance-least-burdensome-provisions.

[17] To search for guidance documents, please see the database at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. Device-specific guidance documents can also be identified by searching for the relevant product code at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm.

[18] The De Novo classification process provides a pathway for certain new types of devices to obtain marketing authorization as class I or class II devices, rather than remaining automatically designated as a class III device, which would require premarket approval under section 513(f)(1) of the FD&C Act.

otherwise in order to protect human health." Therefore, the term "implant" in this guidance refers to devices intended to be implanted continuously for 30 days or more. However, FDA believes that many of the review considerations and associated recommendations in this guidance are also applicable to devices that are intended to remain implanted continuously for fewer than 30 days. For example, while a single catheter may only be used for a few days, a patient may routinely replace catheters as part of living with a chronic condition, and so cumulative patient exposure to a catheter may be significantly longer than 30 days and potentially lifelong. Therefore, we recommend that submitters of 510(k)s for devices intended to be implanted continuously for fewer than 30 days also consider the recommendations in this guidance. We note, however, that the amount and type of non-clinical and/or clinical data needed to support an SE determination may vary depending on the intended duration of implantation.

We recommend that submitters consider the general recommendations in this document and discuss specific questions with the appropriate review division associated with their device by submitting a pre-submission. Additional information on the pre-submission program is available in the FDA guidance, "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[19]

IV. Recommendations for 510(k) Implants

A. General Considerations

We recommend that submitters consider the following questions regarding the evidence and information that may be necessary to support an SE determination for a 510(k) Implant.

(1) What are the indications for use of the device?

FDA recommends that submitters carefully consider the indications for use of the device, taking into account the specific intended patient population, disease state, and conditions of use, when designing and conducting performance testing. For example, some 510(k) Implants may be indicated for palliative use in patients with limited mobility in a hospice care setting. Testing appropriate for these implants may be different than testing appropriate for implants indicated to remain permanently within an ambulating patient (e.g., a hip implant designed to accommodate repetitive mechanical loading). Similarly, FDA recommends that submitters provide performance data that are representative of the way in which the device is indicated to be used, including the anatomical location(s) for which it is indicated. For example, although orthopedic devices and dental devices may both interface with bone, the biochemical and biomechanical environment differ between dental and orthopedic devices and therefore data generated for an orthopedic device may not apply to a dental device.

510(k) Implants specifically indicated for use in pediatric populations may have unique considerations compared to implants indicated for use in adults. For purposes of this guidance, FDA considers pediatric patients to be individuals who are 21 years of age or younger (that is,

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

from birth through the 21st year of life, up to but not including the 22nd birthday).[20] Designing pediatric implants can be challenging: pediatric individuals are often smaller and more active than adults; body structures and functions may change throughout development; and pediatric individuals may be long-term device users, which raises additional concerns about device longevity and long-term exposure to implanted materials. FDA recommends that for 510(k) Implants indicated for use in pediatric patients, submitters follow the recommendations in FDA's guidance "Premarket Assessment of Pediatric Medical Devices"[21] (hereafter called the "Pediatrics Guidance"). Additionally, submitters should consider whether it is appropriate to extrapolate adult data for pediatric use. For example, certain orthopedic devices should be evaluated differently for pediatric patients versus adults due to differences in skeletal maturity. See FDA's guidance "Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices"[22] for more information. Clinical studies with pediatric patients must comply with applicable requirements to protect the rights, safety, and welfare of children[23] involved as study participants, including FDA regulations at 21 CFR Part 50, Subpart D. FDA's Pediatrics Guidance discusses these issues in more detail.

(2) What is the intended duration of implantation?

FDA recommends that submitters consider the intended duration of implantation or of patient exposure to the device when designing and conducting performance testing. While many implants are intended for permanent implantation, others are intended to be implanted for a period of time and then removed; still other implants are implanted and intended to degrade or resorb over time. Testing appropriate for a device that is intended to degrade over 30 days may be different than for a device that is intended to degrade over a year, or one that is not intended to degrade at all but is still subject to wear over its lifetime. In keeping with the least burdensome provisions,[24] in certain cases, FDA may consider whether results from shorter duration testing can be extrapolated to provide information about long-term performance. There may be implants for which non-clinical testing is suitably predictive of longer-term clinical performance, or for which 1-year performance is suitably predictive of 5-year performance. For devices expected to

[20] See section 520(m)(6)(E) of the FD&C Act (21 U.S.C. § 360j(m)(6)(E)(i)), which defines pediatric patients for purposes of a Humanitarian Device Exemption as age 21 years or younger at the time of diagnosis or treatment and specifies categories of pediatric subpopulations; see also 21 CFR 814.3(s).

[21] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/premarket-assessment-pediatric-medical-devices.

[22] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/leveraging-existing-clinical-data-extrapolation-pediatric-uses-medical-devices. The principles discussed in this guidance may be helpful regarding data considerations to support an indication for use of an implant in a pediatric population. We note, however, that if a change in the indications for use to add a pediatric indication constitutes a change in the intended use of the 510(k) Implant, the submitter would need to identify an appropriate predicate device with this same intended use in order to obtain clearance to market the device for the pediatric indication through the 510(k) process.

[23] FDA's human subject protection regulations define "children" as "persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted." See 21 CFR 50.3(o). Therefore, some "pediatric" patients, as that term is used in this guidance, may not meet the definition of "children."

