Medical Devices with Indications Associated with Weight Loss – Premarket Considerations

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Guidance for Industry and Food and Drug Administration Staff

Document issued on March 13, 2026.

The drafts of this document were issued on September 15, 2023.

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

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852-1740. Identify all comments with the docket number FDA-2019-N-4060. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Guidance for Industry and Food and Drug Administration Staff

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

I. Introduction

This guidance document provides recommendations regarding non-clinical testing and clinical study design for medical devices with indications for use associated with weight loss to support premarket submissions (e.g., Premarket Approval Applications (PMA), Investigational Device Exemption (IDE) Applications, Premarket Notifications (510(k)s),[1] and De Novo classification requests). The guidance also includes discussion on how FDA considers the benefit-risk analysis to support such indications.[2] 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.[3] 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.

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[1] Submission of the information recommended in this guidance may help support a demonstration of substantial equivalence of a device, or compliance with a special control. For devices reviewed through the 510(k) process, manufacturers must compare their new device to a similar legally marketed device to support its substantial equivalence (section 513(i) of the FD&C Act; 21 CFR 807.92(a)(3)).
[2] For further information on how FDA considers benefit-risk factors when evaluating substantial equivalence in 510(k)s generally, see FDA's guidance "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics." For further information on how FDA considers benefit-risk factors for PMAs and De Novo requests, see FDA's guidance "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications."
[3] For further information on weight-loss and weight-management devices, see also https://www.fda.gov/medical-devices/products-and-medical-procedures/weight-loss-and-weight-management-devices.

For the current edition of the FDA-recognized consensus standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database. If submitting a Declaration of Conformity to a recognized standard, we recommend you include the appropriate supporting documentation. For more information regarding use of consensus standards in regulatory submissions, refer to the FDA guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for 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. Background

Prior to issuing this guidance, FDA requested public comment on a concept for balancing the benefits of weight loss with the risks of adverse events associated with devices indicated for weight loss in a discussion paper (September 2019).[4] FDA considered public comments and incorporated the feedback as appropriate in developing this guidance. The discussion paper continued FDA's efforts to be transparent and informative about how we regulate devices with indications associated with weight loss.

Additionally, FDA has previously engaged stakeholders regarding how we can help to ensure patients have access to appropriately safe and effective devices indicated for weight loss:[5]

- On November 16-17, 2005, FDA's Pediatric Advisory Committee held a public meeting on Clinical Trial Design Issues for Pediatric Obesity Devices.[6]
- On October 16-18, 2011, FDA, Dartmouth Device Development/GI at Dartmouth Medical School, and the Obesity, Metabolism and Nutrition Institute at Massachusetts General Hospital co-sponsored a two-day workshop, "Device Development in Obesity and Metabolic Disease (DDOMD)."
- On May 10-11, 2012, the Gastroenterology-Urology Devices Panel of the Medical Devices Advisory Committee discussed general issues related to obesity treatment

[4] See Docket No. FDA-2019-N-4060 (https://www.regulations.gov/docket?D=FDA-2019-N-4060) for FDA's discussion paper "Consideration of Benefit-Risk Approaches for Weight-Loss Devices."
[5] See also https://www.fda.gov/medical-devices/weight-loss-and-weight-management-devices/fda-activities-weight-loss-and-weight-management-devices.
[6] FDA Pediatric Advisory Committee, *Development of Trials to Assess the Safety and Efficacy Relevant to Scientific and Ethical Issues Surrounding Trials for Pediatric Devices for Weight Loss.* Gaithersburg, MD. Meeting materials can be accessed at https://wayback.archive-it.org/7993/20170403222257/https://www.fda.gov/ohrms/dockets/ac/oc05.html#Pediatric.

devices and provided clinical study design recommendations to better evaluate the safety and effectiveness of obesity treatment devices.[7]

- In 2013, FDA published a benefit-risk assessment paradigm that could provide an a priori tool for systematic assessment of the risks associated with the devices intended for treatment of obesity and to suggest appropriate levels of benefit for devices with different risk levels.[8]
- In 2015, FDA worked with the Research Triangle Institute Health Solutions (RTI-HS) to conduct the first national benefit-risk patient preference study to provide information on patient risk tolerance for weight loss devices.[9]
- On June 28, 2018, FDA held a listening session with patients who have used FDA-approved devices with indications associated with weight loss.

FDA refers the reader to the Q-Submission Program throughout this guidance document. For details on the Q-Submission Program, refer to the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."

III. 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	Implant, Intragastric For Morbid Obesity	Not applicable[10]
OYF	Aspiration Therapy System	Not applicable[11]
PIM	Neuromodulator For Obesity	Not applicable[12]
ONY	Oral Removable Retainer For Weight Management	21 CFR 876.5981[13]

[7] 2012 Materials of the Gastroenterology-Urology Devices Panel can be accessed at https://wayback.archive-it.org/7993/20170113191551/http:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/ucm286235.htm.
[8] Lerner, H., Whang, J., & Nipper, R. (2013). Benefit-risk paradigm for clinical trial design of obesity devices: FDA proposal. *Surgical Endoscopy*, 27(3), 702-707. doi: 10.1007/s00464-012-2724-3
[9] Ho, M. P., Gonzalez, J. M., Lerner, H. P., Neuland, C. Y., Whang, J. M., McMurry-Heath, M., Hauber, A.B. & Irony, T. (2015). Incorporating patient-preference evidence into regulatory decision making. *Surgical Endoscopy*, 29(10), 2984-2993. doi: 10.1007/s00464-014-4044-2
[10] This is a postamendments class III device.
[11] This is a postamendments class III device.
[12] This is a postamendments class III device.
[13] This classification regulation includes special controls. *See* 21 CFR 876.5981(b).

Product Code	**Product Code Name**	**Regulation Number**
QFQ	Ingested, Transient, Space Occupying Device For Weight Management And/Or Weight Loss	21 CFR 876.5982[14]
QTD	Endoscopic Suturing Device For Altering Gastric Anatomy For Weight Loss	21 CFR 876.5983[15]

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 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 palatal space occupying devices for weight management and/or weight loss, 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.[16] For devices that are subject to special controls, the special controls identified in the classification regulations such as biocompatibility, non-clinical and clinical performance testing, labeling, and training must be met to provide a reasonable assurance of safety and effectiveness.

