The Special 510(k) Program

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on September 28, 2018.

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document regarding CDRH-regulated devices, contact the 510(k) Staff at 301-796-5640. For questions regarding this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD) in CBER at 1-800-835-4709 or 240-402-8010 or by email at ocod@fda.hhs.gov.

When final, this guidance will supersede the Special 510(k) policy in "The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications," issued on March 20, 1998.

U.S. FOOD & DRUG ADMINISTRATION

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

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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. Introduction

This draft guidance provides the Food and Drug Administration's (FDA) current thinking on premarket notifications (510(k)s) eligible to be reviewed as a Special 510(k). The intent of this guidance is to describe an optional pathway for certain well-defined device modifications where a manufacturer modifies its own legally marketed device, and rigorous design control procedures produce highly reliable results that can form, in addition to other 510(k) content requirements, the basis for substantial equivalence (SE). These well-defined modifications may include certain changes to indications for use that are not currently within the scope of the Special 510(k) Program. This draft guidance also clarifies the types of technological changes eligible to be reviewed as Special 510(k)s. Specifically, we are proposing to evaluate whether design and labeling changes can be reviewed under a Special 510(k) by focusing on whether the method(s) to evaluate the change(s) are well-established, and whether the results can be sufficiently reviewed in a summary or risk analysis format.

The Special 510(k) Program is consistent with FDA's statutory mission to protect and promote human health and FDA's commitment to helping patients gain timely access to new medical devices that are high quality, safe and effective by streamlining their review using efficient review practices consistent with least burdensome principles.[1] FDA believes expanding the Special 510(k) Program will also help the Agency meet its 510(k) Total Time to Decision (TTD) goals. In the Medical Device User Fee Amendments of 2017 (MDUFA IV) Commitment Letter from the Secretary of Health and Human Services to Congress,[2] FDA committed to shared outcome goals for 510(k) submissions. These shared outcome goals include decreasing the

[1] Section 1003 of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

[2] See 163 CONG. REC. S4729-S4736 (daily ed. August 2, 2017) (Food and Drug Administration User Fee Reauthorization), also available at https://www.fda.gov/downloads/ForIndustry/UserFees/MedicalDeviceUserFee/UCM535548.pdf.

average TTD for 510(k) submissions to 108 calendar days by Fiscal Year 2022. This draft guidance, when final, will provide consistency, clarity, and transparency to industry to describe when a Special 510(k) is appropriate. When final, this guidance will supersede the Special 510(k) policy in the "The New 510(k) Paradigm: Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications."[3]

For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database Web site at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

FDA's guidance documents, including this draft 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 guidance means that something is suggested or recommended, but not required.

II. Background

FDA established the Special 510(k) Program in 1998, as described in the guidance document "The New 510(k) Paradigm: Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications" ("New 510(k) Paradigm Guidance"). The program was intended to create a streamlined review process for minor changes subject to 510(k) submission requirements.

Design controls were added to the Quality System (QS) Regulation and have been in effect since June 1, 1997 (21 CFR 820.30, 61 FR 52602). The Special 510(k) Program leverages design controls requirements to support SE determinations through the reliance on risk analysis and verification and validation for existing devices. Special 510(k)s allow FDA and industry to rely on previous Agency review of detailed information, where appropriate, without altering any statutory or regulatory requirements related to the premarket notification process under sections 510 and 513 of the FD&C Act, and 21 CFR 807 Subpart E. The Special 510(k) Program provides a least burdensome approach to the review of certain changes to a manufacturer's own legally marketed predicate device ("existing device") because a Special 510(k) provides an efficient pathway for manufacturers to provide the minimum required information necessary to establish SE for a modified device. Because of this efficiency, FDA stated in the New 510(k) Paradigm Guidance that we intend to process Special 510(k)s within 30 days of receipt by the Document Control Center, rather than the 90 days for 510(k)s required by section 510(n)(1) of the FD&C Act.

Currently, the Special 510(k) Program focuses on the review of changes that do not affect the device's intended use or alter the device's fundamental scientific technology. Special 510(k)s

[3] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080189.pdf.

that include changes to the indications for use and/or changes in fundamental scientific technology compared to the manufacturer's own legally marketed predicate device[4] are routinely converted to Traditional 510(k)s. However, we now believe that an update to the Special 510(k) Program is appropriate to both clarify existing policy and expand on the types of changes eligible for the program to improve the efficiency of 510(k) review. This update includes certain changes to the indications for use and clarifications of the types of technological changes eligible to be reviewed as a Special 510(k). For more information about how FDA evaluates whether changes to the indications for use fall within the same intended use and how differences in technology affect FDA's SE determination process, see the FDA guidance document "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]."[5] Special 510(k)s remain subject to the content and format requirements for 510(k) submissions, 510(k) summary or 510(k) statement, and class III certifications (21 CFR 807.87, 807.90, 807.92, 807.93, and 807.94, respectively).

III. Special 510(k) Program

The Special 510(k) Program is intended to facilitate the submission, review, and clearance of a change to a manufacturer's own legally marketed predicate device (existing device) that is already authorized for commercial distribution through 510(k) clearance, preamendments status, reclassification, or through a granted De Novo classification request under section 513(f)(2) of the FD&C Act.

For certain device changes, FDA believes that rigorous design control procedures can produce reliable results that can form the basis for a SE determination without compromising the statutory and regulatory criteria for SE. Under design controls, manufacturers are required to conduct verification and validation (21 CFR 820.30(f) and (g)). Verification and validation include procedures to ensure that design outputs meet design inputs, and that devices conform to defined user needs and intended uses. The QS Regulation, 21 CFR Part 820, has records establishment and maintenance requirements that apply to design changes subject to design controls (21 CFR 820.30 and 820.180). These records must be made available to an FDA investigator upon request under section 704(e) of the FD&C Act.

When a manufacturer considers submitting a Special 510(k), FDA recommends that manufacturers consider all relevant guidance documents, special controls, or recognized voluntary consensus standards that apply to the device type or to a scientific topic area (e.g., biocompatibility or electromagnetic compatibility). For example, if a manufacturer is modifying a powered lower extremity exoskeleton device, then the manufacturer's design inputs should address the special controls that FDA has established for that device type under 21 CFR 890.3480. If a manufacturer modifies an *in vitro* diagnostic (IVD), the manufacturer's design inputs should include any relevant clinical and laboratory standards recognized by FDA. This

[4] A legally marketed predicate device is a device that was legally marketed prior to May 28, 1976 (i.e., preamendments), reclassified from class III to class II or class I, found substantially equivalent through a 510(k), or granted marketing authorization through the De Novo classification process.