[24] Please see the FDA guidance, "The Least Burdensome Provisions: Concept and Principles," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles, for additional discussion of FDA's policies and implementation of the least burdensome provisions in the FD&C Act.

be replaced repeatedly, we recommend that submitters consider testing reflective of the aggregate patient exposure.

FDA recommends that submitters consider whether testing should be provided to address safety and effectiveness questions associated with wear or degradation, whether intended or unintended. Depending on the device and/or device type and its differences from the predicate, a combination of bench performance testing (e.g., wear testing and characterization of wear debris) and biological evaluation (e.g., *in vivo* testing) may be needed to demonstrate SE. Information related to wear and degradation provided in a 510(k) should consider the expected lifespan of the implant and take into account the implant location, potential local and systemic biological responses to the implant, and potential degradation products. When designing and conducting performance testing, we recommend accounting for "worst-case" implantation conditions.

(3) What is the anticipated patient and physician experience with the implant?

FDA recommends that submitters consider both the patient and the physician experience with the implant in performing risk analysis and identifying performance testing that may be needed to demonstrate SE. Submitters should consider whether risks such as the following are relevant to their devices and are adequately addressed in their 510(k) submission. For example, the submitter should consider if certain features of its device could increase the risks identified below relative to the predicate:

- Risks associated with everyday activities (e.g., the effect to the implant during airport security screening or exposure to magnetic fields);
- Risks associated with ongoing or future medical care (e.g., magnetic resonance or interaction with other implants);
- Risks associated with reoperation or revision associated with the implant;
- Risks that may vary between different patient populations based on patient demographics;
- Risks associated with duration of use (e.g., physical discomfort or other adverse events);
- Risks associated with user interaction with the implant, including considerations regarding user training and instructions for ongoing maintenance of the device and/or device updates (e.g., software or firmware updates);
- Risks associated with device design/ergonomics and human factors issues related to use by a physician; and
- Risks associated with the implantation procedure, including shorter or longer operating time, infection, tissue damage caused by implantation, associated operative imaging radiation exposure, etc.

B. Non-Clinical Recommendations

This section highlights non-clinical issues that are generally relevant across 510(k) Implants and provides recommendations for related performance testing and information to include in a 510(k) submission. We recommend that submitters consider the non-clinical issues outlined below. We

believe this will lead to higher quality submissions and a more efficient review process. In addition, we believe that considering the risks identified below and related mitigation strategies during the design process is an important part of efforts to continuously improve the safety of 510(k) Implants. For information on recommended content and format of complete test reports for non-clinical bench performance testing in premarket submissions, generally, refer to FDA's guidance, "Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions,"[25] hereafter called the "Non-Clinical Bench Testing Guidance."

As explained above, the type and quantity of performance data needed to support an SE determination for a particular device will vary depending on the device and/or device type, and on the differences from the predicate device. Accordingly, it may not be necessary to provide all the information or conduct all the performance testing described below for a particular 510(k) submission. In cases where the submitter believes the information or testing described in this guidance does not apply to their device, we recommend that the submitter provides a rationale explaining why they believe the recommended information or testing is not applicable in the 510(k) submission.

(1) Biocompatibility

We recommend that a biocompatibility evaluation for an implant be performed in accordance with the FDA guidance, "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process,"[26] hereafter called the "Biocompatibility Guidance." In general, FDA's recommendations in the guidance align with the framework established in ISO 10993-1 for identification of the nature and duration of contact (e.g., cumulative effects with repeat use).[27] However, FDA's recommendations include several modifications to the evaluations identified in that standard. Attachment A of the Biocompatibility Guidance identifies a framework for developing a biocompatibility evaluation of a medical device, including an implant. For implants within the scope of this guidance (see Section III), regardless of the nature of body contact, we recommend that the following endpoints be considered, at a minimum, as part of a biocompatability evaluation:

- Cytotoxicity
- Sensitization
- Irritation or intracutaneous reactivity
- Acute systemic toxicity

[25] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommended-content-and-format-non-clinical-bench-performance-testing-information-premarket. Note that the Non-Clinical Bench Testing Guidance does not apply to test reports for biocompatibility evaluation, reprocessing or sterilization validation, human factors, software verification and validation, and computational modeling. Information on those assessments is detailed in different guidances. Test reports for clinical studies, animal studies, and studies evaluating the performance characteristics of in vitro diagnostic devices are also excluded from the scope of the Non-Clinical Bench Testing Guidance.

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

[27] See ISO 10993-1:2009, Clause 5.2 "Categorization by nature of body contact" and Clause 5.3 "Categorization by duration of contact."

- Material-mediated pyrogenicity

Additional endpoints are recommended based on the particular nature of body contact:

- Subacute/subchronic toxicity
- Genotoxicity
- Implantation
- Hemocompatibility
- Chronic toxicity
- Carcinogenicity
- Reproductive/developmental toxicity
- Degradation

Note that FDA's Biocompatibility Guidance recommends that biocompatibility endpoints, such as neurotoxicity and immunotoxicity, should be considered for devices where local or end organ toxicity assessments relevant to the implant location or toxicity issues of concern would not be assessed in a traditional biocompatibility study.

(2) Sterility and Shelf Life

a. Sterility and Pyrogenicity

FDA expects most implants to be sterilized prior to implantation for patient safety. We recommend that submitters consider FDA's guidance "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile,"[28] hereafter called the "Sterility Guidance," when preparing their 510(k) submission.

