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Draft – Not for Implementation

Medical Devices with Indications Associated with Weight Loss - Non-Clinical Recommendations

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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

For questions about this document, contact OHT3: Office of Gastro-Renal, ObGyn, General Hospital, and Urology Devices/DHT3A: Division of Renal, Gastrointestinal, Obesity, and Transplant Devices at (301) 796-7030.

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

Preface

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Medical Devices with Indications Associated with Weight Loss - Non-Clinical Recommendations

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. Introduction

This draft guidance document provides recommendations for the non-clinical testing to support premarket submissions (e.g., Premarket Approval (PMA) Applications, Investigational Device Exemption (IDE) Applications, Premarket Notifications (510(k)s), and De Novo classification requests) for medical devices with indications for use associated with weight loss. Examples of indications associated with weight loss include indications for weight loss, weight reduction, weight management, or obesity treatment in patients who are overweight or have obesity. Due to the wide variety of device designs, among other things, there can be variability in the demonstrated weight loss and risk associated with these devices, as well as variability in the applicability of some of the recommended testing. The recommendations reflect current review practices of premarket submissions for these devices and are intended to promote consistency and facilitate efficient review of these submissions.

For the current edition of the FDA-recognized consensus standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database.[1] For more information regarding use of consensus standards in regulatory submissions, please refer to the FDA guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices."[2]

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

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

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. Scope

The scope of this document is limited to devices with indications for use associated with weight loss, including weight loss, weight reduction, weight management, or obesity treatment in patients who are overweight or have obesity. This includes the existing product codes listed in Table 1 below:

Table 1. Existing product codes within the scope of this guidance

Product Code	Product Code Name	Regulation Number
LTI	Intragastric implant for morbid obesity	Not applicable[3]
OYF	Aspiration therapy system	Not applicable[4]
PIM	Neuromodulator for obesity	Not applicable[5]
ONY	Oral removable retainer for weight management	21 CFR 876.5981[6]
QFQ	Ingested, Transient, Space Occupying Device For Weight Management And/Or Weight Loss	21 CFR 876.5982[7]
QTD	Endoscopic Suturing Device For Altering Gastric Anatomy For Weight Loss	21 CFR 876.5983[8]

Although the product codes listed above are current as of the date of issuance of this guidance, new product codes or classification regulations may be created over time and could fall within the scope of this guidance. We recommend that you reference the product code database (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm) or contact OHT3: Office of Gastro-Renal, ObGyn, General Hospital, and Urology Devices if you are uncertain

[3] This is a postamendments class III device.
[4] *Ibid*.
[5] *Ibid.*
[6] This classification regulation includes special controls. *See* 21 CFR 876.5981(b).
[7] This classification regulation includes special controls. *See* 21 CFR 876.5982(b).
[8] This classification regulation includes special controls established in the reclassification order, available at https://www.accessdata.fda.gov/cdrh_docs/pdf21/DEN210045.pdf. The publication of this classification in the Federal Register and codification in the Code of Federal Regulations are currently pending.

whether this guidance applies to your device and the product code for your device is not already captured in this guidance.

Some of the recommendations in this guidance may assist in complying with some of the special controls for devices with indications associated with weight loss. For information regarding special controls for oral removable retainers for weight management, see 21 CFR 876.5981(b). For information regarding special controls for ingested, transient, space occupying devices for weight management and/or weight loss, see 21 CFR 876.5982(b). For information regarding special controls for endoscopic suturing devices for altering gastric anatomy for weight loss, see FDA's website.[9]

This draft guidance should be viewed as a complement to FDA's draft guidance entitled, "Medical Devices with Indications Associated with Weight Loss - Clinical Study and Benefit-Risk Considerations,"[10] which, once finalized, will provide recommendations regarding clinical study design for these devices and also includes discussion on how FDA considers the benefit-risk analysis to support such indications.

III. Premarket Submission Recommendations

A. Device Description

We recommend submitters identify their device by the applicable regulation number and product code indicated in Section II above and include the information described below.

- An explanation of how the device functions, the scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device, such as device design, material(s) used, and physical properties.
- A complete description of the device, which may be facilitated by the submission of engineering schematics or other figures. If the device consists of multiple components, a diagram identifying how the different components of the device system work together, a video, and/or animation, could be beneficial.
- A discussion of the physical specifications and/or tolerances of the device.
- If the device includes nitinol, submitters should include the General Information recommended in the FDA guidance document "Technical Considerations for Non-Clinical Assessment of Medical Devices Containing Nitinol."[11]

[9] See reclassification order, available at https://www.accessdata.fda.gov/cdrh_docs/pdf21/DEN210045.pdf.

[10] When final, this guidance will represent FDA's current thinking on clinical study and benefit-risk considerations for medical devices with indications associated with weight loss. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-devices-indications-associated-weight-loss-clinical-study-and-benefit-risk-considerations.

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

B. Labeling

For a premarket approval application (PMA), submitters must submit all proposed labeling. (21 CFR 814.20(b)(10)). Additionally, a 510(k) submission must include proposed labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). Proposed labels and labeling, sufficient to describe the device, its intended use, and the directions for use must be provided. Lastly, for De Novo requests, submitters must provide labeling sufficient to describe the device, its intended use, and the directions for its use. (21 CFR 860.220(a)(18)).