[5] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.

guidance is not intended to supersede device-specific policies regarding the submission of complete test reports or Special 510(k) eligibility considerations that are identified in some device-specific technical guidances.

Subject to FDA's acceptance review in accordance with the guidance "Refuse to Accept Policy for 510(k)s,"[6] FDA generally reviews Special 510(k) submissions within 30 days of receipt. If a manufacturer submits a Special 510(k) that FDA does not believe is appropriate for review under the Special 510(k) Program, FDA intends to convert the submission to a Traditional 510(k) and notify the submitter.

When FDA converts a Special 510(k) to a Traditional 510(k), review by a supervisor and the CDRH 510(k) Staff or CBER Review Management Staff occurs to ensure programmatic consistency. FDA intends to provide justification to submitters when converting Special 510(k)s to Traditional 510(k)s. The 510(k) conversion process can result in delayed review because complete test reports are not reviewed in a Special 510(k), but are typically requested in a Traditional 510(k). This difference in content between Special and Traditional 510(k)s often results in FDA refusing to accept the 510(k) after conversion to a Traditional 510(k). Therefore, FDA recommends that both FDA and manufacturers apply the below considerations to determine eligibility for a 510(k) to be reviewed as a Special. If the 510(k) submission is accepted for a substantive review and later converted to a Traditional 510(k), the review clock continues into FDA's 90-day statutory deadline under section 510(n)(1) of the FD&C Act and remains subject to MDUFA performance goals for 510(k) submissions.

In accordance with 21 CFR 807.81(a)(3), and as explained in FDA's guidance "Deciding When to Submit a 510(k) for a Change to an Existing Device"[7] (510(k) Modifications Guidance), not all changes require a new 510(k) and manufacturers should use a risk-based assessment approach, as appropriate, to guide their analysis of whether a new 510(k) is likely required. If a manufacturer determines that a new 510(k) is likely required, then the flowchart provided in **Figure 1** and the companion text guide FDA staff and manufacturers through the decision-making process to determine eligibility of a particular submission for review as a Special 510(k).

Subject to the framework identified in sections III.A-E of this guidance, a design or labeling change to an existing device (including certain changes to the indications for use) may be appropriate for a Special 510(k) when:

- The proposed change is made and submitted by the manufacturer authorized to market the existing device;
- Performance data are unnecessary, or if performance data are necessary, well-established methods are available to evaluate the change; and
- All performance data necessary to support SE can be reviewed in a summary or risk analysis format.

[6] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM315014.

[7] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM514771.

These factors and associated decision making are summarized in **Figure 1.**

Although most Class I devices are not subject to the design control requirements of the QS Regulation, manufacturers of Class I (reserved) devices[8] may voluntarily elect to comply with the design controls regulation and submit Special 510(k)s.

[8] See section 510(l) of the FD&C Act.

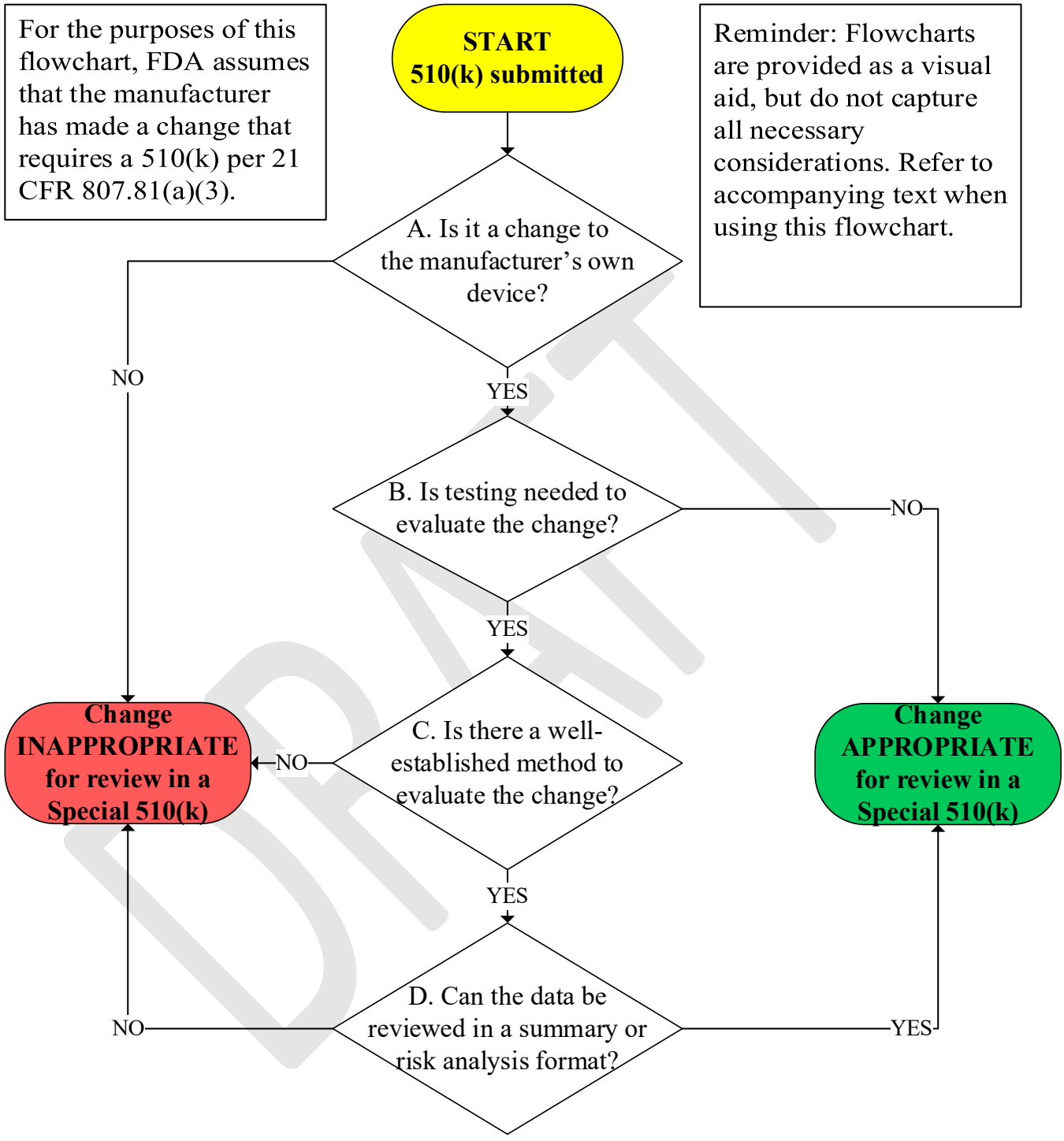

Figure 1. Special 510(k) flowchart.