As stated in the Sterility Guidance, implants should also meet pyrogen limit specifications. Pyrogenicity testing is used to help protect patients from the risk of febrile reaction due to either gram-negative bacterial endotoxins or other sources of pyrogens (e.g., material-mediated pyrogens). Unless the complete removal of pyrogens can be established, devices should be labeled as "non-pyrogenic" or "meets pyrogen limit specifications" instead of "pyrogen free" to more accurately communicate the device's pyrogenicity risk to patients.

Note that the Sterility Guidance excludes from its scope sterilization processes for certain medical devices, including devices that incorporate materials of animal origin (i.e., human or animal tissues). For devices containing animal-derived materials, submitters should consider additional safety issues associated with disease transmission from the biological source. Please see FDA's guidance "Medical Devices Containing Materials Derived from Animal Sources (Except for *In Vitro* Diagnostic Devices)"[29] for additional information concerning the sourcing of animal tissues, viral inactivation, sterilization, and risk management for these devices.

[28] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-and-review-sterility-information-premarket-notification-510k-submissions-devices-labeled.

[29] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-devices-containing-materials-derived-animal-sources-except-vitro-diagnostic-devices.

b. Shelf Life and Packaging

Shelf life testing is typically conducted to support the proposed expiration date of a device through evaluation of the package integrity for maintaining device sterility and/or evaluation of any changes to implant device performance or functionality over time.

With respect to evaluating package integrity for maintaining device sterility, submitters should provide in their 510(k) submissions a description of the packaging, including how it will maintain the device's sterility, and a description of the package integrity test methods, but it generally is not necessary to include the package test data. 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 support package integrity and shelf life claims. We recommend submitters follow the methods described in the FDA-recognized series of consensus standards ANSI/AAMI/ISO 11607-1: *Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems* and ANSI/AAMI/ISO 11607-2: *Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly processes*, or request FDA feedback on appropriate package validation study methods through the Q-Submission Program[30] for packaging that falls outside of the scope of these standards.

With respect to evaluating the effects of aging on device performance or functionality, shelf life studies should evaluate the critical device properties and specifications to ensure the device will perform adequately and consistently during the entire proposed shelf life. To evaluate device functionality, we recommend that relevant bench tests are conducted. We further recommend that all tests that evaluate design components or characteristics that are potentially affected by aging are repeated using aged devices as the test article.

We recommend that submitters provide in their 510(k) submissions a summary of the test methods used for their shelf life testing, the results, and the conclusions drawn from their results. If submitters use accelerated aging of devices to conduct shelf life testing, we recommend that submitters specify the way in which the device was aged and provide a rationale to explain how the results of shelf life testing based on accelerated aging are representative of results based on a device aged in real time. In general, the stability testing results should demonstrate that device performance is comparable at both standard and elevated temperatures, and should demonstrate a linear correlation of accelerated aging data and real-time aging data. We recommend that accelerated aging of implants for shelf life/stability testing be conducted in accordance with the currently FDA-recognized version of ASTM F1980: *Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices* and that submitters specify the environmental parameters established to attain the proposed device expiration date.

For devices or components containing polymeric materials or coatings, testing on real-time, aged samples should be conducted to confirm the results of an accelerated aging study. This

[30] For details on the Q-Submission Program, please refer to the FDA 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.

confirmatory testing can generally be conducted in parallel with 510(k) review, with results documented to file in the design history file (i.e., complete test reports typically would not need to be submitted to FDA). FDA recommends that submitters contact the relevant review division for more information regarding suitable aging protocols based on the device and materials' composition, as some material properties of implants (e.g., animal-derived components) may not be appropriate for accelerated aging testing.

(3) Reprocessing and Cleaning

While implants are generally single-use, sterile devices, there may be implants that are reprocessed prior to implantation. For example, certain orthopedic devices may be provided non-sterile, but sterilized in a healthcare facility just prior to implantation (e.g., intervertebral body fusion devices). To ensure that the device is sterile, as intended, prior to implantation, the instructions provided for device reprocessing should be validated for the device. For devices intended to be reprocessed in this way, submitters should follow the recommendations in FDA's guidance "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling."[31]

(4) Software and Cybersecurity

Implants raise specific concerns associated with the duration of use and risks related to implant removal. Patients may live with an implant for years, or even permanently; therefore, long-lasting implants promote patient safety by minimizing the need for removal due to outdated software or other related vulnerabilities or failures.

For implants containing software, or devices containing software that communicate with implants, FDA recommends that submitters provide information in their 510(k) submission consistent with the recommendations in FDA's guidance, "Content of Premarket Submissions for Device Software Functions."[32]

We also recommend that submitters provide in their 510(k) submissions information regarding the device's cybersecurity risks and related controls to assure device functionality and safety, consistent with FDA's guidance entitled, "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices."[33] Additionally, cybersecurity risk should continue to be addressed throughout the total product lifecycle of these devices using the recommendations in the FDA guidance entitled, "Postmarket Management of Cybersecurity in Medical Devices."[34]

[31] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reprocessing-medical-devices-health-care-settings-validation-methods-and-labeling.
[32] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-device-software-functions.
[33] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-management-cybersecurity-medical-devices.
[34] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarket-management-cybersecurity-medical-devices.