As prescription devices, devices with indications associated with weight loss are exempt from having adequate directions for lay use required under section 502(f)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as long as the conditions in 21 CFR 801.109 are met. For instance, labeling must include adequate information for the intended user of the device, including indications, effects, routes, methods, frequency and duration of administration and any relevant hazards, contraindications, side effects, and precautions (21 CFR 801.109(d)). The following section does not detail all of the elements of proposed labeling that are required within a marketing submission, but instead outlines recommendations for specific content for inclusion in the user manual that may apply specifically to devices with indications associated with weight loss.

(1) Warnings

If the device includes nitinol and has prolonged or permanent contact with the body, we recommend inclusion of the warning regarding nickel allergy as described in FDA guidance "Technical Considerations for Non-Clinical Assessment of Medical Devices Containing Nitinol."[12]

(2) MR Safety Information

We recommend submitters follow the labeling guidance in "Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment."[13] We also recommend that submitters use the standardized terminology and icons specified in the currently recognized version of ASTM F2503: *Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment*.

(3) Overview of Clinical Studies

Submitters should provide a narrative description of the study(ies) relevant to the device. For information regarding clinical study considerations for these devices, we recommend submitters

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

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

follow FDA's draft guidance, "Medical Devices with Indications Associated with Weight Loss-Clinical Study and Benefit-Risk Considerations.[14]" The narrative should be brief, and for each study, it should include a description of the following:

- design of the study, including any randomization, blinding, and the control or controls used;
- number of patients enrolled;
- number of investigational sites both inside the United States (U.S.) and outside the United States (O.U.S.);
- primary study endpoints;
- results of the study (e.g., adverse events, endpoint data, statistical analysis); and
- amount of available follow-up.

Data on the changes in the major weight-related comorbidities (e.g., type 2 diabetes mellitus, hypertension) are important to describe the overall benefit-risk profile of a new device with an indication associated with weight loss and could be included in the Clinical Studies section of the device labeling. Any labeling associated with secondary effectiveness endpoints should be based on results that are both clinically and statistically significant. If any of the secondary endpoint analyses are intended to support the indications for use or to describe device performance in the labeling (e.g., comparing treatment and control groups using p-values and confidence intervals), we recommend that submitters pre-specify this intention in the study protocol and provide a detailed description of the statistical methods submitters plan to follow. To support inclusion in labeling, the overall type I error rate should be controlled. The clinical significance and consistency across studies of any observed differences will be important in determining whether the secondary effectiveness data are appropriate for inclusion in the Clinical Studies section of the labeling.

(4) Adverse Events

In addition to the adverse event information from the clinical study described in Section IV.H of FDA's draft guidance, "Medical Devices with Indications Associated with Weight Loss - Clinical Study and Benefit-Risk Considerations,"[15] submitters should also include potential risks associated with the device.

[14] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-devices-indications-associated-weight-loss-clinical-study-and-benefit-risk-considerations.

[15] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-devices-indications-associated-weight-loss-clinical-study-and-benefit-risk-considerations.

FDA has alerted health care providers about potential risks with liquid-filled intragastric balloons.[16] If the device is a liquid-filled intragastric balloon, we recommend that the specific risks identified in these safety communications be included in the labeling, and occurrence rates be separated by occurrence in the U.S. and globally, if applicable. These risks include, but may not be limited to: spontaneous hyperinflation in patients' stomachs, acute pancreatitis, esophageal perforation, gastric perforation, aspiration, and death.

(5) Patient Labeling (including patient implant card, if applicable)

Submitters should provide examples of all patient labeling, including the patient guide and implant card, that are intended to be provided to patients. When preparing patient labeling, we recommend use of the FDA guidance "Guidance on Medical Device Patient Labeling."[17]

For MR Conditional devices, we recommend submitters include in the patient labeling and on the patient implant card all conditions for safe MR use as specified in "Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment"[18] 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*.

C. Sterility

Devices with indications for use associated with weight loss can be sterile or provided non-sterile.

(1) Sterile Devices

Significance: Devices with indications for use associated with weight loss can be implanted devices or come in contact with breached or compromised tissue and/or the blood path. Such devices should be adequately sterilized to minimize infections and related complications.

Recommendation: For devices labeled as sterile, we recommend submitters provide the information outlined below.[19]

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[16] See "The FDA alerts health care providers about potential risks with liquid-filled intragastric balloons," available at https://www.fda.gov/medical-devices/letters-health-care-providers/fda-alerts-health-care-providers-about-potential-risks-liquid-filled-intragastric-balloons.

[17] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-medical-device-patient-labeling.

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

[19] For 510(k) submissions, we recommend that submitters provide information for the final sterile device in accordance with FDA's guidance "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-and-review-sterility-information-premarket-notification-510k-submissions-devices-labeled).

1. For the sterilization method, submitters should provide the following:
    a. a comprehensive description of the sterilization method/process;
    b. a description of the sterilization chamber if not rigid, fixed (e.g., flexible bag);
    c. the sterilization site;
    d. in the case of radiation sterilization, the radiation dose; and
    e. for chemical sterilants (e.g., ethylene oxide (EO), hydrogen peroxide (H_2O_2)), the maximum levels of sterilant residuals that remain on the device, and an explanation of why those levels are acceptable for the device type and the expected duration of patient contact.

       In the case of EO sterilization, CDRH has accepted EO residuals information based on the currently recognized version of the standard, AAMI/ANSI/ISO 10993-7, *Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals*.
2. For the sterilization method, submitters should provide a description of the method used to validate the sterilization cycle (e.g., the half-cycle method) as well as the sterilization validation data. The submission should also identify all relevant consensus standards used and identify any aspects of the standards that were not met. In the absence of a recognized standard, a comprehensive description of the process and the complete validation protocol should be submitted and reviewed.
3. Submitters should state the sterility assurance level (SAL) of 10^{-6} for devices labeled as sterile unless the device is intended only for contact with intact skin. FDA recommends a SAL of 10^{-3} for devices intended only for contact with intact skin.