A. Is it a change to the manufacturer's own device?

To be eligible for the Special 510(k) Program, the 510(k) should be for a change to the submitter's own legally marketed predicate device. This is because the Special 510(k) Program relies on the Agency's previous review of detailed information and a manufacturer who modifies its own legally marketed device is able to conduct the risk analysis and the necessary verification and validation activities to demonstrate that the design outputs of the modified device meet the design input requirements in a streamlined 510(k) submission. FDA intends to convert Special 510(k)s to Traditional 510(k)s when the submitter is not the manufacturer of the predicate device. In cases where the referenced 510(k) was submitted under a different name than the submitter, FDA recommends that the submitter include a statement affirming that they are the manufacturer of the predicate device.

B. Is testing needed to evaluate the change?

Manufacturers should use their design control procedures and consider the information necessary to support SE to determine whether testing is needed to evaluate the change. As part of design controls, manufacturers must establish and maintain procedures for the validation, or where appropriate, verification, of design changes before their implementation (21 CFR 820.30(i)). Verification and validation testing, however, may not be necessary to support SE. For example, FDA may receive a 510(k) from a manufacturer requesting clearance to label their device as Magnetic Resonance (MR) Unsafe after previously labeling their device as 'Safety in MR Imaging Not Evaluated.' As discussed in the FDA guidance document "Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment,"[9] MR Unsafe labeling is based on a scientific rationale and does not involve any performance data. In other cases, verification and validation testing may be necessary to support changes in indications for use and design. For example, identification of a new environment of use in the indications for use or labeling without changes to the intended users or user interface may result in the need for additional verification and validation testing to support continued electromagnetic compatibility and other performance characteristics.

In cases where manufacturers determine under their design control procedures that no additional verification or validation testing is necessary to evaluate a change that otherwise requires submission and clearance of a 510(k), manufacturers may submit these changes as a Special 510(k) with a scientific rationale supporting their conclusion that no test data is necessary. When FDA does not agree with the manufacturer's assessment about whether performance data will be necessary to support a SE determination, FDA intends to continue with the additional Special 510(k) eligibility factors discussed in sections III.C-E before considering whether the 510(k) submission should be converted to a Traditional 510(k).

C. Is there a well-established method to evaluate the change?

[9] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM107708.

FDA believes that in order to qualify for the Special 510(k) Program, well-established methods should be available to evaluate the change under design controls. The Special 510(k) Program should not include the submission and review of complete test reports, but summary information generated from well-established methods. Well-established methods are those that have been established for evaluation of the device, device type, or scientific topic area, and are validated according to scientific principles. Significant deviations to the protocol or acceptance criteria of a well-established method can result in the 510(k) being no longer eligible for review as a Special 510(k). FDA believes that well-established methods include:

- The submitter's methods, protocols, and acceptance criteria used to support the previously cleared 510(k) that can be applied to the subject 510(k);
- Methods found in an FDA-recognized voluntary consensus standard; or
- Widely available and accepted methods published in the public domain, scientific literature, or found acceptable by FDA through a 510(k)-clearance, a granted De Novo classification request, or premarket application (PMA) approval.

FDA recommends that manufacturers describe why the methods applied to evaluate the impact of the changes included in a Special 510(k) are well-established. This description can include a discussion that the methods and acceptance criteria were the same as the predicate device and are relevant to the change under review. Such methods should rely on established acceptance criteria, or a comparison of performance to the predicate device and/or reference device[10] under the same testing methodology. For example, Traditional 510(k)s often identify the verification and validation approaches that are used for software such that many subsequent software changes may occur under a Special 510(k). To remain eligible for a Special 510(k), *all* test methods used to support the 510(k) should be well-established.

Submissions that use methods that rely on clinical studies or animal data to support SE are not typically appropriate for the Special 510(k) Program because the methodologies and endpoints vary, are often dependent on the condition(s) being studied, and cannot be appropriately summarized. When FDA does not agree that a well-established method exists to evaluate the change, FDA intends to convert the Special 510(k) to a Traditional 510(k).

D. Can the data be reviewed in a summary or risk analysis format?

To be eligible for a Special 510(k), the results from verification and validation associated with design or labeling changes should be able to be placed in a summary or risk analysis format without losing information necessary to support SE. Complete test reports should not be submitted in a Special 510(k). If complete test reports are submitted, FDA intends to assess

[10] Consistent with "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]" (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443), reference devices are other legally marketed devices that may be used to support scientific methodology or standard reference values for Decisions 5a and 5b of the 510(k) decision-making flowchart after a manufacturer successfully navigates through Decision Point 4 using a single predicate device.

whether the information can be reviewed in a summary format before converting to a Traditional 510(k). This assessment should occur during FDA's acceptance review in accordance with the 510(k) Refuse to Accept policy. Given the shorter timeframe for review of Special 510(k)s, if the submitter cannot provide summary test reports within the timeframe identified during interactive review, FDA intends to convert the submission to a Traditional 510(k).

FDA does not believe that data can be summarized when the SE determination will depend on the Agency's interpretation of the underlying data, such as images, raw graphs, or line item data. For example, FDA does not believe that data can be placed in a summary format when fatigue to failure testing involves the review of graphical images to interpret the failure modes observed. In limited circumstances where a small number of representative images for non-clinical performance are submitted, such would be appropriate for a Special 510(k). For example, representative images used to demonstrate radiopacity for guidewires or devices with radiopaque markers may be included in a Special 510(k). FDA has included anticipated common scenarios for when data may be unable to be summarized without loss of information in section III.E.

FDA believes that the results from risk management activities, including relevant verification and validation information, produced under design controls procedures can be used to support a SE determination of the Special 510(k) under the conditions described in this guidance. As described in Appendix A, this information should include a concise summary of design control activities and verification and validation testing required to comply with 21 CFR 820.30 based on a manufacturer's procedures. To have sufficient information to establish SE under a Special 510(k), your summary or table should describe, for each change that required a 510(k), the specific verification and validation activities, how the methods applied are appropriate for the change, acceptance criteria, any changes or deviations from testing methods in previous 510(k) submissions, and a summary of the results. When FDA does not agree that the performance data can be summarized, FDA intends to convert the submission to a Traditional 510(k). This should typically occur during the RTA review.

In accordance with the flexibility of the QS Regulation, there can be different approaches to the summary of design control activities and verification and validation that can be included in a Special 510(k). This can include redlined software requirements specification (SRS) and design documentation that clearly documents the changes that were made, consistent with well-established methods. Manufacturers can include their risk management documentation, such as a Design Failure Modes and Effects Analysis (DFMEA), along with a separate summary of supporting verification and validation. Manufacturers could also summarize their risk management activities with the specifics of verification and validation that provide information necessary for FDA's SE determination process. To facilitate FDA review, different approaches to the summary of design control activities and verification and validation should highlight and focus on the information that is relevant to the changes under review. FDA has provided examples in Appendix C of this guidance.