Consideration of cybersecurity information is often necessary as part of a premarket submission and as part of an adequate software validation and risk analysis required by 21 CFR 820.30(g).[35]

The 510(k) premarket review process for implants containing software or devices containing software that communicate with implants will consider cybersecurity-related risks, including those that might necessitate the need for implant removal, in the context of comparing the new device to a predicate device. Specific consideration of cybersecurity risks early in the design process can significantly reduce or mitigate these risks (e.g., design with sufficient excess memory to allow for significant architecture updates that may be needed to maintain or reestablish security, or consideration for management of implants when End of Service and/or End of Life are reached).

(5) Electrical Safety and Electromagnetic Compatibility

FDA recommends that submitters of 510(k)s for implants with electrical components consider risks related to those electrical components, including the risks of electrical shock and electromagnetic interference with other devices, and provide information to support that those risks have been adequately mitigated. As an initial approach, FDA recommends that the electrical safety and electromagnetic compatibility (EMC) of implants with electrical components demonstrate conformity with consensus standards for electrical safety.

510(k) submissions for electrically-powered medical devices often reference FDA-recognized consensus national or international standards for EMC. For medical electrical equipment or medical electrical systems (as defined in the International Electrotechnical Commission (IEC) 60601-1 *Medical Electrical Equipment – Part 1: General Requirements For Basic Safety and Essential Performance*), submissions primarily reference the IEC 60601-1-2 standard or the equivalent United States (US) version.[36] In addition, there are device-specific consensus standards, or "particular" standards, under the IEC 60601-1 family (e.g., IEC 60601-2-X, where

[35] On February 23, 2022, FDA proposed to amend the device Quality System Regulation, 21 CFR Part 820, to align more closely with international consensus standards for devices (87 FR 10119; available at https://www.federalregister.gov/documents/2022/02/23/2022-03227/medical-devices-quality-system-regulation-amendments). Specifically, FDA proposed to withdraw the majority of the current requirements in Part 820 and instead incorporate by reference the 2016 edition of the International Organization for Standardization (ISO) 13485, Medical devices – Quality management systems for regulatory purposes, in Part 820. As stated in that proposed rule, the requirements in ISO 13485 are, when taken in totality, substantially similar to the requirements of the current Part 820, 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 FD&C Act. FDA intends to finalize this proposed rule expeditiously. When the final rule takes effect, FDA will also update the references to provisions in 21 CFR Part 820 in this guidance to be consistent with that rule.

[36] IEC 60601-1-2 Edition 3: 2007: *Medical Electrical Equipment - Part 1-2: General Requirements for Safety - Collateral Standard: Electromagnetic Compatibility - Requirements and Tests*, IEC 60601-1-2 Edition 4.0:2014: *Medical Electrical Equipment, Part 1-2: General Requirements for Basic Safety and Essential Performance – Collateral Standard: Electromagnetic Disturbances – Requirements and Tests*, AAMI/ANSI/IEC 60601-1-2: 2007/(R)2012: *Medical Electrical Equipment - Part 1-2: General Requirements for Safety - Collateral Standard: Electromagnetic Compatibility - Requirements and Tests*, and AAMI/ANSI/IEC 60601-1-2: 2014: *Medical Electrical Equipment - Part 1-2: General Requirements for Safety - Collateral Standard: Electromagnetic Disturbances - Requirements and Tests*.

X denotes a particular device standard). These particular standards may augment or supersede the specifications in the IEC 60601-1-2 standard.

Note that the IEC 60601-1 series of medical electrical equipment standards excludes implants. However, some implants are used with external devices, where the external device transmits energy to the implant; IEC 60601-1 may therefore apply to the external device and should be considered, if applicable. There are also consensus standards for certain active implantable medical devices that include information on EMC. One example is ISO 14708 *Implants for surgery – Active implantable medical devices – Part 3: Implantable neurostimulators*.

In cases where an implant may include radio frequency (RF) wireless technology, the recommendations in FDA's guidance, "Radio Frequency Wireless Technology in Medical Devices,"[37] should be considered.

In some cases, additional electrical safety and EMC testing may be needed to demonstrate SE, depending on the device and/or device type and the differences from the predicate device.

(6) Magnetic Resonance (MR) Compatibility

All implants have risks associated with exposure to an MR environment. FDA recommends that submitters consider the risks associated with their device when exposed to an MR environment and provide information to support that those risks have been adequately mitigated. FDA has provided recommendations on testing and labeling for implants for safety and compatibility in the MR environment in the FDA guidance "Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment."[38] FDA recognizes that implants are subject to various magnetic resonance-related hazards, including the following, and recommends that submitters consider how to mitigate these hazards and other relevant hazards, as applicable, when designing their devices:

- Magnetically induced displacement forces or torque, leading to unwanted movement of the medical device and tissue damage;
- Heating of the medical device itself and/or tissue adjacent to the medical device from RF and switching gradient fields (dB/dt) of the MR system;
- Vibrations or electric potential induction due to an MR system's pulsed gradient magnetic fields;
- Unintended tissue stimulation caused by rectified voltages generated by implants subject to RF exposure;
- Medical device malfunctions, either temporary or permanent, caused by exposure to an MR environment; and
- Corruption of MR images, including image artifacts, caused by the presence of metallic implants.

[37] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/radio-frequency-wireless-technology-medical-devices-guidance-industry-and-fda-staff.
[38] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/testing-and-labeling-medical-devices-safety-magnetic-resonance-mr-environment.