(2) Non-Sterile Devices

Significance: If the single-patient use device makes contact with only non-sterile areas of the body (e.g., intact gastrointestinal tract) and will not breach mucosal tissues, it may be acceptable to be provided to the user and used as non-sterile. However, the use of a non-sterile device in the gastrointestinal tract can introduce microbes that can cause illness, introduce antibiotic-resistant organisms, and/or alter the gut microflora. Therefore, it is important to monitor microbial levels during the manufacturing process to minimize these risks.

Recommendation: Submitters should describe the type and frequency of microbial monitoring that is conducted to ensure that the types of microbes and the levels of bioburden on any gastrointestinal tract-contacting components of the device will, within reason, not negatively impact human health in regard to the risk of infection.

Submitters should provide test reports and protocols with the following information for devices intended to be provided non-sterile:

1. Description of the microbiological controls in the manufacturing process, which should include processes to maintain low bioburden levels and the absence of pathogens (e.g., *Escherichia coli*, *Salmonella spp.*, *Clostridium spp.*) on the device;
2. Description and justification of the type and frequency of microbial monitoring conducted;
3. The level of bioburden on the device and the historical data and scientific justification used to determine alert and action levels;
4. Bioburden recovery efficiency validation and bioburden culture methods; and
5. The identities of predominant bioburden species and a justification for how the types of microorganisms and the levels of bioburden on the device do not negatively impact human health.

For intragastric devices filled with liquid (e.g., balloons), FDA recommends that the fill fluid for the device is provided sterile. The presence of microorganisms in the fill fluid of these devices may lead to hyperinflation of the device beyond the intended maximum fill volume described in the labeling, which could lead to patient complications and/or device failure.

a. Clean Devices

If the device is intended to be labeled as "clean, non-sterile," we recommend that submitters describe the method of cleaning conducted to support that the device is clean, and include the cleaning methods, assays to assess cleanliness, and acceptance criteria used. Submitters should consider the FDA-recognized version of ASTM F3127: *Standard Guide for Validating Cleaning Processes Used during the Manufacture of Medical Devices* for further recommendations related to the validation of critical cleaning processes to reduce manufacturing contaminants on medical devices to acceptable levels prior to packaging.

D. Pyrogenicity

Significance: Pyrogenicity testing is used to help protect patients from the risk of febrile reaction due to gram-negative bacterial endotoxins and/or chemicals that can leach from a medical device (e.g., material-mediated pyrogens).

Recommendation: To address the risks associated with the presence of bacterial endotoxins, if applicable, the device should meet applicable pyrogen limit specifications.[20] Submitters should also follow the recommendations in "Pyrogen and Endotoxins Testing: Questions and Answers."[21] To address the risks associated with material-mediated endotoxins, follow the

[20] For 510(k) submissions, submitters should meet pyrogen limit specifications by following the recommendations outlined in FDA's guidance "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-and-review-sterility-information-premarket-notification-510k-submissions-devices-labeled).

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

recommendations in FDA's guidance "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.'"[22]

For devices intended to be labeled as "non-pyrogenic," we recommend that both bacterial endotoxins and material-mediated pyrogens be addressed. As discussed in Section III.F, material-mediated pyrogenicity assessment can be evaluated as part of a non-clinical animal study.

E. Shelf Life and Packaging

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

Recommendation: With respect to package integrity, submitters should provide a description of the packaging, including how it will maintain the device's sterility, bioburden, or cleanliness, the protocol(s) used for package integrity testing, the results of the testing, and the conclusions drawn from results.[23] We recommend that a package validation study include simulated distribution and associated package integrity testing, as well as an aging process (accelerated and/or real-time) and associated seal strength testing, to validate package integrity and shelf life claims. We recommend following the methods described in the FDA-recognized series of consensus standards AAMI/ANSI/ISO 11607-1: *Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging* and AAMI/ANSI/ISO 11607-2: *Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly processes.*

With respect to evaluating the effects of aging on device performance or functionality, shelf life studies should evaluate the critical device properties to ensure it will perform adequately and consistently during the entire proposed shelf life. To evaluate device functionality, we recommend submitters assess each of the bench tests described in Section III.K and repeat all tests that evaluate design components or characteristics that are potentially affected by aging using aged devices.

For non-sterile devices that contact only non-sterile areas of the body (e.g., intact gastrointestinal tract, intact skin), a risk assessment should be performed to identify if the device or device component has the potential to support microbial growth during the shelf life (e.g., lubricants, oils, organic substances). Non-sterile devices with a high risk of supporting microbial growth should undergo bioburden testing at the end of the proposed shelf life to ensure that the device does not exceed microbial action levels at the end of the proposed shelf life. If the device is

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

[23] For 510(k) submissions, submitters should provide a description of the packaging, including how it will maintain the device's sterility, and a description of the package integrity test methods, but not the package test data.

determined to have a low risk of microbial growth during shelf life, then the microbiological testing at the end of the proposed shelf life may not be necessary.