E. Additional considerations

Because FDA intends to review a Special 510(k) within 30 days, FDA believes there are some circumstances when it is not appropriate to submit a Special 510(k), including:

- When evaluation of the change(s) to the device involve several different scientific disciplines;
- For multiple devices with unrelated changes;
- When a recent QS inspection has resulted in the issuance of a violative inspection report identifying observations related to design controls that are relevant to the design changes under review in the 510(k). If a manufacturer believes such violations are unrelated to the subject 510(k), they should provide a rationale for why the 510(k) should still be eligible for review under the Special 510(k) Program;
- When Special 510(k)s are submitted for common scenarios that FDA anticipates a review of complete test reports will be necessary to establish SE, such as:
    - Changes to the indications for use that are supported by clinical, animal,[11] or cadaver data;
    - Use of novel sterilization methods as described in the FDA guidance "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile;"[12]
    - Changes to introduce *initial* MR Conditional labeling, or *significant deviations* from the test methods used to establish MR Conditional labeling in the original 510(k);
    - Change from single-use to reusable when reprocessing validation or human factors data should be provided; and
    - Use of chemical characterization with toxicological risk assessment to address biocompatibility.
- For a reprocessed single-use device (SUD) that requires the submission of cleaning, sterilization, and functional performance validation data under section 510(o) of the FD&C Act and in FDA's Federal Register notice published in 70 FR 56911 requiring the submission of SUD validation data; and
- For changes that could affect the reprocessing of reusable devices required by section 510(q) of the FD&C Act to include reprocessing validation in 510(k) submissions. These devices are identified in FDA's Federal Register notice published in 82 FR 26807 and Appendix E of the FDA guidance "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling."[13]

[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.

[12] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM109897.

[13] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM253010.

Appendix A. Recommended content of a Special 510(k)

A Special 510(k) should include:

- A coversheet clearly identifying the submission as a "Special 510(k): Device Modification;"
- The name of the manufacturer's legally marketed (existing) device and the 510(k) number under which it was cleared;
- Information required under 21 CFR 807.87, including a description of the modified device, a comparison to the cleared device, the indications for use of the device, and the proposed labeling for the device. To help ensure that FDA has a complete understanding of the device under review, this should include:
    - A detailed description of the change(s) made to the device that resulted in the submission of a new 510(k). When certain information remains unchanged, the submission should clearly state that no changes were made;
    - A comparison of the modified device to the cleared device in a tabular format;
    - Clean and redlined copies of documents that were updated because of the device change (e.g., labeling, risk analysis); and
    - Other changes to labeling or design since the most recently cleared 510(k) (i.e., those that did not require submission of a new 510(k)) that would have been documented as part of the original 510(k), in accordance with the recommendations in the guidance "Deciding When to Submit a 510(k) for a Change to an Existing Device."[14]
- If the Special 510(k) includes reference(s) or a declaration of conformity to a recognized voluntary consensus standard, we recommend that you consult the FDA guidance "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices;"[15]
- A concise summary of the design control activities. Appendix C provides examples of narratives and a table of this information that has been historically provided. FDA considers the information generated from the design control activities to be "appropriate supporting data" within the meaning of 21 CFR 807.87(g). Your risk management file may already contain some of the design control activities in a risk analysis format. In lieu of creating a new table that addresses all recommended content, you may instead submit your risk analysis as an attachment or appendix to your submission. This summary should include the following:
    - Identification of the risk analysis method(s) used to assess the impact of the change on the device and the results of the analysis;
    - Identification of the device change(s);
    - Identification of all risks associated with each device change, including identification of risks that are considered new because of the change; and

[14] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM514771.
[15] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM396568.pdf.

- Risk control measures to mitigate identified risks (e.g., labeling, verification).

- Based on the risk analysis, an identification of the verification and/or validation activities required to comply with 21 CFR 820.30. This identification should include a summary of test methods, acceptance criteria, and results, and why each is adequate to establish SE. When the results are quantitative in nature, the submission should include basic descriptive statistics, such as the mean, standard deviation, and range of the data. Notable protocol deviations observed during testing should be provided and justified, if applicable. When appropriate, the summary of verification and validation should include:
  - For non-standardized test methods only:
    - A reference to the protocol used for the existing device with an identification of any notable differences (e.g., protocol, test conditions, pre-defined acceptance criteria, sample size) from the previous 510(k). If protocol changes were made, the results summary should describe why the test methods, acceptance criteria, and results support SE.
  - For test methods described in an FDA-recognized standard:
    - Cross-reference to the relevant section of the Special 510(k) where a declaration of conformity was submitted under section 514(c) of the FD&C Act; and
    - When a declaration of conformity is not submitted, the standard does not have explicit acceptance criteria, or the standard has multiple testing options for which FDA should review to assess conformity, the submitter should provide a description of methods with deviations, selected options and the reasons for their selection, acceptance criteria, and a results summary. See the FDA guidance "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices"[16] for more information about the use of voluntary consensus standards.
- Indications for Use form (Form FDA 3881);[17] and
- A signed statement by the manufacturer's designated individual(s) responsible for design control activities that includes:
  - A statement that, as required by the risk analysis, all design verification and validation activities were performed by the designated individual(s) and the results demonstrated that the predetermined acceptance criteria were met; and
  - A statement that the submitter has complied and is not currently in violation of the design control procedure requirements as specified in 21 CFR 820.30 and the records are available for review, upon request.

[16] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM396568.pdf.

[17] https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM360431.

Appendix B. Examples of changes

These examples are for illustrative purposes and may not include all details for each change. The examples are intended to help FDA staff and industry determine which changes can be submitted as a Special 510(k).

Example B.1

Change: The submitter wants to change their 2-D chest x-ray image processing software to add a feature that highlights nodules in the lung. The submitter is also requesting to modify their indications for use to describe this new software feature that now quantifies and characterizes information about the nodules.

Relevant Questions:

A - *Is it a change to the manufacturer's own device?*
Yes, the submitter is the manufacturer of the predicate device.

B - *Is testing needed to evaluate the change?*
Yes. Clinical testing should be provided to support marketing clearance for such a change in the indications for use to assess the performance of the software on patients with and without nodules in the lung. This clinical testing should support that the software can successfully quantify and characterize information about the nodules.

C - *Is there a well-established method to evaluate the change?*
No. There are no well-established methods identified in the predicate's submission for the evaluation of lung nodules, consensus standards, or widely available and accepted methods published in the public domain to address the change in the indications for use.