(7) Other Non-Clinical Performance Testing

Additional kinds of non-clinical performance testing are often needed to demonstrate SE of a 510(k) Implant to a predicate device. For example, materials used in implants can cause adverse biological responses depending on the material, implant duration, and implant location, that may not be identified in standard biocompatibility evaluations. Beyond the non-clinical evaluations discussed above, FDA recommends that submitters consider whether additional performance testing should be conducted to evaluate safety and effectiveness issues raised by differences between the new device and the predicate to demonstrate SE and help ensure that the device will perform safely and effectively across its expected lifespan. We recommend that all testing be conducted on final, finished devices. The amount and types of additional testing that should be considered can vary widely with the device or device type (e.g., testing considerations may vary based on the intended use of the device, implant duration, materials used, various failure modes related to implant geometry, manufacturing procedures and tolerances, and other unique implant characteristics) and with the differences between the new device and the predicate. Depending on these factors, some or all of the following testing may be applicable and needed to demonstrate SE, and the issues below should be considered when evaluating the risks associated with a 510(k) Implant:

- **Corrosion**: Corrosion is the deterioration of a metal due to electrochemical reactions with its environment. Multiple corrosion mechanisms (pitting, fretting, galvanic) can result in the release of metal ions or other byproducts. Most device alloys form a protective oxide layer that reduces corrosion, but the biochemical and mechanical stresses of the implant environment can damage the protective layer and increase corrosion. Given sufficient time, corrosion can weaken the structural integrity of a medical device to the point of device collapse and failure. To help understand how the host body responds to metal devices, FDA recommends a combination of non-clinical studies on corrosion, the release of metal ions, and device-specific fatigue testing as well as animal and clinical studies, in some cases, to assess biological responses. FDA uses this information to evaluate biocompatibility issues, such as risk of immunological response, tissue destruction or overgrowth, and other adverse reactions. For recommendations related to corrosion testing of implants or materials, please see the FDA guidance "Technical Considerations for Non-Clinical Assessment of Medical Devices Containing Nitinol."[39]

- **Fatigue**: Devices that are subject to repetitive stresses may fail and break. Implants should demonstrate adequate fatigue life under conditions simulating *in vivo* use to mitigate the risk of device breakage and failure during the expected lifespan of the device. FDA recognizes a variety of voluntary consensus standards to support mechanical fatigue tests for certain device types.[40]

[39] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-non-clinical-assessment-medical-devices-containing-nitinol. The submitter may consider whether the recommendations regarding performance testing in this guidance may be informative for implants containing other metals.

[40] See the FDA-Recognized Consensus Standards Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

- **Degradation**: Devices that are intended to degrade or resorb over time, or for which the technological characteristics are such that the device inevitably degrades after implantation, may lead to the release of degradation products into the local or systemic biological environment, causing inflammation or other biological reactions. An evaluation of the degradation profile of the device should be conducted under anticipated conditions of use, including worst-case scenario conditions, to understand the degradation profile over time and any conditions that may accelerate or modulate device degradation.

- **Particulate Characterization**: For implants subject to wear or degradation under repetitive motion or other processes, the characterization of particulates can be an important consideration. Therefore, the body's response to any associated degradation products, including those leached from wear debris, should be assessed. This may be accomplished via injecting degradation products from non-clinical testing or other representative particles into an appropriate animal model.[41] Alternatively, it may be possible to demonstrate that the particulates generated have similar size/number/shape of particles as other similar, legally marketed devices, and that the degradation products are not bioavailable. Finally, devices may introduce particulates outside of wear or degradation scenarios (e.g., particulates left over from manufacturing) that should be characterized. For example, infusion pump systems may introduce particulates in the solutions they infuse.

- **Coating Characterization**: The surfaces of implants may have a coating (e.g., in the case of orthopedic or dental devices, to improve joint fixation through a porous rough surface texture). Although coatings may represent a small portion of an implant by volume, coatings can have a significant impact on safety and effectiveness. For implants with coatings, FDA recommends that submitters provide in their 510(k), at a minimum, information on the intended function of the coating, as well as detailed information regarding the materials used in the coating or its generation, bond method and bond strength between a coating and its substrate, and salient material or biochemical properties of the coating, including thickness, pore size, and overall volume of porous coatings. Note that there may be other FDA guidances related to coatings that apply to your device. For example, for detailed information regarding coatings for orthopedic implants, see FDA's "Guidance Document for Testing Orthopedic Implants With Modified Metallic Surfaces Apposing Bone Or Bone Cement."[42]

[41] FDA supports the principles of the "3Rs" to replace, reduce, and/or refine animal use in testing, when feasible. We encourage submitters to consult with FDA if they wish to use a non-animal testing method that they believe is suitable, adequate, validated, and feasible. We will consider if a proposed alternative method could be assessed for equivalency to an animal test method. FDA also encourages the use of the Q-Submission Program to obtain feedback on the design of an animal study if an animal study is warranted.

[42] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-document-testing-orthopedic-implants-modified-metallic-surfaces-apposing-bone-or-bone.