This guidance provides recommendations regarding information included in premarket submissions for devices with indications for use associated with weight loss.[17] The recommendations in this guidance may be applicable to devices that are reviewed via the De Novo classification,[18] PMA,[19] or 510(k)[20] pathways. This guidance document supplements other

[14] This classification regulation includes special controls. *See* 21 CFR 876.5982(b).
[15] This classification regulation includes special controls established in the classification 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.
[16] See classification order, available at https://www.accessdata.fda.gov/cdrh_docs/pdf21/DEN210045.pdf.
[17] The recommendations contained in this guidance are intended to help submitters meet certain applicable premarket submission and other requirements (e.g., compliance with special controls). We note that some of the information discussed is required in certain premarket submissions. For example, a PMA must generally include a device description, i.e., an explanation of how the device functions, the basic scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device. (21 CFR 814.20(b)(3)(ii)). The applicable premarket submission requirements in the regulations and FD&C Act should be reviewed for information on these requirements.
[18] For devices that are reviewed via the De Novo classification pathway, refer to 21 CFR Part 860, subpart D, and FDA's guidance "De Novo Classification Process (Evaluation of Automatic Class III Designation)."
[19] For devices that are reviewed via the Premarket Approval pathway, refer to 21 CFR Part 814 and PMA guidance documents available at https://www.fda.gov/medical-devices/premarket-approval-pma/pma-guidance-documents.
[20] For devices that are reviewed in premarket notification submissions, refer to 21 CFR Part 807, subpart E, and FDA's guidance "Electronic Submission Template for Medical Device 510(k) Submissions."

FDA documents regarding the specific content requirements of and recommendations for premarket submissions.

IV. Premarket Submission Recommendations

A. Device Description

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

- 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.
- 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 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 "Technical Considerations for Non-Clinical Assessment of Medical Devices Containing Nitinol."

B. Labeling

For a PMA, submitters must generally 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 its use must be provided. (21 CFR 807.87(e)). Lastly, for De Novo requests, submitters must generally provide labeling sufficient to describe the device, its intended use, and the directions for its use. (21 CFR 860.220(a)(18)).

Prescription 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, to be so exempt, labeling that furnishes information for use of the device must, among other things, contain adequate information for such use, including indications, effects, routes, methods, and frequency and duration of administration and any relevant hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to employ the device can use the device safely and for the purposes for which it is intended (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 and/or in other labeling materials that may apply specifically to devices with indications associated with weight loss.[21]

(1) Warnings

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

(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." 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 refer to Section IV.M and Section V. 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 study participants[22] enrolled;
- Number of investigational sites both inside the United States (U.S.) and outside the United States (O.U.S.);
- Primary study endpoints;
- Secondary study endpoints, as applicable;
- 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 (T2DM), 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

[21] Notably, not including relevant hazards, contraindications, side effects, and precautions, as described in 21 CFR 801.109(c), may mean that the device is not exempt from section 502(f)(1) of the Act and could be deemed to be misbranded under that provision.
[22] Throughout this document, FDA uses the terms *human subject*, *subject*, *study participant*, and *participant* interchangeably. See 21 CFR 50.3(g), 812.3(p).

section of the device labeling. Any labeling associated with secondary effectiveness endpoints should be based on results that are both clinically and statistically significant (*See* Section IV.M(7)). 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.M(8), submitters should include potential risks associated with the device.[23]

FDA has alerted health care providers about potential risks with liquid-filled intragastric balloons.[24] 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."

For MR Conditional devices, we recommend submitters include in the patient labeling, including 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" 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.

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[23] See also 21 CFR 801.109(c), which requires that labeling on or within the package from which the device is to be dispensed bear information for use, including any relevant hazards, contraindications, side effects, and precautions, as described in that regulation, for the device to be exempt from section 502(f)(1) of the Act.
[24] 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.

(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.[25]

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, 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 followed. In the absence of a recognized standard, a comprehensive description of the process and the complete validation protocol should be submitted and reviewed.
3. FDA recommends a 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. Submitters should state the SAL in their submission.

(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

[25] For 510(k) submissions, we recommend that submitters provide information for the final sterile device as described in FDA's guidance "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile."

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:

- 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;
- Description and justification of the type and frequency of microbial monitoring conducted;
- The level of bioburden on the device and the historical data and scientific justification used to determine alert and action levels;
- Bioburden recovery efficiency validation and bioburden culture methods; and
- 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 follow recommendations regarding pyrogen limit specifications.[26] Submitters should also follow the recommendations in "Pyrogen and Endotoxins Testing: Questions and Answers." To address the risks associated with material-mediated endotoxins, refer to the 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.'"

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 IV.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.[27] 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 the proposed shelf life. We recommend following the methods described in the FDA-recognized series of consensus standards ISO 11607-1 *Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems* and ISO 11607-2 *Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly processes.*

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 IV.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,

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[26] For 510(k) submissions, submitters should follow the pyrogencity testing recommendations outlined in FDA's guidance "Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile."

[27] 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.

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 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.[28] 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. (See 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, manufacturing, 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

[28] 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.

- Part 1: Evaluation and testing within a risk management process.'" The evaluation should explain the relationship between the identified biocompatibility risks, the information available to mitigate the identified risks, and knowledge gaps that remain. Submitters should then identify any biocompatibility testing or other evaluations that were conducted to mitigate remaining risks. We recommend that submitters consider the recommendations in that guidance, which identifies the types of biocompatibility assessments that should be considered and recommendations regarding how to conduct related tests.

Data from an animal study[29] 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."

G. Software

Significance: When a device has indications associated with weight loss and contains device software function(s), the device software function(s) should ensure that the device is operating within safe parameters for the intended patient population(s), and that adequate alarms are provided to the user if warranted. Adequate software testing helps provide assurance that the device functions as intended.

Recommendation: Refer to the FDA guidance "Content of Premarket Submissions for Device Software Functions" for a discussion of the software documentation that submitters should provide in the marketing submission. The premarket software guidance outlines the

[29] 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.

recommended information to be provided in a premarket submission for a device that includes a device software function 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 premarket software guidance, the submitter should provide a scientific justification that supports the rationale of the Documentation Level based on the risks of the device software function(s) in the context of the device's intended use.

We recommend submitters provide a full description of the device software function(s) supporting the operation of the subject device following this software guidance. This recommendation applies to original devices as well as to any software changes made to already-marketed devices. Changes to software[30] must be revalidated and reverified in accordance with your quality management system.[31]

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. Refer to FDA's guidance "Cybersecurity in Medical Devices: Quality Management System Considerations and Content of Premarket Submissions" for a discussion of the cybersecurity documentation that submitters should provide in the submission.

If the device includes off-the-shelf software, submitters should provide the additional information as recommended in the FDA guidance document "Off-the-Shelf Software Use in Medical Devices."

Overall, the documentation related to the device software function(s) should provide sufficient evidence to describe the role of the software in the context of the device's intended use, and testing to demonstrate that the software functions as designed.

H. Electrical Safety and Electromagnetic Compatibility (EMC)

Significance: If the device 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:

[30] For 510(k)-cleared devices, some software changes may warrant the submission of a new 510(k). For further information on this topic, refer to FDA's guidance "Deciding When to Submit a 510(k) for a Software Change to an Existing Device."

[31] Manufacturers are required to establish and maintain an appropriate quality management system as set forth in 21 CFR Part 820.