D - *Can the data be reviewed in a summary or risk analysis format?*
N/A.

Decision: Change cannot be reviewed in a Special 510(k).

Example B.2

Change: The submitter wants to add wireless control capabilities to their bilevel positive airway pressure (BiPAP) device intended to treat patients with obstructive sleep apnea.

Relevant Questions:

A - *Is it a change to the manufacturer's own device?*
Yes, the submitter is the manufacturer of the predicate device.

B - *Is testing needed to evaluate the change?*
Yes. The predicate device did not contain and was not tested for wireless functionality. Verification and validation should be conducted to ensure that the BiPAP has acceptable wireless quality of service, coexistence, cybersecurity, and maintains electromagnetic

compatibility (EMC) in its intended environment of use, as described in the FDA guidance "Radio Frequency Wireless Technology in Medical Devices."[18]

C - *Is there a well-established method to evaluate the change?*
No. While International Electrotechnical Commission (IEC) 60601-1-2[19] can be used to support EMC, this standard does not at present adequately address wireless technology EMC. Additionally, there are not well-established methods in an FDA-recognized voluntary consensus standard or in the manufacturer's previous 510(k) that address the methods to evaluate the addition of wireless control for this BiPAP. The test methods vary depending on the wireless quality of service necessary for the device's intended use and environment of use.

D - *Can the data be reviewed in a summary or risk analysis format?*
N/A.

Decision: Change cannot be reviewed in a Special 510(k).

Example B.3

Change: The submitter wants to modify their general indications for delivering illumination and laser energy for photocoagulation to include specific clinical applications for treatment of retinopathy.

Relevant Questions:
A - *Is it a change to the manufacturer's own device?*
Yes, the submitter is the manufacturer of the predicate device.

B - *Is testing needed to evaluate the change?*
Yes. Clinical testing is typically provided to support marketing clearance for such a change in the indications for use. The requested change in the indications for use now identify a specific disease condition. The clinical outputs have changed from general coagulation of blood vessels to treatment of retinopathy. Clinical testing should be conducted to assess new outcomes such as decrease in vision impairment, whereas the predicate assessed the general outcome of successful vessel coagulation.

C - *Is there a well-established method to evaluate the change?*
No. There is no well-established method identified in the predicate's submission or a consensus standard to evaluate clinical endpoints for this device. The SE determination rests on a review of the underlying clinical performance data.

D - *Can the data be reviewed in a summary or risk analysis format?*
N/A.

[18] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM077272.
[19] IEC 60601-1-2 Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests.

Decision: Change cannot be reviewed in a Special 510(k).

Example B.4

Change: The submitter currently markets a cardiac output monitor that is cleared for use with their endotracheal tube. The submitter is requesting clearance to modify the indications for use so that the submitter's cardiac output monitor can be used with their 510(k)-cleared endobronchial tube that also includes integrated electrodes for sensing.

Relevant Questions:

A - *Is it a change to the manufacturer's own device?*
Yes, the submitter is the manufacturer of the predicate device.

B - *Is testing needed to evaluate the change?*
Yes. Verification should be completed to demonstrate that the newly identified tube can be used for cardiac output by impedance cardiography as safely and effectively with the monitor as the endotracheal tube does with the monitor, and that the monitor and endobronchial tube both continue to function as intended.

C - *Is there a well-established method to evaluate the change?*
Yes. The submitter stated that because the bench testing to verify the change uses the same protocol as the predicate device, and that the methods and acceptance criteria have not changed, the protocol is considered a well-established method. In addition, this type of connection for the specified tube and monitor has been included in other cleared 510(k) submissions for this device, and the submitter referenced these devices in their submission.

D - *Can the data be reviewed in a summary or risk analysis format?*
Yes. The submitter stated that the protocol, methods and acceptance criteria were not modified from those used in the predicate submission to evaluate the change. The existing methods were appropriate to evaluate the change because the same cardiac output parameters are intended to be monitored and displayed. The acceptance criteria and a summary of the results were provided for each test. The results can be summarized because the SE determination does not depend on the Agency's interpretation of the underlying data, such as images, raw graphs, or line item data.

Decision: Change can be reviewed in a Special 510(k).

Example B.5

Change: The company is requesting clearance to change the environment of use identified in their labeling for their transcutaneous electrical nerve stimulation (TENS) device from a professional healthcare facility only to both professional healthcare facility and home use. The device is still intended to be used under the direction and supervision of a healthcare professional.

Relevant Questions:

A - *Is it a change to the manufacturer's own device?*

Yes, the submitter is the manufacturer of the predicate device.

B - *Is testing needed to evaluate the change?*
Yes. There are different acceptance criteria for electrical safety and electromagnetic compatibility (EMC) to address home use.

C - *Is there a well-established method to evaluate the change?*
Yes. For example, the FDA-recognized standard methods American National Standards Institute/Association for the Advancement of Medical Instrumentation (ANSI/AAMI) ES60601-1[20] and IEC 60601-2-10[21] address basic safety and essential performance, EMC (IEC 60601-1-2[22]), and basic safety for home use devices (ANSI/AAMI HA60601-1-11[23] or IEC 60601-1-11[24]), along with the International Special Committee on Radio Interference (CISPR) 11 emission limits for Group 1 and Class B. The manufacturer provided their statement of essential performance and associated device-specific acceptance criteria.

D - *Can the data be reviewed in a summary or risk analysis format?*
Yes. The particular standard used was identified. The acceptance criteria and results were summarized in a tabular format. A justification was provided for all results that were outside the bounds of an acceptance range or differed from the predicate. The results can be summarized because the SE determination does not depend on the Agency's interpretation of the underlying data, such as images, raw graphs, or line item data.

Decision: Change can be reviewed in a Special 510(k).

Example B.6

Change: The submitter is requesting clearance to market metal bone screws terminally sterilized via gamma irradiation that were previously only supplied non-sterile. The indications for use and materials of construction remain unchanged from the clearance for the manufacturer's existing device.

Relevant Questions:

A - *Is it a change to the manufacturer's own device?*
Yes, the submitter is the manufacturer of the predicate device.

[20] ANSI/AAMI ES60601-1 Medical electrical equipment - Part 1: General requirements for basic safety and essential performance.
[21] IEC 60601-2-10 Medical electrical equipment - Part 2-10: Particular requirements for the basic safety and essential performance of nerve and muscle stimulators.
[22] IEC 60601-1-2 Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests.
[23] ANSI/AAMI HA60601-1-11 Medical electrical equipment Part 1-11: General requirements for basic safety and essential performance - Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment.
[24] IEC 60601-1-11 Medical electrical equipment - Part 1-11: General requirements for basic safety and essential performance - Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment.