- **Imaging Compatibility and Radiotherapy Compatibility**: After implantation, implants may need to be visualized by various imaging techniques to identify their position or orientation, including X-ray based techniques such as fluoroscopy or computed tomography (CT). Over their lifetime, many patients will also undergo imaging exams for other medical reasons. We recommend that implants be evaluated to determine whether the presence of the device impacts the image quality (e.g., image artifacts). For devices where detection via imaging is necessary to support future device removal or to support the safety of future surgical procedures, FDA recommends that you conduct radiopacity testing or other suitable imaging compatibility testing to demonstrate the device can be located. Additionally, as with MR, discussed above, other imaging exams and radiation therapy may also interact with implants. Even if the probability of an adverse event is low, we recommend that submitters assess the risks associated with exposure of the implant to other imaging exams and radiotherapy devices, including electronic component failure. FDA recommends that submitters consider the risks associated with their device when exposed to other types of imaging exams and radiation therapy and provide information to support that those risks have been adequately mitigated, such as by the device's technical design, inclusion of appropriate information in the labeling, or a combination of these mitigation strategies. We recommend that manufacturers provide evidence-based recommendations for patients and physicians in the implant labeling on what to do if a patient needs to undergo an imaging exam. Since it is not feasible to evaluate all imaging protocols that may be considered for patients after they receive an implant, FDA recommends that manufacturers specify in the implant labeling the methods and results of imaging safety testing that has been performed and other safety information relevant to an imaging exam that should be considered to help inform physicians.

- **Engineering Analysis**: It may be appropriate to evaluate some 510(k) Implants based on a combination of material specifications, finite element analysis (FEA), and/or other computational modeling approaches. A combination of engineering analyses and non-clinical testing may, in some cases, be sufficient to support SE, especially in circumstances where such analyses and testing have been validated to represent clinically-relevant failure modes. For more information on submitting computational modeling studies to support a device marketing submission, see the FDA guidance "Reporting of Computational Modeling Studies in Medical Device Submissions."[43]

- **Bench Model Testing**: While analyses of components and possible failure modes are important to a comprehensive understanding of device performance, in some cases, it may be necessary for submitters to provide the results of testing using model systems with representative materials, geometries, and/or other simulated use parameters to evaluate the implant and demonstrate SE. In such cases, FDA recommends that submitters provide a rationale for the test set up and a discussion of how testing with

[43] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-computational-modeling-studies-medical-device-submissions.

a bench model represents device performance under the anticipated conditions of use, considering worst-case scenarios, as appropriate.

Given the variety of implant types and unique considerations that different implants may raise, this guidance cannot provide recommendations regarding all bench-based performance tests that may be relevant for a specific implant. When considering performance testing to support an SE determination, submitters should consider the total product lifecycle experience with the implant type, available information on performance testing conducted for relevant predicate devices, device-specific guidance, and voluntary consensus standards applicable to a given device type.

(8) Animal Testing

In many cases, non-clinical bench performance testing alone may not be adequate to demonstrate SE. For example, engineering analyses and mechanical tests may provide objective measurements for comparing an implant's technological characteristics to those of a predicate device, but may not fully capture complexities related to clinical use to allow for a full assessment of how differences in technological characteristics affect safety and effectiveness. In these cases, evaluating *in vivo* performance may be the least burdensome way to demonstrate that an implant is SE to the predicate. While FDA's primary purpose in recommending an animal study is often to generate safety information, these studies are frequently used to provide insight into other performance measures that can impact effectiveness as well.

Below are some representative examples of situations where FDA may recommend animal testing:

- For implants that degrade, wear, or otherwise introduce foreign material into the local environment that is not intended to be removed (e.g., an implant that may abrade or damage tissue it contacts or against which it articulates);
- For implants where *in vivo* device migration or behavior is not well characterized in a bench model;
- To evaluate safety concerns where histological analysis is needed and human tissue biopsy is not feasible (e.g., local inflammation around the implant, or thrombogenicity/embolic effects in downstream tissues);
- To evaluate an anatomically similar clinical procedure/technique, where healthcare practitioner (HCP) training (e.g., knowledge and refinement of surgical technique, expertise in specialized procedures) is important for the device to be used safely; and
- To assess functional outcomes, including outcomes for devices intended to mitigate symptoms of injury or disease, where an animal model can be suitably extrapolated to human clinical performance.

When considering the appropriate number of animals to use and amount of data, FDA recommends considering the ethical principles of replacement, reduction, and refinement, as well as the least burdensome principles,[44] with the goal of using the minimum number of animals

[44] Please see the FDA guidance, "The Least Burdensome Provisions: Concept and Principles," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-

necessary to generate valid scientific evidence sufficient to demonstrate SE. We encourage submitters to take advantage of the Q-Submission Program[45] to ensure that their animal study protocol addresses relevant safety issues and contains elements that are appropriate for studies intended to support a regulatory submission (e.g., is consistent with applicable Good Laboratory Practice (GLP) regulations in 21 CFR Part 58).

FDA supports the principles of the "3Rs"[46] to replace, reduce, and/or refine animal use in testing, when feasible. We encourage submitters to consult with FDA if they wish to use a non-animal testing method that they believe is suitable, adequate, validated, and feasible. We will consider if a proposed alternative method could be assessed for equivalency to an animal test method. FDA also encourages the use of the Q-Submission Program[47] to obtain feedback on the design of an animal study if an animal study is warranted.