- IEC 60601-1 *Medical electrical equipment - Part 1: General requirements for basic safety and essential performance* (with relevant U.S. national differences applied).
- 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 FDA-recognized standards, we recommend that appropriate supporting documentation[32] be provided. Information regarding test methods chosen should be provided, because this series of standards includes general methods with multiple options and, in some cases, does not include specific acceptance criteria. For additional information on providing electromagnetic compatibility information in a premarket submission, see FDA's guidance "Electromagnetic Compatibility (EMC) of Medical Devices."

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

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.

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."

We recommend submitters consult FDA's guidance "Radio Frequency Wireless Technology in Medical Devices" 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:

[32] For more information on Declarations of Conformity and on appropriate supporting documentation, refer to FDA's guidance "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices."

- 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 induction of 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 issues affecting 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."

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

K. Non-Clinical Bench Performance Testing

Non-clinical bench performance testing supports device use, 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 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."

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."

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.

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.[33] 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

[33] 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.

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 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 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."

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 IV.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.[34, 35] 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:

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

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[34] Bortolotti, M., Annese, V., and Coccia, G. (2000). Twenty-four hour ambulatory antroduodenal manometry in normal subjects (co-operative study). *Neurogastroenterology and Motility,* 12(3): 231-238. doi:10.1046/j.1365-2982.2000.00204.x

[35] 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. *American Journal of Physiology. Gastrointestinal and Liver Physiology,* 280(5): G844-849. doi:10.1152/ajpgi.2001.280.5.G844

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 leading to delayed or inadequate treatment, and patient injury.

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, 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.[36] FDA is also aware of published cases of fungal and bacterial colonization of intragastric balloons.[37] 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 to occur as easily as a device design that includes external appendages (e.g., external valve).

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[36] 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.

[37] 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. doi:10.3748/wjg.15.5751

- 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 proton pump inhibitors). 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," to 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 also 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." 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.

(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 procedures and duration, as well as device retrieval/explant, while considering the limitations inherent to the animal model.

Animal model limitations can sometimes be managed by protocol modifications. For example, altering device deployment procedures in animal testing may help address anatomic differences between species. In such cases, we recommend that submitters consider how clinical deployment procedures could be evaluated in other testing. Including a control or sham arm can also help to differentiate device- from animal model-related adverse events, which could otherwise confound the study data. We recommend that submitters include a scientific justification if they believe observed adverse events are related to the animal model.

Whenever possible, animal testing should evaluate the final finished version of the device. This helps ensure applicability of the animal studies data to clinical use in humans. FDA recognizes that some animal studies are performed to help support safety while a device is still in development. In these cases, we recommend that submitters include a description of any differences between the tested and final finished version of the device, and an explanation of why these differences would not be expected to affect data interpretation in the submission.

In some cases, biocompatibility testing recommendations may also be addressed as part of other animal studies, such as to assess device safety (*See* Section IV.F). In these cases, we also recommend that submitters use the Q-Submission Program to obtain feedback on the feasibility of this approach and how best to design the animal study protocol.

M. Clinical Performance Testing Considerations

Significance: Generally, non-clinical evaluation does not fully characterize all clinical experience, outcomes, and risks for these devices. We recommend submitters conduct *in vivo* (i.e., clinical) studies to evaluate device safety and effectiveness for new or significantly modified devices with indications associated with weight loss.

Recommendation: For novel device designs, feasibility clinical studies can provide important safety and some effectiveness data that can be used to support a pivotal study. Pivotal studies can provide important safety and effectiveness data used to support marketing authorization.

Devices within the scope of this guidance document are generally considered significant risk devices and subject to all requirements of the Investigational Device Exemptions (IDE) regulation, 21 CFR Part 812, for studies conducted in the U.S. See the FDA guidance titled "Significant Risk and Nonsignificant Risk Medical Device Studies." In addition to the requirements of 21 CFR Part 812, sponsors of such trials of a device conducted in the U.S. must generally comply with the regulations governing institutional review boards (21 CFR Part 56) and the protection of human subjects (21 CFR Part 50), including informed consent (21 CFR Part 50, subpart B).

Obesity represents a heterogeneous disease impacted by demographic, clinical and behavioral factors.[38] Additionally, culture and public health policy can impact weight loss.[39] Thus, FDA has encountered challenges about the applicability of foreign effectiveness data to the U.S. population for devices with indications associated with weight loss. Therefore, we recommend that pivotal studies be conducted in the U.S. If foreign data is collected, we recommend that no more than 50% of the pivotal study data be collected from outside the U.S. (O.U.S.). We also recommend that no more than 20% of the total enrollment population be from one site to avoid the study outcome being dominated by sites with large enrollment.

[38] Jimenez, M. P., Green, M. A., Subramanian, S. V., & Razak, F. (2018). A demographic, clinical, and behavioral typology of obesity in the United States: an analysis of National Health and Nutrition Examination Survey 2011-2012. *Annals of Epidemiology*, 28(3), 175–181.e4. doi: 10.1016/j.annepidem.2018.01.001

[39] Waxman A. WHO Global Strategy on Diet, Physical Activity and Health. *Food and Nutrition Bulletin*. 2004;25(3):292-302. doi: 10.1177/156482650402500310

When data from clinical investigations conducted O.U.S. are submitted to FDA, the requirements of 21 CFR 812.28 may apply.[40] 21 CFR 812.28(a) outlines the conditions for FDA acceptance of data from clinical investigations conducted O.U.S. to support an IDE or a device marketing application or submission. For more information, see the FDA guidance "Acceptance of Clinical Data to Support Medical Device Applications and Submissions: Frequently Asked Questions."

If a submitter would like specific feedback on any of the following aspects of a proposed clinical study design, we recommend submitters use the Q-Submission Program.

(1) Study Design

We recommend that pivotal studies to support a weight loss indication be double-blinded, randomized, controlled trials (RCTs). We recommend that additional study staff remain blinded throughout the study (e.g., dieticians, personnel collecting study data).

Where scientifically feasible, we recommend a sham-controlled study to minimize any anticipated placebo effect. Particularly for first-in-kind devices, a sham control in a clinical study can provide an important comparator from which to determine the effectiveness of device therapy in comparison to the placebo effect. Therefore, a sham control is beneficial to reduce the uncertainty regarding the treatment effects of the device.[41] We recommend the sham device and/or sham procedure be designed in a way to minimize the study participant's ability to determine whether they have the study device or the sham device. We recommend that submitters consider how blinding will be assessed if using a sham control. We appreciate that a sham control may not be appropriate in all circumstances. If a sham device or sham procedure is not appropriate for a clinical trial design, we recommend a concurrent control arm where the control and treatment groups follow the same lifestyle programs. For all study designs, we recommend standardized dietary and behavioral study aspects between study arms and among centers involved in the study, and that these study aspects be representative of real-world diet and behavior regimens.

For additional information on principles for the design of premarket clinical studies, refer to FDA's guidance "Design Considerations for Pivotal Clinical Investigations for Medical Devices."

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[40] 21 CFR 812.28 applies to relevant clinical investigations that enroll the first subject on or after February 21, 2019, and that support an IDE or a device marketing application or submission to FDA.