B - *Is testing needed to evaluate the change?*
Yes. The sponsor should include an evaluation of biocompatibility, sterility, pyrogenicity, package integrity, and shelf-life to support the proposed change. Nonclinical testing to address performance of the device outside of biocompatibility, sterility, packaging, and shelf-life is not necessary based on a scientifically-based rationale from the submitter that gamma irradiation does not impact the material composition or properties of this metallic device. Based on the recommendations in 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,'"[25] the sponsor provided a valid scientifically-based rationale supporting the decision that no further biocompatibility testing was necessary to address this change.

C - *Is there a well-established method to evaluate the change?*
Yes. The FDA guidance "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile"[26] indicates that gamma irradiation is an Established Sterilization Method, Established Category A. The FDA-recognized standards International Organization for Standardization (ISO) 11137-1[27] and ISO 11137-2[28] can be used to support the sterilization validation. Pyrogenicity can be assessed using the recommendations discussed in the FDA guidance documents "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile"[29] and "Pyrogen and Endotoxins Testing - Questions and Answers,"[30] and the methods described in the FDA-recognized versions of ANSI/AAMI ST72[31] and United States Pharmacopeia (USP) <161>.[32] Package integrity and shelf-life for this change can be evaluated through accelerated aging using American Society for Testing and Materials (ASTM) F1980[33] and package integrity testing for visual integrity, seal integrity, and seal strength using the methods identified in ASTM F1886/F1886M,[34] ASTM F2096,[35] and ASTM F88/F88M,[36] respectively.

D - *Can the data be reviewed in a summary or risk analysis format?*

[25] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM348890.
[26] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM109897.
[27] ISO 11137-1 Sterilization of health care products - Radiation - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices.
[28] ISO 11137-2 Sterilization of health care products - Radiation - Part 2: Establishing the sterilization dose.
[29] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM109897.
[30] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM310098.pdf.
[31] ANSI/AAMI ST72 Bacterial endotoxins - Test methods, routine monitoring, and alternatives to batch testing.
[32] USP <161> Medical Devices - Bacterial Endotoxin and Pyrogen Tests.
[33] ASTM F1980 Standard guide for accelerated aging of sterile barrier systems for medical devices.
[34] ASTM F1886/F1886M Standard test method for determining integrity of seals for flexible packaging by visual inspection.
[35] ASTM F2096 Standard test method for detecting gross leaks in packaging by internal pressurization (bubble test).
[36] ASTM F88/F88M Standard test method for seal strength of flexible barrier materials.

Yes. The methods are standardized, and the results can be summarized because the SE determination does not depend on the Agency's interpretation of the underlying data, such as images, raw graphs, or line item data. The FDA guidance "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile"[37] discusses how sterilization validation, package integrity, and pyrogenicity information can be summarized in 510(k) submissions.

Decision: Change can be reviewed in a Special 510(k).

Example B.7

Change: The submitter wants to increase the number of channels for their receive-only magnetic resonance (MR) coil.

Relevant Questions:

A - *Is it a change to the manufacturer's own device?*
Yes, the submitter is the manufacturer of the predicate device.

B - *Is testing needed to evaluate the change?*
Yes. Consistent with the FDA guidance "Submission of Premarket Notifications for Magnetic Resonance Diagnostic Devices,"[38] performance testing should be provided for the increased number of coils to address image quality metrics and patient safety from surface heating. For a receive-only coil, this should include signal-to-noise ratio, image uniformity, and coil surface heating assessments.

C - *Is there a well-established method to evaluate the change?*
Yes. There are standard test methods for MR devices such as FDA-recognized consensus standards National Electrical Manufacturers Association (NEMA) MS 9[39] and NEMA MS 6.[40] The predicate device used the same standards, protocols, and acceptance criteria.

D - *Can the data be reviewed in a summary or risk analysis format?*
Yes. The methods can be summarized and the results can be placed into a summary format for each test conducted because the SE determination does not depend on the Agency's interpretation of the underlying data, such as images, raw graphs, or line item data. While a small, representative subset of sample images were included, the manufacturer did not include a complete dataset of images that would be necessary for FDA to evaluate SE. Instead, the manufacturer provided a statement from a U.S. Board Certified radiologist attesting that images produced by the device are of sufficient quality for diagnostic use.

Decision: Change can be reviewed in a Special 510(k).

[37] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM109897.
[38] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM454613.
[39] NEMA MS 9 Characterization of Phased Array Coils for Diagnostic Magnetic Resonance Images.
[40] NEMA MS 6 Determination of Signal-to-Noise Ratio and Image Uniformity for Single-Channel Non-Volume Coils in Diagnostic MR Imaging.

Example B.8

Change: The submitter wants to add analytical sensitivity data for the new H7N9 influenza strain to their diagnostic test.

Relevant Questions:

A - *Is it a change to the manufacturer's own device?*
Yes, the submitter is the manufacturer of the predicate device.

B - *Is testing needed to evaluate the change?*
Yes. Analytical reactivity testing should be provided to address the addition of analytical sensitivity data for the new strain into the labeling.

C - *Is there a well-established method to evaluate the change?*
Yes. The same protocol as the original submission was used for collecting and assessing the data. The acceptance criteria were not altered from those used for the original device. No additional types of evaluation are needed.

D - *Can the data be reviewed in a summary or risk analysis format?*
Yes. The results can be summarized because the SE determination does not depend on the Agency's interpretation of the underlying data, such as images, raw graphs, or line item data. In addition, the methods and acceptance criteria are unmodified from the predicate testing.

Decision: Change can be reviewed in a Special 510(k).

Example B.9

Change: The submitter wants to change the labeling of their blade-form endosseous dental implant from "Safety in MRI Not Evaluated" to "MR Conditional."

Relevant Questions:

A - *Is it a change to the manufacturer's own device?*
Yes, the submitter is the manufacturer of the predicate device.

B - *Is testing needed to evaluate the change?*
Yes. Non-clinical performance testing to support SE should be provided by manufacturers seeking MR Conditional labeling for a device that contains metallic components. The FDA guidance document "Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment"[41] provides recommendations for such testing.

C - *Is there a well-established method to evaluate the change?*

[41] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM107708.

Yes. There are FDA-recognized voluntary consensus standards such as ASTM F2503,[42] ASTM F2052,[43] ASTM F2213,[44] ASTM F2182,[45] and ASTM F2119[46] for MR compatibility testing of passive implants.

D - *Can the data be reviewed in a summary or risk analysis format?*
No. Although there are consensus standards for all test methods, FDA does not believe this data can be summarized because the SE determination will depend on FDA's interpretation of the underlying data to support the MR Conditional label. This is referenced in section III.E as an anticipated common scenario for when data may be unable to be summarized.