We recommend submitters provide the protocol(s) used for shelf life testing, the results of the testing, and the conclusions drawn from results.[24] In the context of a PMA, if the submitter intends to extend the shelf life of the device after initial approval, we recommend they provide the protocol(s) to support the extension in the original submission per 21 CFR 814.39(a)(7). We recommend all test samples undergo real-time aging to assess the effects of aging on the maintenance of sterility and device performance.

If devices subjected to accelerated aging are used, we recommend 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 the results if the device were aged in real time. We recommend submitters age the devices as per the currently FDA-recognized version of ASTM F1980: *Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices* and specify the environmental parameters established to attain the expiration date. For devices or components containing polymeric materials or coatings, submitters should conduct testing on real-time aged samples to confirm the results of the accelerated aging study. This testing should be conducted in parallel with FDA review and results documented to file in the design history file (i.e., complete test reports do not need to be submitted to FDA).

F. Biocompatibility

Significance: Devices with indications associated with weight loss contain patient-contacting materials, which, when used for their intended purpose, may induce a harmful biological response.

Recommendation: Submitters should determine the biocompatibility of all patient-contacting components present in the device. If the device is identical in chemical composition and processing methods to a device with a history of successful use, submitters can reference previous testing experience or the literature, if appropriate. For some device materials, it may be appropriate to provide a reference to either a recognized consensus standard, or to a Letter of Authorization (LOA) for a device Master File (MAF). Submitters should refer to the following FDA webpage for additional information on using device MAFs: https://www.fda.gov/medical-devices/premarket-approval-pma/master-files.

If submitters are unable to identify a legally marketed device with the same nature of contact and contact duration that uses the same materials and manufacturing process as used in the subject device, we recommend conducting the biocompatibility evaluation as recommended in FDA's guidance "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process.'"[25] The evaluation should

[24] For 510(k) submissions, we recommend submitters provide a summary of the test methods used for shelf life testing, results, and the conclusions drawn from your results.

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

explain the relationship between the identified biocompatibility risks, the information available to mitigate the identified risks, and any knowledge gaps that remain. Submitters should then identify any biocompatibility testing or other evaluations that were conducted to mitigate any remaining risks. We recommend that submitters consider the recommendations in this guidance, which identifies the types of biocompatibility assessments that should be considered and recommendations regarding how to conduct related tests.

Data from a non-clinical animal study[26] that uses the device in its final finished form could be used in lieu of some biocompatibility tests, if the study is designed to include assessments for those biocompatibility endpoints. For example, an implantation study could be used to evaluate local tissue responses, material-mediated pyrogenicity, and acute, subacute/subchronic, and chronic systemic toxicity evaluation, by including the parameters of clinical biochemistry, hematology, gross pathology, and organ histopathology examinations.

For an intragastric device filled with gas or liquid, submitters should provide:

- Information to describe the source, chemical name, composition, purity, and amount/dose of the filling gas or liquid.
- A toxicological risk assessment on the gas or liquid when it is expelled into the stomach, upon emptying or rupture of the device.
- Information or test data (e.g., chemical leachable/extractable analysis) to evaluate the potential chemical reaction of the filling gas or liquid with the device and assess the toxicological risks to patients if any compounds leach out of the device.

If the device includes nitinol, we recommend that submitters consider the biocompatibility recommendations in the FDA guidance "Technical Considerations for Non-Clinical Assessment of Medical Devices Containing Nitinol."[27]

G. Software

Significance: When the device contains software, adequate software performance testing provides assurance that the device is operating within safe parameters and that adequate alarms are provided to the user if warranted. Software should conform to user needs and the intended use(s) of the device.

Recommendation: Refer to the FDA software guidance "Content of Premarket Submissions for Device Software Functions"[28] for a discussion of the software documentation that submitters

[26] FDA supports the principles of the "3Rs," to replace, reduce, and/or refine animal use in testing when feasible. We encourage sponsors to consult with us if 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 study.

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

[28] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-device-software-functions.

should provide in the marketing submission. The software guidance outlines the recommended information to be provided based on the Documentation Level associated with the device. If a submitter believes that the device warrants a Basic Documentation Level as defined in this software guidance, the submitter should provide a scientific justification that supports the rationale of the Documentation Level based on the possible consequences of software failure.

We recommend submitters provide a full description of the software/firmware supporting the operation of the subject device following this software guidance, commensurate with the appropriate Documentation Level. This recommendation applies to original devices/systems as well as to any software/firmware changes made to already-marketed devices. Changes to software must be revalidated and reverified in accordance with Design Controls, 21 CFR 820.30(g)(i),[29] and documented in the Design History File, 21 CFR 820.30(j).[30]

If the device meets the definition of a cyber device under section 524B(c) of the FD&C Act, cybersecurity documentation under section 524B(b) of the FD&C Act is required as part of the premarket submission. For more information on this topic, see FDA's guidance "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices."[31]

If the device includes off-the-shelf software, submitters should provide the additional information as recommended in the FDA guidance documents "Off-the-Shelf Software Use in Medical Devices"[32] and "Cybersecurity for Networked Medical Devices Containing Off-The-Shelf (OTS) Software,"[33] which provide additional information regarding medical devices utilizing off-the-shelf software.

[29] 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.

[30] For 510(k) submissions, some software changes may warrant the submission of a new 510(k). For further information on this topic, refer to "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-software-change-existing-device).

[31] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-management-cybersecurity-medical-devices-0.

[32] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/shelf-software-use-medical-devices.

[33] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cybersecurity-networked-medical-devices-containing-shelf-ots-software.