(9) Implant Device Design Considerations

Medical devices are manufactured from a wide variety of materials, using a variety of manufacturing processes. For certain implants, information regarding raw materials and critical aspects of manufacturing and processing steps, and how these impact device design and specifications, may be important to understanding the safety and effectiveness of the final, finished device relative to a predicate device. Examples where this information may be particularly important include:

- Implants composed of nitinol, as nitinol may release different amounts of nickel under fatigue (for more information, please see the FDA guidance "Technical Considerations for Non-Clinical Assessment of Medical Devices Containing Nitinol"[48]);
- Implants that may have different wear characteristics *in vivo* (e.g., please see the recommendations in the FDA guidance "Characterization of Ultrahigh Molecular Weight Polyethylene (UHMWPE) Used in Orthopedic Devices"[49]);
- Implants composed of degradable polymers, hydrogels, or other materials that may undergo material changes (e.g., form changes, degradation, *in situ* polymerization) *in vivo*;
- Implants for which residuals and impurities from manufacturing processes may remain in the packaged final finished form (e.g., animal derived materials following viral inactivation);

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and-principles, for additional discussion of FDA's policies and implementation of the least burdensome provisions in the FD&C Act.

[45] For details on the Q-Submission Program, please refer to the FDA 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.

[46] Animal Use Alternatives (3Rs), available at https://www.nal.usda.gov/animal-health-and-welfare/animal-use-alternatives.

[47] See footnote 45.

[48] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-non-clinical-assessment-medical-devices-containing-nitinol.

[49] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/characterization-ultrahigh-molecular-weight-polyethylene-uhmwpe-used-orthopedic-devices.

- Implants manufactured using additive manufacturing processes, as they may have different mechanical properties compared to devices made using traditional manufacturing methods; and
- Implants with biologically-derived materials, because information regarding animal husbandry and materials processing may be necessary to evaluate risks of disease transmission and the adequacy of viral inactivation.

We recommend that submitters consider providing certain information regarding materials, specifications, and design for such implants. Specifically, submitters should consider providing information regarding materials and their sourcing and critical processing information, such as reaction parameters and/or solvents used in processing or cleaning. This information may allow FDA to better understand the final, finished form of the implant and its similarities to and differences from the predicate device, for purposes of determining if the new device is SE to the predicate device. This information may also be particularly important when evaluating the effect of changes to the manufacturing process (e.g., for uses of novel manufacturing processes) or for changes to device design (e.g., incorporation of a new surface treatment for a metal implant) on the safety and effectiveness of a previously cleared device.[50]

C. Human Factors/Usability

Human factors information may be needed to demonstrate SE for certain 510(k) Implant devices. For example, as part of an SE determination, FDA may need to evaluate the impact of differences between the user interfaces of the new device and the predicate device on safety and effectiveness. In addition, differences between the new device and predicate device could affect how the device may be used (e.g., by additional users or in different use environments) in a way that raises safety and effectiveness issues.

As part of their design controls, manufacturers should conduct a use-related risk analysis that includes the risks specific to the device use and the measures implemented to reduce those risks.[51] ANSI/AAMI/ISO 14971, *Medical Devices – Application of risk management to medical devices,* defines risk as the combination of the probability of occurrence of harm and the severity of that harm. However, because probability is generally difficult to determine accurately for use errors, and in fact many use errors cannot be anticipated until device use is simulated or observed, the severity of the potential harm is more meaningful for determining the need to eliminate (design out) or reduce resulting harm. If the results of the use-related risk analysis indicate that use errors could cause serious harm to the patient or the device user, then we recommend that appropriate human factors/usability (HF/U) engineering processes are applied

[50] See 21 CFR 807.81(a)(3). For more information on evaluating changes to a previously cleared device, and whether such changes require the submission of a new 510(k), see the FDA guidance, "Deciding When to Submit a 510(k) for a Change to an Existing Device," available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device.

[51] Under 21 CFR 820.30(g), design validation must "ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions." It must also "include software validation and risk analysis, where appropriate."

according to the FDA guidance "Applying Human Factors and Usability Engineering to Medical Devices."[52]

FDA recommends that HF/U engineering processes are followed during 510(k) Implant development, focusing specifically on the user interface, where the user interface includes all points of interaction between the product and the user(s), including elements such as displays, controls, packaging, product labels, and directions for use. The goal is to ensure that the device user interface has been designed such that use errors that could cause harm, including by compromising medical care, are either eliminated or reduced to the furthest extent possible. This is particularly important to consider for devices with complex interfaces designed to be implanted by HCPs and implants that involve post-implantation management by the patient and/or HCP (e.g., programming, monitoring, maintenance). FDA recommends that you consider the workflow and interactions between different user groups and with the device throughout the overall lifecycle of the device (including maintenance and removal). In general, HF/U testing should capture all critical tasks, including those related to the relevant workflows and expected lifespan of your device. As an example, you should consider whether there are any surgical implantation completion time endpoints that, if not met, could potentially result in serious patient harm or death; if so, this endpoint should be included as a critical task to be tested in HF/U validation testing.

510(k) Implants may have specialized implantation instructions. Instructions and any training the manufacturer offers for the implanting physician should take into account how the device user interface and implantation technique(s) differ from similar device user interfaces and current standard of care, respectively. In any summative evaluation, the training provided to the human factors validation test participants should approximate the training that actual users would receive.

D. Clinical Performance Testing

While clinical data is not generally necessary to demonstrate SE in most 510(k) submissions, there are scenarios where clinical data may be needed to support an SE determination. The most common scenarios of when clinical data may be necessary in a 510(k) are discussed in the 510(k) Program Guidance[53] and the draft guidance, "Recommendations for the Use of Clinical Data in Premarket Notification [510(k)] Submissions,"[54] which, when final, will represent FDA's current thinking on that topic. FDA's draft guidance on "Recommendations for the Use of Clinical Data in Premarket Notification [510(k)] Submissions" is intended to clarify and provide additional context for situations when clinical data may be necessary to support SE. It discusses when such data may be needed in the context of a benefit-risk assessment conducted as part of determining if a new device with different technological characteristics that do not raise different questions of

[52] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices.
[53] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/510k-program-evaluating-substantial-equivalence-premarket-notifications-510k.
[54] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-use-clinical-data-premarket-notification-510k-submissions.

safety and effectiveness is as safe and effective as a legally marketed device, as well as other decision points in the 510(k) decision-making process.