[41] Members of the Gastroenterology and Urology Devices Panel generally agreed at their May 10, 2012 meeting "that a sham is appropriate when technically and scientifically feasible for first in kind devices." For more information, see https://wayback.archive-it.org/7993/20170113120437/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/UCM306942.pdf Additional discussion of the general use of sham controls is available at https://wayback.archive-it.org/7993/20170113120440/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/UCM306943.pdf

(2) Study Duration and Follow-up Schedule

The study should be designed to include adequate follow up to support the indications for use. The follow-up period should also account for the risk posed by device use.

To support device effectiveness, study duration and the follow-up schedule should be selected with the proposed indication in mind.

- For a proposed indication of "weight loss," the duration of device use and primary endpoint should typically demonstrate weight loss at 12 months or more.
- A proposed indication of "short term weight loss" can typically be supported with a duration of device use and primary endpoint demonstrating weight loss at six months or more, but less than 12 months.
- Weight loss measured at, or a device that is used for, less than six months could be supportive of a proposed "weight management" indication.
- Additional follow-up may also be warranted to understand the durability of weight loss. Sometimes a supplemental marketing submission is submitted after these additional follow-up data are collected, for example, to update labeling. Consequently, we recommend consenting study participants long enough for any anticipated additional follow-up which may be necessary to support such labeling (or other) modifications.

To support device safety, study duration and follow-up should be adequate to collect sufficient adverse event information depending on the device design and how it is used. The duration of follow-up needed to support device safety may be longer than that to support effectiveness, if warranted, due to the risk that the device may pose to patients.

(3) Inclusion/Exclusion Criteria

As body mass index (BMI) increases, risk of weight-related morbidity and mortality increases. The BMI range for inclusion in a clinical study should be the result of a risk-based decision to ensure that study participants will have an appropriate level of anticipated benefit to offset the risks associated with the device.

In general, clinical trials of implanted or surgically-placed devices should enroll individuals with a BMI greater than or equal to 35 kg/m^2, or greater than or equal to 30 kg/m^2 if accompanied by weight-related comorbidities (e.g., T2DM).[42] In studies of lower risk devices, study participants with a BMI of 27 kg/m^2 with weight-related comorbidities may be included. Higher-risk device studies may warrant additional specification of the BMI range and/or weight-related comorbidities to ensure that the anticipated benefit outweighs the probable risks.

[42] This recommendation is consistent with the 2018 position statement of the American Society of Metabolic and Bariatric Surgery (ASMBS): Aminian, A., Chang, J., Brethauer, S. A., Kim, J. J. (2018). ASMBS updated position statement on bariatric surgery in class I obesity (BMI 30–35 kg/m^2), *Surgery for Obesity and Related Diseases*, 14(8), 1071-1087. doi: 10.1016/j.soard.2018.05.025

Given the risks associated with implanted or surgically-placed devices, participants in studies of such devices should have failed more conservative, first-line weight loss methods such as diet, exercise, and behavior modification.

Use of these medical devices in a clinical study may not be appropriate for certain study participants. We recommend that submitters consider the following for the exclusion criteria as applicable:

- Participants who are unable or unwilling to follow the dietary restrictions specified by the clinical protocol;
- Altered anatomy (e.g., sleeve gastrectomy);
- History of dysmotility, delayed gastric emptying, and syndromes associated with recurrent vomiting;
- Pregnancy or breastfeeding;
- Current smokers, because of the contribution of smoking to obesity-linked comorbidities and increased risk of complications;
- Persons with a history of eating disorder(s), or a serious or uncontrolled psychiatric illness that could compromise understanding or compliance with visits and device maintenance/removal;
- Active substance abuse;
- Untreated endocrine or metabolic cause for obesity;
- Previous gastrointestinal surgery (e.g., bowel resection);
- Older participants for whom the risks of the procedure are not acceptable and/or the anticipated lifespan conflicts with the expected period of benefit; and
- Persons without access to adequate follow up to monitor device safety and/or function (e.g., participants who live alone, lack home support, or live outside of a reasonable distance from the study site).

(4) Study Participant Demographics

We recommend that submitters include in their study a representative sample of participants from various demographic groups (e.g., sex, age, ethnic, and racial) in which the prevalence of obesity is highest. FDA recommends that clinical studies for these devices enroll participants that reflect the demographics for clinically relevant populations, where feasible.

For more information regarding the evaluation and reporting of age, race, ethnicity and sex-specific data in medical device clinical studies, see FDA's guidances "Evaluation of Sex-Specific Data in Medical Device Clinical Studies" and "Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies."

(5) Treatment Parameters/Protocol

The study-specific treatment protocol should minimize risk to participants. The protocol should not only consider the risks associated with the device and device placement, but any additional risk that may be applicable to all populations included in the study. For example, if submitters choose to include participants with certain comorbidities (e.g., T2DM), the protocol should explain how these participants will be protected from complications that may arise due to their disease.

Specifically, when designing trials that include participants with T2DM, we recommend that a safety monitoring plan be included in the protocol to detect and manage hypoglycemia or continued uncontrolled hyperglycemia. The management plan should consider an algorithm for the lowering or elimination of oral hypoglycemics or insulin based on fasting glucose levels and/or glycated hemoglobin (HbA1c)[43] (for participants who lose clinically significant amounts of weight).

For a device with novel technology and/or with an undefined risk profile, it may also be appropriate to prospectively define stopping rules in the study protocol and/or initially enroll a limited number of participants in a phased manner to better manage risk.

If the device is a permanent implant, the study design should include considerations for how a device should be explanted if warranted or requested during or at termination of the study. Considerations should include, at a minimum, removal instructions and a plan for tracking reasons for device explant, including association with any adverse events as noted in Section IV.M(6) below. There should also be evidence that removal instructions in device labeling are sufficient to safely remove the device if explant is warranted. Removal instructions should be evaluated during the course of the clinical study if devices are explanted from participants.

Throughout the study, participants should receive the standard of care, including medication and monitoring for comorbidities such as hypertension, dyslipidemia, and glycemic control.

(6) Safety Endpoints and Data

The primary safety endpoint should be reporting of all device- and procedure-related adverse events, as FDA intends to consider all adverse events in our assessment of the premarket submission. Additional safety assessments may be warranted based on the design and principles of operation of the specific device.

(7) Effectiveness Endpoints and Data

Demonstrated weight loss should be based on percent total body weight loss (% TBWL),[44] which is typically captured in a clinical study with co-primary effectiveness endpoints that include:

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[43] HbA1c (glycated hemoglobin) is a term commonly used in relation to diabetes - the higher the HbA1c, the greater the risk of developing diabetes-related complications.

[44] For the purposes of this guidance, FDA defines $\% \text{ TBWL} = [(\text{initial weight} - \text{final weight})/\text{initial weight}] \times 100\%$.

- a hypothesis with a pre-specified superiority margin of the mean % TBWL over control; and
- a performance goal for a responder rate based on individual participant success.