Overall, the documentation related to the software contained in the medical device should provide sufficient evidence to describe the role of the software included in the device, and performance testing to demonstrate that the software functions as designed.

H. Electrical Safety and Electromagnetic Compatibility (EMC)

Significance: If the device or device system is electrical, it may expose the operator and patient to hazards associated with the use of electrical energy or may fail to operate properly in the presence of electromagnetic disturbance.

Recommendation: These devices should be tested to demonstrate that they perform as anticipated in their intended use environment. We recommend that this testing be performed as described in the currently FDA-recognized versions of the following standards for medical electrical equipment safety and electromagnetic compatibility:

- AAMI/ANSI ES60601-1: *Medical electrical equipment - Part 1: General requirements for basic safety and essential performance*.
- AAMI/ANSI/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*.
- If the device is an implanted electrical stimulator, we also recommend that submitters conduct the specific tests for electrical safety and EMC that are described in the currently FDA-recognized version of ISO 14708-3: *Implants for Surgery – Active implantable medical devices – Part 3: Implantable neurostimulators.*

If submitting a declaration of conformity to the above standards, we recommend that appropriate supplemental documentation such as an assessment of the results and how conformity was determined, and information regarding test methods used should be provided, because this series of standards includes general methods with multiple options and, in some cases, does not include specific acceptance criteria or address assessment of results. For additional information on providing electromagnetic compatibility information in a premarket submission, see FDA's guidance "Electromagnetic Compatibility (EMC) of Medical Devices."[34]

Additionally, implanted devices that use a battery should remain functional through the battery life to limit the need for unplanned surgical intervention.

[34] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electromagnetic-compatibility-emc-medical-devices.

I. Wireless Technology

Significance: In the design, testing, and use of wireless medical devices, the correct, timely, and secure transmission of medical data and information is essential for the safe and effective use of medical devices and systems.

Recommendation: If the device incorporates radiofrequency wireless technology such as Bluetooth, IEEE 802.11 (Wi-Fi), or RFID (radio frequency identification) technology; testing beyond what is specified in the IEC 60601 standards is recommended to demonstrate that the wireless device functions will perform as intended in environments with other wireless products. For additional recommendations for home use devices with wireless technology, if applicable, refer to FDA's guidance "Design Considerations for Devices Intended for Home Use."[35]

We recommend submitters consult FDA's guidance "Radio Frequency Wireless Technology in Medical Devices"[36] for additional recommendations on this topic.

J. Magnetic Resonance (MR) Compatibility for Implants

Significance: MR imaging of patients with implanted devices poses the following potential hazards:

- Movement of the implant, resulting in tissue damage or displacement of the device; heating of the tissue surrounding the implant and subsequent tissue damage; image artifacts that may render the MR images uninterpretable or misleading; and/or
- Malfunction of electrically active devices or induce voltages in leads or other long conductive portions of the device which can result in a failure of the device to deliver the intended therapy.

Recommendation: We recommend submitters address the safety and compatibility of the device in the MR environment as described in the FDA guidance "Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment."[37]

If the submitter would like to market devices of various sizes and shapes, then we recommend following the recommendations in the FDA guidance "Assessment of Radiofrequency-Induced

[35] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-devices-intended-home-use.
[36] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/radio-frequency-wireless-technology-medical-devices-guidance-industry-and-fda-staff.
[37] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/testing-and-labeling-medical-devices-safety-magnetic-resonance-mr-environment.

Heating in the Magnetic Resonance (MR) Environment for Multi-Configuration Passive Medical Devices."[38]

K. Non-Clinical Bench Performance Testing

Non-clinical performance bench testing supports device usability, device safety, and device performance. Typical bench performance testing should demonstrate that the device functions as intended. To assist in determining the appropriate non-clinical bench performance testing for their device, submitters can seek input from the Agency via the Q-Submission Program. For details on the Q-Submission Program, refer to the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[39]

For information on recommended content and format of test reports for the testing described in this section, refer to FDA's guidance "Recommended Content and Format of Test Reports for Non-Clinical Bench Performance Testing in Premarket Submissions."[40]

The non-clinical bench performance tests referenced in this section are intended to be general recommendations. They are not an exhaustive list due to the variety of device technologies with indications associated with weight loss.

(1) Corrosion Resistance

Significance: When made of metallic materials, device corrosion can cause or contribute to premature device failure. In addition, corrosion byproducts may be toxic or cause other adverse biological and tissue responses.

Recommendation: If the device includes nitinol, we recommend characterizing the corrosion potential of the device as described in the FDA guidance "Technical Considerations for Non-Clinical Assessment of Medical Devices Containing Nitinol."[41]

If the device includes metallic materials other than nitinol, we recommend that the submitter assess corrosion susceptibility as described below. Note that corrosion testing is generally not warranted for limited contact devices; however, such testing may be requested in situations such as devices with an electrically active component, a dissimilar metal couple, or a degradable metal/polymer component where these features could accelerate metal corrosion. In these cases, we recommend that submitters seek more detailed feedback via the Q-Submission Program.

[38] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessment-radiofrequency-induced-heating-magnetic-resonance-mr-environment-multi-configuration.
[39] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.
[40] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommended-content-and-format-non-clinical-bench-performance-testing-information-premarket.
[41] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-non-clinical-assessment-medical-devices-containing-nitinol.

a. Pitting Corrosion

We recommend conducting pitting corrosion testing on the as-manufactured device according to the currently recognized version of ASTM F2129: *Standard test method for conducting cyclic potentiodynamic polarization measurements to determine the corrosion susceptibility of small implant devices* (or an equivalent method with justification). Testing should be performed after subjecting the device to simulated use testing that mimics *in vivo* anatomic conditions.. This device conditioning is intended to simulate the clinical conditions of the device at the time of implantation. Appropriate simulated fluid (e.g., gastric or intestinal) should be used as the standard test solution.