Decision: Change cannot be reviewed in a Special 510(k).

Example B.10

Change: The submitter wants to increase the size of their MR Conditional blade-form endosseous dental implant from 4mm long to 5mm long.

Relevant Questions:
A - *Is it a change to the manufacturer's own device?*
Yes, the submitter is the manufacturer of the predicate device.

B - *Is testing needed to evaluate the change?*
Yes. FDA has designated special controls for blade-form endosseous dental implants in 21 CFR 872.3640(b)(2)(i)-(ix) that must be addressed, including performance testing for fatigue, corrosion, biocompatibility evaluation, sterility, and evaluation of the device in the MR environment. The FDA guidance document "Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment"[47] recommends that manufacturers seeking MR Conditional labeling for a device that contains metallic components provide non-clinical performance testing to support SE. The manufacturer also submitted a biocompatibility evaluation based on a scientific justification.

C - *Is there a well-established method to evaluate the change?*

[42] ASTM F2503 Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment.
[43] ASTM F2052 Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment.
[44] ASTM F2213 Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment.
[45] ASTM F2182 Standard Test Method for Measurement of Radio Frequency Induced Heating On or Near Passive Implants During Magnetic Resonance Imaging.
[46] ASTM F2119 Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants.
[47] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM107708.

There are FDA-recognized voluntary consensus standards such as ASTM F2503,[48] ASTM F2052,[49] ASTM F2213,[50] ASTM F2182,[51] and ASTM F2119[52] for MR compatibility testing of passive implants. There are also FDA-recognized voluntary consensus standards for fatigue testing of endosseous dental implants, such as American National Standards Institute/American Dental Association (ANSI/ADA) Standard No. 127[53] and ISO 14801[54] to address the performance of the device. In addition, ISO 14801 and ANSI/ADA Standard No. 127 are applicable to all dental implants.

D - *Can the data be reviewed in a summary or risk analysis format?*
Yes. There are consensus standards for test methods, and guidance documents for reference. The fatigue testing can be placed into a summary format because the size change does not necessitate protocol or acceptance criteria deviations. In addition, the size change (4mm to 5mm) does not necessitate clinical or animal data. Because there has been no material change, and the 1 mm size change is not expected to alter the safety of the device with respect to MR compatibility, and the protocol and acceptance criteria has not changed, the MR testing results can be placed into a summary format because the SE determination does not depend on the Agency's interpretation of the underlying data, such as images, raw graphs, or line item data.

Decision: Change can be reviewed in a Special 510(k).

[48] ASTM F2503 Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment.
[49] ASTM F2052 Standard Test Method for Measurement of Magnetically Induced Displacement Force on Medical Devices in the Magnetic Resonance Environment.
[50] ASTM F2213 Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment.
[51] ASTM F2182 Standard Test Method for Measurement of Radio Frequency Induced Heating On or Near Passive Implants During Magnetic Resonance Imaging.
[52] ASTM F2119 Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants.
[53] ANSI/ADA Standard No. 127 Fatigue Testing for Endosseous Dental Implants.
[54] ISO 14801 Dentistry - Implants - Dynamic loading test for endosseous dental implants.

Appendix C. Examples of the summary of design control activities

This section provides sample design control activities summaries that can be used to support a Special 510(k). Because of the inherent flexibility of design controls and the QS regulation, this summary may differ depending on a manufacturer's internal procedures. The examples are intended to show different formats that have been used in previously cleared Special 510(k) submissions.

Example C.1

In the subject 510(k), the manufacturer requested clearance to modify their lacrimal stent to remove a metal ring, change the shape of the stent's duct tube, and alter the surface area of a hydrophilic coating. The manufacturer's design controls narrative described that a risk analysis was conducted to assess the impact of the changes on the subject device using internal design control procedures and a fault tree analysis described in the FDA-recognized version of ISO 14971.[55] The manufacturer included their fault tree analysis specific to this design change in an attachment for the Special 510(k) to identify the hazardous situations, causes, risk control measures, and acceptability before and after risk control measures. The manufacturer explained that the protocol, test methods, and acceptance criteria used were the same as those used in the predicate submission and provided references to the applicable sections in the previous submission. The risk analysis identified the verification and validation activities necessary to establish SE, and summarized that information in the following table:

Table 1. Example design control activities summary for a hypothetical lacrimal stent

Device Change	Risks	Verification/Validation Method(s)	Acceptance Criteria	Summary of results
Removal of ring	• Damaged tissue • Damage to device during insertion with bougie causes delay in patient treatment	Penetration test performed with bougie (Protocol and acceptance criteria same as Kxxxxxx without any deviations)	Breaking load shall be greater than 9N	Pass (12/12) Mean: 15.0 Standard deviation: 0.39 Range: 14.4-15.6
Shape change	• Damaged tissue • Damage to device causes delay in patient treatment	• Simulated insertion test with bougie • Bending test with bougie (Protocol and acceptance criteria same as Kxxxxxx without any deviations)	For both tests, visual inspection shall demonstrate that the device can be inserted without damage.	Pass (20/20) for both tests

[55] ANSI/AAMI/ISO 14971 Medical devices - Application of risk management to medical devices.

Device Change	Risks	Verification/Validation Method(s)	Acceptance Criteria	Summary of results
Change in hydrophilic coating surface area	• Difficulty inserting causes delay in patient treatment • Abnormalities on catheter causes damage to tissue	• Insertion test with simulated lacrimal duct • Visual inspection (Protocol and acceptance criteria same as Kxxxxxx without any deviations)	• No visual damage after simulated insertion • No droplets, extraneous matter, or abnormalities are visualized under a microscope	• Pass (15/15) • Pass (10/10)
	Adverse tissue reaction from material coating area and geometric changes.	Biocompatibility evaluation in agreement with recommendations in "Use of International Standard ISO 10993 -1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process'" (CDRH's 2016 Biocompatibility Guidance).[56] Leveraged all biocompatibility testing from another device with similar type and duration of contact, greater surface area, and same formulation and processing by the same device manufacturer.	Materials of construction and manufacturing materials do not introduce chemicals that raise a biocompatibility concern.	Biocompatibility testing is not needed because device does not introduce a biocompatibility risk.
			Materials of construction and manufacturing materials do not introduce chemicals that raise a material-mediated pyrogenicity concern.	Material-mediated pyrogenicity testing is not needed because device does not introduce a material-mediated pyrogenicity risk.

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[56] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM348890.