FDA recommends a pre-specified superiority margin for mean % TBWL be included in the clinical protocol depending on the indication being sought in the premarket submission:

- For an indication of "weight loss," we recommend at least a 5% superiority margin of the mean % TBWL over the control.[45] However, the minimum value over the control arm should be appropriate for the risk associated with device use and any device-related procedures.
- For an indication of "limited weight loss," we recommend at least a 2% superiority margin of the mean % TBWL over the control.[46] However, the minimum value over the control arm should be appropriate for the risk associated with device use and any device-related procedures.
- For an indication of "weight management," a superiority margin of less than 2% may be supportive if additional benefit is measured (i.e., responder rate endpoint is met).[47] However, the benefit should be appropriate for the risk associated with device use and any device-related procedures.

For the responder rate, we recommend that at least 50% of treated participants achieve at least 5% TBWL for any indication associated with weight loss (i.e., weight loss, limited weight loss, weight reduction, weight management, or obesity treatment).

For an indication of "obesity treatment," we recommend endpoint(s) demonstrating clinical benefits in addition to weight loss alone. Support for additional benefits should be appropriately powered in the study design.

We recommend submitters consider the following secondary effectiveness endpoints:

- Percent excess weight loss (% EWL);[48]
- Change in weight;
- Change in BMI; and

[45] See FDA's discussion paper "Consideration of Benefit-Risk Approaches for Weight-Loss Devices."
[46] *Ibid.*
[47] Jensen, M. D., Ryan, D. H., Apovian, C. M., Ard, J. D., Comuzzie, A. G., Donato, K. A., & Yanovski, M. (2014). 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*, 129(25 Suppl 2), S102-138. doi: 10.1161/01.cir.0000437739.71477.ee
[48] For the purposes of this guidance, FDA defines % EWL =
$[(\text{initial weight } - \text{weight to be at a BMI of } 25)/\text{initial weight}] \times 100\%$.

- Change in waist circumference.[49, 50]

We also recommend that submitters consider including patient-reported outcomes (PROs)[51] and patient preference information (PPI)[52]. The treatment's ability to improve relevant aspects of the patient's quality of life, the value patients associate with the treatment, their willingness to accept the risk of this treatment to achieve the benefit, and the patient's ability to understand the benefits and risks of the treatments are important factors in evaluating a device's benefit-risk profile.

Changes in common weight-related comorbidities are often secondary endpoints in studies of devices with indications associated with weight loss. 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 or confidence intervals), we recommend pre-specifying this intention in the study protocol and providing a detailed description of the statistical methods planned to follow. The study should be powered appropriately to evaluate such changes if comparative statements are intended to be made in the labeling.

(8) Adverse Events

We recommend that all adverse event data be collected during the study and that events be adjudicated as to whether they are device- and/or procedure- related. In general, we recommend that studies have a data safety monitoring board (DSMB) and establish an endpoint assessment/adjudication committee. We refer the submitter to FDA's guidance "Establishment and Operation of Clinical Trial Data Monitoring Committees" for more information. Independent data monitoring committees help to ensure the safety of enrolled participants as follows:

- The committee can provide a comparative assessment of accumulating safety and effectiveness data to inform recommendations to the study sponsor whether to continue, modify, or stop the study;
- Potential complications may warrant robust study oversight from a third party that is advisory to the study sponsor; and

[49] Ross R., Neeland I.J., Yamashita S., Shai I., Seidell J., Magni P., Santos R.D., Arsenault B., Cuevas A., Hu F.B., Griffin B.A., Zambon A., Barter P., Fruchart J.C., Eckel R.H., Matsuzawa Y., Després J.P. (2020) Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. *Nature Reviews. Endocrinology*, 16(3):177-189. doi: 10.1038/s41574-019-0310-7

[50] Bener A., Yousafzai M.T., Darwish S., Al-Hamaq A.O., Nasralla E.A., Abdul-Ghani M. (2013) Obesity index that better predict metabolic syndrome: body mass index, waist circumference, waist hip ratio, or waist height ratio. *Journal of Obesity*, 2013:269038. doi: 10.1155/2013/269038

[51] See FDA guidances "Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation," and "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims"

[52] See FDA guidance "Patient Preference Information - Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling."

- Unbiased adjudication of adverse events reduces the uncertainty in study safety outcome data.

We recommend an adverse event classification modeled after the Clavien-Dindo Classification of Surgical Complications,[53] shown in Table 2, where the severity of each adverse event is graded based on the treatment used to address the event.

Table 2. Adverse event classification for clinical studies

Grade	Definition
Grade I	Any deviation from the normal treatment course without the need for surgical, endoscopic, and radiological interventions. Includes all over-the-counter pharmacological interventions and non-narcotic prescription pain medications (including anti-emetics, antipyretics, analgesics, diuretics, electrolytes, physiotherapy, and bedside wound care)
Grade II	Requiring pharmacological treatment with prescription drugs (excluding non-narcotic pain medications in Grade I), the administration of intravenous fluids, blood transfusions, or total parenteral nutrition
Grade III	Requiring surgical, endoscopic, or radiological interventions
Grade IV	Life-threatening complications requiring intensive care/intensive care unit management (including single and multiorgan dysfunction, and central nervous system complications)
Grade V	Death

The classification scheme identified in Table 2 focuses on deviations from the normal treatment course for a device. For example, the normal treatment course for a device may include use of concomitant medications, and additional therapy (e.g., anti-emetics, pain medication) typically provided as part of the practicing physician's treatment plan. While concomitant medications are not considered as adverse events per this classification scheme, FDA does consider such as part of the overall benefit-risk determination for a device, as described in Table 4 in Section V.A.

A single type of adverse event can be categorized into different grades, depending on the treatment required for resolution. For example, vomiting can be resolved with over-the-counter medication (Grade I), or vomiting can require administration of intravenous fluids (Grade II). The grades are to be considered mutually exclusive, and together the grades should cover all event outcomes. All events that fit into a single grade are of approximately equal severity/risk to the study participant.

[53] Dindo, D., Demartines, N., & Clavien, P. A. (2004). Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery*, 240(2), 205-213. doi: 10.1097/01.sla.0000133083.54934.ae

We recommend submitters present adverse event information to FDA in their premarket submission as follows:[54]

- Tabulate all adverse events and categorize as device-related, procedure-related, or not related to the device or procedure and categorize all adverse events as explained in Table 2;
- Tabulate all serious adverse events (SAEs) and categorize as device-related, procedure-related, or not related to the device or procedure and categorize all SAEs as explained in Table 2;
- Identify any and all unanticipated adverse device effects;
- Provide the time to onset as well as duration for all gastrointestinal-associated device- and/or procedure-related adverse events, including resolution status; and
- Tabulate all unanticipated device removals and the reason for removal.