On the test report, when practical, we recommend plotting all polarization curves in one graph. Results should be assessed against acceptance criteria. ASTM F2129 does not include acceptance criteria. While there is limited data directly linking *in vitro* corrosion testing to *in vivo* corrosion outcomes, there is published data that could be used to establish acceptance criteria.[42] The criteria should be justified based on pitting and crevice corrosion performance as well as risk of metal leaching for the device. If breakdown occurred, submitters should include results of the visual inspection of the device before and after testing to assess evidence of pitting and location of pits. Images of sufficient magnification should be provided to support the assessment. Literature or previous performance data may support the pitting susceptibility assessment of the device. However, the materials, design, and fabrication processes specific to the device may reduce or eliminate the applicability of literature or previous experience with the device.

b. Galvanic Corrosion

Similar to pitting corrosion, galvanic corrosion may lead to higher than anticipated rates of metal ion release or compromised mechanical integrity. If the device consists of contacting dissimilar metals, galvanic corrosion testing should be considered. We recommend the methods described in the currently recognized version of ASTM F3044: *Standard Test Method for Evaluating the Potential for Galvanic Corrosion for Medical Implants*. As an alternative to using devices for galvanic corrosion testing, coupons representing an expected worst-case galvanic coupling that are subjected to identical manufacturing processes could be used. In addition, a scientific justification may be provided, in lieu of testing, if the expected worst-case potential shift due to galvanic coupling is small and if the relative surface ratios of the cathodic to anodic materials are low.

c. Metal Ion Release

If a metal device does not meet the submitter's pre-specified acceptance criteria for corrosion resistance or does not employ an established surface finishing process or if your device has an electrically active component, we recommend metal ion release testing be performed per the currently recognized version of ASTM F3306: *Standard Test Method for Ion Release Evaluation*

[42] Corbett, R. A. (2004). Laboratory corrosion testing of medical implants. In *Proceedings of Materials and Processes for Medical Devices Conference* (pp. 166-171). ASM International, Materials Park, OH.

of Medical Implants. A risk assessment should be performed to compare the amount of metal ion(s) released from the device to a Tolerable Intake (TI) value for the metal(s). A TI value is defined in the currently recognized version of ISO 10993-17: *Biological evaluation of medical devices – Part 17: Establishment of allowable limits for leachable substances* as an "estimate of the average daily intake of a substance over a specified time period, on the basis of body mass, that is considered to be without appreciable harm to health."

(2) Dimensional Verification

Significance: Accurate device dimensions help the user to achieve proper device sizing and accurate placement in the body. They also affect the functional behavior of a device.

Recommendation: FDA recommends submitters include in the submission verification of dimensional specifications for the device.

(3) Strength

Significance: Failure of bonds between materials used in the device can lead to device failure and clinical complications.

Recommendation: We recommend that tensile strength testing be performed for any device system that includes materials that are bonded, welded, or susceptible to fatigue. We recommend that submitters test until failure or provide a justification why acceptance criteria are clinically appropriate with a margin of safety.

(4) Durability and Fatigue

Significance: Failure of a device to maintain its integrity throughout the duration of use can result in adverse clinical consequences or loss of therapy. For liquid-filled intragastric balloons, susceptibility to leakage is believed to increase the risk of hyperinflation.

Additionally, exposure to the gastrointestinal environment can cause or contribute to degradation of material coatings, which could expose patients to materials that are not intended to contact body tissue. In addition to causing potential device failure, exposure of coated materials may release chemicals that may be toxic or cause other adverse biological and tissue responses.

Recommendation: If the device can burst (e.g., an intragastric balloon) or leak, is subjected to peristaltic forces, consists of material(s) that may be degraded by the gastrointestinal environment, and/or consists of a protective plastic or polymer coating, then submitters should demonstrate that the device will function as intended throughout its intended use life. As applicable, we recommend conducting the following testing:

- Mechanical integrity and fatigue;
- Leak susceptibility;

- Coating integrity; and
- Burst strength.

If the device includes nitinol, we recommend following the recommendations for mechanical testing in the FDA guidance "Technical Considerations for Non-Clinical Assessment of Medical Devices Containing Nitinol."[43]

a. Mechanical Integrity and Fatigue

If the device is left indwelling in the body, the device should function as intended continuously throughout the implant period under clinically relevant worst-case conditions. Testing submitted should support that the device can withstand the implant environment and, if in the gastrointestinal tract, simulated gastrointestinal motion (including simulated vomiting conditions, if appropriate) while maintaining integrity and functionality. Devices should be aged to the labeled shelf life prior to testing (*See* Section III.E).

We recommend that the device be in contact with simulated fluid (e.g., gastric, intestinal) at 37ºC for a time that is representative of the implantation time of the device plus a safety factor. The safety factor should account for a reasonable worst-case scenario in the event that the device remains in the body longer than intended. If applicable, the device should be subjected to simulated gastrointestinal motion (i.e., peristalsis) during this period. An elevated temperature can be used for accelerated testing over a shorter period of time, as supported by valid kinetic calculations for impact of temperature and actual clinical use conditions.