Example C.2

In the subject 510(k), the manufacturer requested clearance to modify the geometric design and constructive materials of the single-use sheath used in a self-retaining retractor for neurosurgery. The manufacturer's design controls narrative described that a design failure modes and effects analysis (DFMEA) was included in the submission. In accordance with their risk management procedures, the manufacturer identified their design inputs, identified risks with their evaluation, risk control measures, and residual risk. The risk analysis identified the verification and validation activities and summarized them in this table:

Table 2. Example design control activities summary for a hypothetical sheath

Device Change	Risks	Verification/Validation Method(s)		Acceptance Criteria	Summary of results
Material change to polyethylene	Adverse tissue reaction from material change	Biocompatibility evaluation in agreement with recommendations in CDRH's 2016 Biocompatibility	Cytotoxicity (ISO 10993-5)[58] using the ISO minimum essential medium (MEM) Elution method. The protocol used the same test article preparation and extraction conditions as the predicate (MEM with 10% serum, 37 ºC, 24 hours, at a surface area/volume ratio of 6 cm^2/ml), appropriate controls, extracts were not stored for more than 24 hours, and were not altered (e.g., filtered or pH adjusted). These testing conditions are the same as the predicate device, the extracts did not change color, appear turbid or have particulates, and there were no deviations/amendments from the protocol.	Reactivity grade shall be 0, which is the same as for the predicate device.	There was no evidence of the test extract causing cell lysis or toxicity (Grade = 0) for three replicates at 48 hours. Latex Positive Control = Grade 3 High Density Polyethylene Negative Control = Grade 0 The test article is non-cytotoxic.

[58] ISO 10993-5 Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity.

Device Change	Risks	Verification/Validation Method(s)		Acceptance Criteria	Summary of results
		Guidance.[57] Based on our risk management procedures, biocompatibility testing was repeated for some endpoints.	Irritation (ISO 10993-10)[59] using the intracutaneous reactivity method. The protocol used the same test article preparation and extraction conditions as the predicate (saline and sesame seed oil extract solvents, 50 ºC, 72 hours, at a surface area/volume ratio of 6 cm^2/ml), appropriate controls, extracts were not stored for more than 24 hours, and extracts were not altered (e.g., filtered or pH adjusted). These testing conditions are the same as the predicate device, the extracts did not change color, appear turbid, or have particulates, and there were no deviations/amendments from the protocol.	The difference between the mean reaction score for the test article and control shall be ≤1.0, which is the same as the predicate device.	The polar extract showed no irritation (Grade 0) and the non-polar extract showed minimal irritation (Grade 0/1) at 24, 48 and 72 hours, which was consistent with the negative vehicle control results. Saline Vehicle Control = Grade 0 at all timepoints Sesame Vehicle Control = Grade 0/1 at all timepoints No adverse in vivo findings were noted in any of the test or control animals. The test article is a non-irritant.

[57] "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process,'" available at: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM348890.

[59] ISO 10993-10 Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization.

Device Change	Risks	Verification/Validation Method(s)		Acceptance Criteria	Summary of results
			Sensitization (ISO 10993-10)[60] using the guinea pig maximization test. The protocol used the same test article preparation and extraction conditions as the predicate (saline and sesame oil extract solvents, 50 ºC, 72 hours, at a surface area/volume ratio of 6 cm^2/ml), appropriate controls, extracts were not stored for more than 24 hours, and extracts were not altered (e.g., filtered or pH adjusted). These testing conditions are the same as the predicate device, the extracts did not change color, appear turbid or have particulates, and there were no deviations/amendments from the protocol.	Grade 0 in both test and control animals, which is the same as the predicate device.	Both the polar and non-polar extracts scored 0 at 24 and 48 hours for all test subjects, which was consistent with the negative control. The extracts did not change color or have particulates. The test article is a non-sensitizer.

[60] ISO 10993-10 Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization.

Device Change	Risks	Verification/Validation Method(s)		Acceptance Criteria	Summary of results
			Acute systemic toxicity Reviewed: 1) Literature; and 2) Safety Data Sheets (SDS) that are in accordance with Appendix D of 29 CFR 1910.1200.[61]	Materials of construction and manufacturing materials do not introduce chemicals that elicit acute systemic toxicity. SDS meets 29 CFR 1910.1200 content.	Acute systemic toxicity testing is not needed because device does not introduce an acute systemic toxicity risk.
			Material-mediated pyrogenicity Leveraged material-mediated pyrogenicity testing from another polyethylene device with similar type and duration of contact, greater surface area, and same formulation and processing by the same device owner.	Materials of construction and manufacturing materials do not introduce chemicals that raise a material-mediated pyrogenicity concern.	Material-mediated pyrogenicity testing is not needed because device does not introduce a material-mediated pyrogenicity risk.

[61] For more information about Safety Data Sheets, see 77 FR 17574.

Device Change	Risks	Verification/Validation Method(s)	Acceptance Criteria	Summary of results
	• Patient infection • Device failure causes patient injury or delay in procedure.	Sterilization validation was completed using an established method (gamma irradiation) in conformity with ISO 11137-1 without deviation.[62] The sterilization validation approach was Verification Dose Maximum (VD_{max}) for a Sterility Assurance Level (SAL) of 10^{-6} in accordance with AAMI Technical Information Report (TIR) 33.[63] Package integrity testing was also conducted using methods consistent with the predicate device (seal integrity, dye penetration, and visual inspection).	Devices shall maintain package integrity and have SAL of 10^{-6}.	Package integrity testing results all passed (n=30 each). Bioburden studies passed.
Geometric design change	• Damage to devices causes patient injury or delay in procedure. • Adverse tissue reaction from geometric	Specification review and dimensional analysis.	Dimensional verification shall demonstrate that the sheath geometric change does not interfere with obturator.	Pass (n=20)
		Design validation to confirm that the sheath continues to meet manufacturer-defined user requirements. Simulated-use testing was conducted with a prospective user to confirm that the device can achieve its intended use. (Protocol and acceptance criteria same as Kxxxxxx without any deviations)	The sheath shall be able to be used with third-party accessories and provide access to the tissue identified in labeling.	Pass

[62] ISO 11137-1 Sterilization of health care products – Radiation – Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices.
[63] AAMI TIR33 Sterilization of health care products — Radiation — Substantiation of a selected sterilization dose — Method VDmax.

Device Change	Risks	Verification/Validation Method(s)	Acceptance Criteria	Summary of results
	shape change.	Implantation and thrombogenicity Reviewed geometric changes per CDRH's 2016 Biocompatibility Guidance[64] (Attachment A, Table A.1) to determine whether implantation or thrombogenicity (which can be impacted by geometry) are recommended for this device type/duration of contact.	For externally communicating devices in contact with tissue or bone for < 24 hours, Table A.1 indicates that implantation and thrombogenicity assessments are not necessary.	Additional biocompatibility evaluation to assess the impact of the geometric change on the biological response is not needed.

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[64] "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process,'" available at: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM348890.