We recommend the use of PRO instruments to assess non-serious adverse events using validated tools such as the gastrointestinal symptom scales included in the National Institutes of Health (NIH) PRO Measurement Information System (PROMIS).[55]

(9) Statistical Analysis Considerations

a) Sample Size

For pivotal studies, we recommend that co-primary effectiveness endpoints include a hypothesis with a pre-specified superiority margin for percent total body weight loss and a performance goal for a responder rate. The number of study participants should be the maximum of sample sizes calculated based on the co-primary endpoints considering anticipated loss to follow-up; however, additional participants should be enrolled to assess device safety to support premarket submission. In general, calculations should be based on two-sided tests of significance at the 5% level and at least 80% power. Effect sizes for the calculations should represent clinically meaningful differences.

b) Analysis Methods

Endpoints should be analyzed based on the intent-to-treat (ITT) population, defined as study participants that were enrolled and randomized into the study, regardless of whether the participant received the treatment to which they were randomized.

Note that in general, FDA considers modified intent-to-treat (mITT) analysis to be a supportive analysis. The use of a mITT population may be suboptimal because the estimated treatment

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[54] As described in Section IV.B(4) of this guidance, FDA recommends that the adverse event information in this list also be included in the device's labeling.

[55] Spiegel, B. M., Hays, R. D., Bolus, R., Melmed, G. Y., Chang, L., Whitman, C., ... & Khanna, D. (2014). Development of the NIH patient-reported outcomes measurement information system (PROMIS) gastrointestinal symptom scales. *The American Journal of Gastroenterology*, 109(11), 1804-1814. doi: 10.1038/ajg.2014.237

effects could be confounded by imbalanced baseline prognostic factors and because inference using the mITT population may not be generalizable to the overall intended use population. If a submitter proposes to use a mITT analysis to support study endpoints, FDA recommends including a study-specific definition for the mITT group as mITT analysis may vary based on the device type and area of disease. We encourage submitters to utilize FDA's Q-Submission Program if the use of a mITT primary analysis population is proposed.

The analysis of % TBWL should use analysis of variance (ANOVA) or analysis of covariance (ANCOVA) with baseline weight as a covariate in the model.

Response rates should be compared between the treatment and control groups using statistical methods appropriate for categorical data. A sensitivity analysis should be conducted that considers participants who are treated, drop out, and do not have complete post-baseline data as treatment failures. Additionally, a tipping point analysis for binary response variables should be considered.

Type I error should be controlled across all clinically relevant secondary effectiveness endpoints intended for product labeling.

c) Missing Data

i. Efforts to reduce missing data

We recommend you describe the efforts that will be used during the course of the study to monitor and minimize the incidence of study participant dropouts, such as monitoring activities, special incentives to participants for study compliance, methods to remind participants of scheduled visits, and specific efforts to contact participants who miss their visit (e.g., telephone calls, postcards, contact family members or caretakers).

ii. Document reasons for missing data

We recommend you identify the steps to document:

- the reason for each missed visit, e.g., complications, difficulty getting transportation to the site; and
- the reason for each dropout, e.g., seeking alternate therapy, complications or intolerance to the device, dissatisfaction with the device, moved away.

To permit a complete and detailed accounting of all study participants, we recommend you collect complete information regarding the occurrence of missing data during the study because loss to follow-up jeopardizes the conclusions that can be made about the long-term safety and effectiveness of a device.

iii. Handling missing primary endpoint data

To allow for a true ITT analysis, we recommend obtaining body weight measurements in all participants who prematurely withdraw from studies near the calendar date at which they were scheduled. This will reduce uncertainty in the ultimate outcome of the study by having a data measurement at the primary effectiveness endpoint rather than imputing the measurement. For example, a participant who withdraws from a 12-month study after six months of treatment should have a body weight measurement at the time he or she would have completed 12 months of study participation. If this is not possible, we recommend conducting sensitivity analyses to determine the best mechanism to account for missing data.

iv. Sensitivity analyses

Sensitivity analyses employing imputation strategies should assess the effect of dropouts on the results. The imputation strategy should be prespecified and should consider the expected dropout patterns and the time-course of weight changes in the treatment group. No imputation strategy will work for all situations, particularly when the dropout rate is high, so a primary study objective should be to keep missing values to a minimum. We recommend multiple imputation when a "missing at random" assumption is plausible. For early exit due to adverse events or ineffectiveness of the device, we recommend you use "unfavorable clinical outcome" to impute missing data.

d) Subgroup Analyses

We recommend submitters conduct sex-based subgroup analyses.[56] We recommend submitters conduct subgroup analyses based on race and ethnicity[57] as the prevalence of obesity varies among these groups in the U.S. population.[58] If the study includes sites O.U.S., then we recommend conducting a U.S. subgroup analysis.

(10) Pediatric Studies

Planning clinical trials for pediatric subjects includes additional considerations beyond those of adult subjects, such as ethical issues of studying a population that is vulnerable to coercion or undue influence,[59] and an altered benefit-risk profile because of potential interference of a medical device with physical growth and maturation. Consistent with the FDA guidance "Premarket Assessment of Pediatric Medical Devices," FDA considers study participants below 22 years of age to be pediatric (that is, from birth up to but not including the 22nd birthday) for medical device studies.

The increased prevalence of children being overweight or having obesity emphasizes an unmet need to provide therapy to children who have a disease that impacts their health, quality of life,

[56] See also FDA's guidance "Evaluation of Sex-Specific Data in Medical Device Clinical Studies - Guidance for Industry and Food and Drug Administration Staff."
[57] See also FDA's guidance "Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies."
[58] https://www.niddk.nih.gov/health-information/health-statistics/overweight-obesity
[59] See also 21 CFR 56.111(b).

and psychosocial factors. FDA remains open to considering risk-based clinical study designs and intends to consider both the benefits and risks to adolescent[60] study participants when determining the amount of benefit-risk evidence needed before initiation of an adolescent weight-loss device study.

We recommend using the U.S. Centers for Disease Control and Prevention (CDC) National Center for Health Statistics definitions for classifying pediatric-aged participants as overweight or obese, and the American Heart Association recommendation for classifying severe obesity based on age- and sex-matched BMI cutoffs as follows:[61, 62, 63, 64]

- BMI-for-age between the 85th and 95th percentile is overweight;
- BMI-for-age at or above the 95th percentile is obesity; and
- BMI ≥120% of the 95th percentile or an absolute BMI ≥35 kg/m^2, whichever is lower based on age and sex, is severe obesity.

FDA developed the following recommendations considering outcomes from the 2005 FDA Pediatric Advisory Committee (PAC) meeting on weight loss device clinical trial designs for pediatric participants,[65] changes in the field of childhood obesity since the PAC's recommendations,[66] and input from external experts, including clinicians. Additionally, the following recommendations are intended to supplement and not supersede those discussed in the FDA guidance "Premarket Assessment of Pediatric Medical Devices." These recommendations are in addition to those discussed elsewhere in this document for adult participants.

Recommendations specific for pediatric participants include:

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[60] Consistent with the FDA guidance "Premarket Assessment of Pediatric Medical Devices," for purposes of this guidance, FDA considers adolescent study participants to be greater than 12 through 21 years of age.