The model for simulated gastric motion should be based on current literature on gastric motion dynamics.[44, 45] Submitters should consider that a gastric implant will be exposed to circumferential pressures of variable intensity specifically during and following eating. The amount of pressure used should be justified based on current literature and be representative of a worst-case scenario. The number of pressure events (squeezes) that the device is subjected to should consider the number of anticipated pressure events per minute using conservative assumptions (e.g., assuming 100 minutes per meal and six meals per day).

An example calculation for a six-month gastric implant is:

$$\frac{3\ \text{events}}{\text{minute}} \times \frac{100\ \text{minutes}}{\text{meal}} \times \frac{6\ \text{meals}}{\text{day}} \times 180\ \text{days} = 324{,}000\ \text{events (or squeezes)}$$

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

[44] Bortolotti, M., Annese, V., and Coccia, G. (2000). Twenty-four hour ambulatory antroduodenal manometry in normal subjects (co-operative study). *Neurogastroenterol Motil* 12(3): 231-238.

[45] Marciani, L., Gowland, P. A., Fillery-Travis, A., Manoj, P., Wright, J., Smith, A., Young, P., Moore, R., and Spiller, R. C. (2001). Assessment of antral grinding of a model solid meal with echo-planar imaging. *Am J Physiol Gastrointest Liver Physiol* 280(5): G844-849.

Testing should include appropriate acceptance criteria considering the device design, and analyses of device integrity should be performed after exposure to the implant environment as described above. Appropriate analyses should include burst strength testing and strength testing if applicable to the device design.

b. Leak Susceptibility

We recommend that leak susceptibility testing be incorporated into mechanical integrity and fatigue testing. If the device is inflated and has an inflation/deflation valve, or other design component(s) that may leak, then we recommend that the integrity of the device throughout the implantation period be assessed for its ability to prevent deflation and prevent ingress of surrounding contents (e.g., stomach contents). The amount of leakage recorded should be justified considering the clinical use of the device (e.g., risks of hyperinflation, infection, and gastric and/or intestinal obstruction due to deflation).

c. Coating Integrity

This testing could be incorporated into the testing protocol for mechanical integrity and fatigue. If the device consists of a protective plastic or polymer coating intended to eliminate patient contact with a certain material, then we recommend submitters assess the device for coating degradation potential in the implant environment as described above for mechanical integrity and fatigue testing. After exposure to the simulated fluid, the tensile strength of the device material should be measured and compared to an untreated device. Visual inspection of the device using optical microscopy should also be performed.

d. Burst Strength

If the device has a balloon, or is an intragastric balloon, then we recommend assessing the volume at which the balloon will burst. The purpose of this test is to evaluate the ability of the balloon to withstand rupture under a worst-case clinically anticipated scenario. We recommend that balloons not burst at least at a volume of "X" times the maximum labeled volume, where "X" represents a worst-case scenario supported by a clinical justification considering the likelihood of over inflation during device placement and/or hyperinflation during device use.

(5) Delivery/Removal System Testing

Significance: The device should be able to be safely and reliably delivered to, and removed from (if applicable), the intended location in the patient according to the instructions for use, without device failure and patient injury.

Recommendation: Simulated use testing, as part of bench testing, can be useful to ensure that a device can be placed in and/or removed from the intended location in the patient without complication. We recommend utilizing a simulated use test model that is representative of a clinically relevant worst-case tortuous anatomy that the device is anticipated to encounter when used as intended. Forces associated with deployment of the device should be measured against

pre-defined acceptance criteria. Additionally, if the device is intended to be filled with gas or liquid once placed inside the body (e.g., an intragastric balloon), then submitters should measure the inflation/deflation time against pre-defined acceptance criteria. Submitters should provide a clinically relevant justification for all acceptance criteria.

(6) Interactions with Other Devices

Significance: Interactions between an implanted device and other implants or external medical devices may impact the performance of the device.

Recommendation: If the device is implanted and may interact with other implants, or external medical devices, in particular, implanted pumps, implanted neurostimulators, external pumps like insulin pumps, other products that contain magnets, or devices such as pacemakers that may contain magnetically operated switches, then we recommend the following:

- If the device includes magnets, then submitters should provide data confirming the magnetic strength specification, and provide data showing the magnetic field strength of the device at its surface and as a function of distance from the device.
- Submitters should analyze how the device might interact with other devices like those listed above, and determine if additional warnings in labeling are warranted.

(7) Microorganism Susceptibility

Significance: Devices that are left indwelling in the gastric environment can become contaminated with microorganisms (e.g., fungi, bacteria). This is especially of concern when stomach pH is increased due to concurrent use of proton pump inhibitors (PPIs), creating a favorable growth environment. Microorganisms that colonize a device can degrade the device material(s) and compromise the functionality of the device. Hyperinflation of intragastric balloons could be associated with microbial contamination.[46] FDA is also aware of published cases of fungal and bacterial colonization of intragastric balloons.[47] This may lead to adverse events and/or loss of effectiveness. For example, a compromised intragastric balloon may deflate and move into the bowels, potentially causing an obstruction.

Recommendation: If the device is an intragastric implant, we recommend conducting a risk assessment to assess susceptibility to microorganism colonization on the device and subsequent material breakdown. The risk assessment should include, at a minimum:

- Device geometry: The device's geometry may contribute to "capturing" gut microorganisms. For example, a smooth spherical shape may not allow colonization

[46] See "The FDA alerts health care providers about potential risks with liquid-filled intragastric balloons," available at: https://www.fda.gov/medical-devices/letters-health-care-providers/fda-alerts-health-care-providers-about-potential-risks-liquid-filled-intragastric-balloons.