E. Patient Experience Information

Where relevant to determinations of SE, FDA encourages the collection, analysis, and integration of patient experience data for implants. Patient experience data includes patient preference information (PPI) and patient-reported outcomes. Patients' perspectives on living with implants are most useful when they are relevant to the regulatory decision and reliably measured. Patient-reported outcome instruments facilitate the systematic collection of how patients feel, function, and survive as valid scientific evidence to support the regulatory and healthcare decision-making process. These instruments can be used to capture endpoints in clinical studies.

We recommend that submitters consider the FDA guidance entitled "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims"[55] and the FDA guidance entitled "Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation."[56]

CDRH has been a leader in incorporating PPI into regulatory decision-making. PPI may be used to help understand the relative value or the tradeoffs patients are willing to make among different benefits and risks associated with their condition and its diagnosis or management. PPI may be considered with the totality of evidence to inform an SE determination when evaluating the overall benefit-risk profile of an implant and whether that implant is as safe and effective as a predicate device.[57] For example, in the context of a 510(k), PPI has been used as valid scientific evidence to support clearance of expanded indications for use. We recommend that submitters considering use of PPI in a 510(k) Implant submission consult the FDA guidance entitled "Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling."[58] Though the aforementioned guidance is not intended to cover 510(k) submissions, the content and recommendations regarding features of well-designed and -conducted patient preference studies may be helpful for submitters who are planning to include PPI studies in 510(k) submissions as well.

[55] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims.
[56] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-selecting-developing-modifying-and-adapting-patient-reported-outcome-instruments-use.
[57] See the FDA guidance, "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-factors-consider-when-determining-substantial-equivalence-premarket-notifications-510k.
[58] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications.

F. Labeling and Other Recommendations

(1) Instructions for Use

A 510(k) submission must include proposed labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e), which requires a 510(k) to contain proposed labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for use. Given the nature of implants, they are generally prescription devices and are exempt from having adequate directions for lay use required under section 502(f)(1) of the FD&C Act (21 U.S.C. § 352(f)(1)) as long as the conditions in 21 CFR 801.109 are met. For instance, any labeling distributed by or on behalf of the manufacturer, packer, or distributor of the device that provides information for use of the device must include adequate information for the use of the device, including indications, effects, routes, methods, 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, including all purposes for which it is advertised or represented (21 CFR 801.109(d)).

Recognizing that implants are generally intended to remain with a patient for a long time, FDA expects that the physician would typically provide information to the patient about the implantation procedure and the benefits and risks of the device after implantation. FDA considers it important for manufacturers to provide information for the practitioner and also for patients about the risks of the device – including, but not limited to, information that can mitigate risks to health associated with layperson use errors after device implantation. This information is important to ensuring that implants are used safely and effectively across their expected lifespan. It is also important for practitioners to know how to educate their patients about risks that might arise throughout the implant's expected lifespan. As such, we recommend that manufacturers provide patient information in a format that the practitioner could easily convey directly to the patient (e.g., separate patient labeling), which will help to ensure the implant is used safely and effectively. In particular, permanent implants may have risks for which labeling is especially important for safety during everyday activities or other medical procedures, such as during a magnetic resonance imaging (MRI) procedure, radiation exposure, or security screening. Labeling submitted in a 510(k) for an implant should take into account these risks.

To the extent not already required under 21 CFR Part 801 or by applicable special controls, FDA recommends that all implants be accompanied by labeling that includes information on device operation, implantation instructions, and implant removal, if the device is intended to be removed.

(2) Implant Cards and Other Patient Information

As noted above, to help ensure continued safety over the expected lifespan of the implant, FDA considers it important for manufacturers to provide patients with 510(k) Implants information regarding their device. Certain information may be appropriate for inclusion in the form of an implant ID card for the patient or caregiver, while other information may be more appropriate for other forms of labeling. The choice to use a particular implant is often made by a physician or other licensed HCP based on their clinical experience and expertise. However, patients may not

always know which implants they have, how to best manage their implants, or if there are adverse events reported for that implant model. Implant information is also important for parents or other caregivers responsible for patient care outside of a healthcare facility. FDA recommends including the information listed below on an implant ID card or other labeling that can be provided to patients or their caregivers for a 510(k) Implant:

- Implant identifying information, including model name and manufacturer, and implant location;
- Salient details regarding device composition and patient contacting materials, including pertinent information related to any known allergic reactions;
- Information regarding how to report malfunctions or other adverse events to the manufacturer; and
- For MR conditional implants, all conditions for safe MR use as described in the FDA guidance "Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment,"[59] as well as the MR Conditional icon from the currently recognized version of ASTM F2503: *Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment*.

FDA recommends that manufacturers provide such information in a format that can be easily conveyed to patients. We encourage submitters to discuss patient labeling for 510(k) Implants with the appropriate FDA review division.

[59] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/testing-and-labeling-medical-devices-safety-magnetic-resonance-mr-environment.