[61] Kelly, A. S., Barlow, S. E., Rao, G., Inge, T. H., Hayman, L. L., Steinberger, J., ... & Daniels, S. R. (2013). Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. *Circulation*, 128(15), 1689-1712. doi: 10.1161/CIR.0b013e3182a5cfb3

[62] Gulati, A. K., Kaplan, D. W., & Daniels, S. R. (2012). Clinical tracking of severely obese children: a new growth chart. *Pediatrics*, 130(6), 1136-1140. doi: 10.1542/peds.2012-0596

[63] Ogden, C. L., & Flegal, K. M. (2010). Changes in terminology for childhood overweight and obesity. *National Health Statistics Reports*, 25, 1-5.

[64] Flegal, K. M., Wei, R., Ogden, C. L., Freedman, D. S., Johnson, C. L., & Curtin, L. R. (2009). Characterizing extreme values of body mass index-for-age by using the 2000 Centers for Disease Control and Prevention growth charts. *The American Journal of Clinical Nutrition*, 90(5), 1314-1320. doi: 10.3945/ajcn.2009.28335

[65] FDA Pediatric Advisory Committee, *Development of Trials to Assess the Safety and Efficacy Relevant to Scientific and Ethical Issues Surrounding Trials for Pediatric Devices for Weight Loss*. Gaithersburg, MD. Meeting materials can be accessed at https://wayback.archive-it.org/7993/20170403222257/https://www.fda.gov/ohrms/dockets/ac/oc05.html#Pediatric.

[66] Marrone A.K., Venkataraman-Rao P., Gottschalk L. (2021). Food and Drug Administration insights on clinical study of weight-loss devices intended for adolescent patients. *Pediatric Obesity,*16(7): e12768. doi: 10.1111/ijpo.12768

1. In general, the device should not be studied in the pediatric population until enough data has been obtained to show that the study does not involve greater than minimal risk.[67,68] Additionally, if the device is a permanent implant, sufficient data should exist to support anticipated benefit in the pediatric population.[69] Other sources of data, including animal or other relevant modeling and simulation data, may preclude or mitigate the need to preliminarily collect data on older populations. This may be especially relevant when designing clinical investigations to meet the more immediate needs of patients, such as younger adolescents, experiencing co-morbidities associated with the severe end of the obesity spectrum.
2. If the device is a permanent implant, risk associated with potential explantation of the permanent implant should be well defined.
3. Pediatric participants should have a documented history of failing to achieve weight-loss goals with lifestyle modification before enrollment into a clinical study for these devices. In general, study participants should have participated in a comprehensive, multi-disciplinary pediatric weight management program for at least six months without adequate results.
4. Studies should have a lead-in period that allows for adequate time for the clinical team to get to know the participant, for the failure of adequate therapy programs to be documented, for the participant to understand the therapy and its impact, and for the participant's ability to comply with diet, protocol, and other considerations (e.g., psychosocial comorbidities) to be assessed.[70]
5. FDA considers the risk profile of the device for the appropriate study population in a pediatric clinical study. Table 3 illustrates recommended percentiles for BMI-for-age for inclusion of adolescent participants into a study for a device with indications associated with weight loss. Generally, higher risk devices should have the potential for greater benefit, as indicated by the percentiles for BMI-for-age in Table 3. If the submitter believes that the device is low-risk, FDA encourages discussion of a risk-based justification for inclusion of study participants with lower BMI-for-age percentiles.

[67] In general, the 2005 FDA PAC recommended that "devices, especially implants, should not be studied in the pediatric population until enough data has been gained from adult study and use." For more information, see https://wayback.archive-it.org/7993/20170404062450/https://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4179m_summary.pdf.
[68] In general, the 2005 FDA PAC recommended that "A staged introduction should be used when studying devices for obesity in the pediatric population. Namely, after adequate information is available in adult populations, the device can be studied in the older adolescent group (12 or 14 to 17). Sufficient experience and data should be collected before studying the device in subjects younger than this." *Ibid.*
[69] In general, the 2005 FDA PAC recommended that "post-approval data should be collected through 5 years" and "parties should be encouraged to have registries for long-term implants which follow patients for 5-10 years." *Ibid.*
[70] In general, the 2005 FDA PAC recommended that "studies should have a lead-in period during which the physician team got to know the patient and it could be documented that the patient had failed adequate conservative therapy programs and to ensure the patient's ability to comply with diet, protocol, etc." *Ibid.*

Table 3. Recommended percentiles (%ile) for BMI-for-age values for inclusion of adolescent participants into a study for a device with an indication associated with weight loss. Risk-dependent value should fall within specified ranges.

	Comorbidity	**No comorbidity**
Temporary[71] device	≥85th %ile BMI	≥95th %ile BMI
Permanent[72] device	≥85th %ile to 120% of the 95th %ile BMI	≥95th %ile to 140% of the 95th %ile BMI

6. A study endpoint of less than 12 months is likely not appropriate to evaluate a permanent device in the pediatric population, as these participants are still growing and maturing.[73]
7. Obesity-related comorbidities that should be considered for inclusion include:[74]
    - Obstructive sleep apnea;
    - Prediabetes;
    - T2DM;
    - Uncontrolled hypertension;
    - Orthopedic complications;
    - Pseudotumor cerebri;
    - Non-alcoholic steatohepatitis (NASH);
    - Polycystic ovary syndrome (PCOS); and
    - Hyperlipidemia/dyslipidemia.
8. Exclusion criteria should include:
    - Uncontrolled psychiatric conditions;
    - Study participants who are ill-equipped or unwilling to change behavior;

[71] For the purposes of interpreting this table, a temporary device is intended to be implanted or used for a pre-determined, limited amount of time (for example: a six-month intragastric balloon). A permanent device is one that is implanted without intention to remove or one that permanently alters the patient's anatomy and/or physiology. For the purposes of device classification procedures, the definition of an implant is provided in 21 CFR 860.3.
[72] *Ibid.*
[73] In general, the 2005 FDA PAC recommended that "Premarket data should be collected for 2 years although patients should be consented/assented for 5 years." For more information, see https://wayback.archive-it.org/7993/20170404062450/https://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4179m_summary.pdf.
[74] Obesity-related comorbidities listed are also applicable to adult study populations. These comorbidities are listed in this section of this guidance document due to the relevant general recommendations from the 2005 FDA PAC: 1) "[L]ong-term implant devices should be studied in patients with significant disease," i.e., those who are "in the 99th percentile for BMI for age," and have "at least one significant comorbidity," such as sleep apnea, diabetes, pseudotumor cerebri, or NASH (Non-Alcoholic Steatohepatitis); and 2) "Comorbidity reduction or resolution would be an important secondary effectiveness endpoint although the study would need to be powered appropriately to evaluate such changes." *Ibid.*

- Participants who are unwilling to undergo the intervention themselves;
- Participants with anatomical issues that may put them at unreasonable risk;
- Participants with connective tissue disorders that may result in tissue breakdown, if the device is an implant or changes anatomy; and
- Developmentally disabled participants who cannot follow recommendations.