[47] For example, see Coskun, H., & Bozkurt, S. (2009). A case of asymptomatic fungal and bacterial colonization of an intragastric balloon. *World journal of gastroenterology*, 15(45), 5751–5753.

to occur as easily as a device design that includes external appendages (e.g., external valve).

- Impact on device material: Colonizing microorganisms may impact material properties; for example, change of elasticity could result in increased risk of material rupture.
- Gastric environment: Gastric pH may be altered during device indwelling (e.g., via concomitant use of PPIs). Additionally, if the device causes delayed gastric emptying, increased exposure times to microorganisms in the stomach may increase the likelihood of colonization.
- Clinical experience: If the device is already marketed in other countries, submitters should provide an evaluation of known microorganism contamination issues. An example of this evaluation could include an analysis of complaint data from marketing the device in other countries.
- Colonization testing: As appropriate, submitters should conduct an assessment of the affinity for anticipated microorganisms to colonize the device under anticipated use conditions. The assessment should evaluate fungal and bacterial species, as applicable.

L. Animal Studies

Significance: Due to limitations of bench models, animal studies may be warranted to support medical device premarket submissions. The *in vivo* setting generally provides an initial assessment of how a medical device interacts with biological systems, including physiological, pathological, and toxicological effects of the device, and how the biological system may affect the device.

Recommendation: We recommend submitters assess whether an animal study(ies) is warranted in the non-clinical testing plan. Study in an animal model should address factors that cannot be evaluated through bench tests alone. The study design and endpoints should be based upon the intended use of the device and clinical risk assessment. We recognize that there is no single best animal study design; however, we have the following recommendations for designing an animal study.

FDA supports the principles of the "3Rs," replace, reduce and/or refine animal use in testing when feasible. We encourage submitters to consult with us if 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 study.

We encourage submitters to take advantage of the Q-Submission Program to ensure that the animal study protocol addresses safety concerns and contains elements that are appropriate for a regulatory submission. Additionally, for information and recommendations regarding animal studies used to support medical device submissions, refer to the guidance "General

Considerations for Animal Studies Intended to Evaluate Medical Devices."[48] If the submitter is proposing to use a non-animal testing method in lieu of an animal study, we recommend discussing the proposal using the Q-Submission Program. For details on the Q-Submission Program, refer to the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[49]

(1) Animal Model

Large animal models are typically chosen for device safety evaluations, because they simulate human gastrointestinal anatomy and size. Submitters should consider relevant comparative anatomy and physiology when choosing the animal model for device safety testing. Porcine and canine models are common choices because of similarities in gastrointestinal anatomy and physiology to humans. FDA recognizes that device safety testing in an animal may be limited in some cases by model anatomy or physiology. For example, quadruped animal models may present a different anatomical device orientation *in vivo* given their stance versus the human biped. Nevertheless, the chosen animal model should be scientifically justified and able to address the safety characteristics that will be evaluated with an animal study.

(2) Study Endpoint Considerations

The primary objective of animal studies performed to support a submission to FDA is typically to evaluate safety. Animal safety studies must be performed under the Good Laboratory Practice for Nonclinical Laboratory Studies (GLP) regulation (21 CFR part 58) to help ensure the quality and integrity of the safety data submitted to the Agency. Though the objectives of some animal studies may also include usability or effectiveness, effectiveness can be challenging to meaningfully assess in animal studies for devices with indications associated with weight loss. Proof-of-concept studies, such as those evaluating device-related endocrine effects in an animal model may provide valuable data to support a future FDA submission. However, animal models of disease often present study confounders that complicate data interpretation. Therefore, effectiveness can be more difficult to interpret in an animal model, particularly if animals are still growing. FDA recognizes these limitations and believes that demonstration of effectiveness via animal testing may not be appropriate for some devices with indications associated with weight loss.

(3) Animal Study Protocol

We recommend that the animal study protocol address identified safety concerns via pre-defined objectives and acceptance criteria. Study procedures should follow the planned clinical use as closely as possible to help ensure applicability of data to device safety when used in humans. The protocol should mimic the intended device deployment, implant location, treatment

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

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

767 procedures and duration, as well as device retrieval/explant, while considering the limitations
768 inherent to the animal model.
769
770 Animal model limitations can sometimes be managed by protocol modifications. For example,
771 altering device deployment procedures in animal testing may help address anatomic differences
772 between species. In such cases, we recommend that submitters consider how clinical deployment
773 procedures could be evaluated in other testing. Including a control or sham arm can also help to
774 differentiate device- from animal model-related adverse events, which could otherwise confound
775 the study data. We recommend that submitters include a scientific justification if they believe
776 observed adverse events are related to the animal model.
777
778 Whenever possible, animal testing should evaluate the final finished version of the device
779 intended for commercial distribution. This helps ensure applicability of the animal studies data to
780 clinical use in humans. FDA recognizes that some animal studies are performed to help support
781 safety while a device is still in development. In these cases, we recommend that submitters
782 include a description of any differences between the tested and final finished version of the
783 device and an explanation of why these differences would not be expected to affect data
784 interpretation in the submission.
785
786 In some cases, biocompatibility testing recommendations may also be addressed as part of other
787 animal studies, such as to assess device safety (*See* Section III.F). In these cases, we also
788 recommend that submitters use the Q-Submission Program to obtain feedback on the feasibility
789 of this approach and how best to design the animal study protocol.
790