9. To determine suitability for participating in a clinical study, maturity level and psychosocial comorbidities should be assessed by a specialist trained in psychology and in discussing mental health issues, stigma, bias, bullying, binge-purge behaviors, readiness for change, and other related considerations.
10. Study participants should be screened for known genetic causes of obesity such as Prader-Willi Syndrome.[75] For these participants, as well as those with hypothalamic obesity related to craniopharyngioma surgery that are about eight years old and above, inclusion into a study could be considered, though FDA recommends that the submitter consider separately evaluating the data for this subpopulation.
11. As for adult studies, clinically meaningful weight loss may be defined by % TBWL that should be linked to the health risk in the desired pediatric patient population. Consistent with clinical guidelines based on cardiometabolic risk,[76] we consider at least a 5-10 % TBWL clinically meaningful, and these values could be applicable to the pediatric population. However, linear growth should be considered when assessing changes in body weight of children and adolescents. Thus, the primary effectiveness parameter could be a function of the change in % BMI-for-age and/or % TBWL. This should depend on what is most clinically meaningful in the desired patient population considering age, BMI range, and any additional disease factors (e.g., associated comorbidities). Additionally, endpoint(s) should be able to demonstrate a positive outcome on the disease status (e.g., change in class of obesity).
12. If applicable, comorbidity reduction or resolution should be a secondary effectiveness endpoint.
13. The overall clinical study duration and follow-up should be justified considering the anticipated benefit and device risk. However, for devices that result in the modification of anatomy or involve a permanent implant, we recommend that premarket evaluation include follow-up for two years to account for weight loss durability. Study participants should be consented or assented, as applicable, for five years to allow for longer-term follow-up post-marketing. Parental permission should be obtained when applicable.
14. For a device that is temporary, durability of device-effect should be measured at least six months post device use unless a shorter assessment period is justified.

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[75] In general, the 2005 FDA PAC recommended that "patients should be screened for known genetic causes of obesity and for Prader Willi, and if included in the study, should be evaluated separately." *Ibid.*

[76] Jensen, M. D., Ryan, D. H., Apovian, C. M., Ard, J. D., Comuzzie, A. G., Donato, K. A., & Yanovski, M. (2014). 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*, 129(25 Suppl 2), S102-138. doi: 10.1161/01.cir.0000437739.71477.ee

15. Height measurements should be obtained from a wall-mounted stadiometer by study personnel trained in its use. A bone age study to obtain radiographic imaging of the growth plates can also be considered.

Other clinically relevant issues to consider when designing a pediatric study include endocrinologic causes of obesity, assessing neuropsychiatric symptoms and/or psychosocial environment, compliance, nutritional issues, and reproduction issues. We recommend addressing and/or monitoring these issues as appropriate.

We encourage submitters to utilize FDA's Q-Submission Program to ensure that the pediatric study protocol addresses safety concerns depending on the facts and circumstances of the device and study.

V. Benefit-Risk Considerations

A. Benefit-Risk

FDA evaluates whether a device has a reasonable assurance of safety and effectiveness during the PMA review, or whether general or general and special controls provide such assurance for a device in a De Novo classification, or whether it is substantially equivalent to a valid predicate in 510(k) review, by weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use,[77] or assessing the benefit-risk profile of a device as compared to a valid predicate when there are different technological characteristics,[78] among other relevant factors. To aid in this process, submitters include valid scientific evidence, including one or more clinical investigations, where appropriate, and/or non-clinical information, which FDA reviews to determine, among other things, whether the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling of the device.[79]

When assessing the benefits of devices, FDA considers the types of benefits, the magnitude of benefits, the probability of patients experiencing one or more benefits, and the duration of effects.[80] When assessing the risks of devices, FDA considers severity, type, number, and rate of harmful events associated with use of the device or procedure associated with the device, probability of harmful events, and duration of harmful events. Additional factors considered when assessing the probable benefits and risks of devices might include uncertainty[81] surrounding the benefit and risk, patient-centric assessments and PROs, characterization of the

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[77] The criteria for determining the safety and effectiveness of a device are set forth in section 513(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 860.7.
[78] See FDA guidance "Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics."
[79] Section 513(a)(3)(A) of the FD&C Act.
[80] See FDA guidance "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications."
[81] See FDA guidance "Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions."

disease or condition, patient preferences,[82] availability of alternate treatments, risk mitigation, device-type post-market data, and novel technology for addressing unmet medical needs.

Specific to devices with indications associated with weight loss, important considerations include the factors listed in Table 4.

Table 4. Factors considered as part of the benefit-risk evaluation for devices with indications associated with weight loss

Factor	Example(s)
Assessment of Benefits from a Clinical Study	
Weight loss	amount of weight loss attributed to the device, proportion of participants experiencing weight loss, and durability of weight loss
Changes in comorbidities	improvements in cardiometabolic risk factors, as well as other obesity-related comorbidities (e.g., clinically significant reduction in HbA1c, hypertension, and/or dyslipidemia), reduction in medication(s)
Other benefit	improvement in quality of life
Assessment of Risks from a Clinical Study	
Device- and procedure-related adverse events	seriousness, severity, types, numbers, rates, duration, resolution of adverse events and exacerbation of pre-existing conditions
Effects of the device	permanent implantation, anatomic changes, restriction of future treatment options, reversibility limitations, effect on drug and/or nutrient absorption
Clinical treatments/procedures related to the device	risk associated with expected concomitant medications or therapies, rate of early device removal due to participant request, risks related to placement/removal procedures, risks related to procedures necessary to diagnose adverse events, hospitalization (need, duration, and reason for)
Additional Factors	
Evaluation matrices decision aid[83]	extent of weight loss and duration of device use versus prevalence and severity of adverse events reported in a clinical study
Uncertainty	uncertainty resulting from study design, study conduct, potential for sham effect, and range of confidence intervals
Additional clinical data	studies from outside the U.S., feasibility studies, real-world evidence, use of the device repeatedly or in sequence
Additional considerations	availability of alternative therapies, risk mitigation measures, patient-reported outcomes, patient preferences

[82] See FDA guidance "Patient Preference Information - Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling."
[83] The evaluation matrices are applicable to devices with indications outlined in Table 5.

There is a wide range of technology and techniques being attempted for devices with indications associated with weight loss. These different approaches can translate into different impacts or outcomes, such as duration of device implantation, adverse event profiles, and different amounts of weight loss. As innovators conceive and develop the next generation of devices with plans to market such devices in the U.S., the recommendations below explain how FDA intends to consider, in the context of premarket submission decision, adverse events in light of varying degrees of benefit (specifically extent of weight loss and duration of device use).

B. Use of Modified Clavien-Dindo to Assess Risk

As described in Section IV.M(8), we recommend an adverse event classification modeled after the Clavien-Dindo Classification of Surgical Complications,[84] where the severity of each device- and procedure-related adverse event is graded based on the treatment used to address the event (*See* Table 2). The Clavien-Dindo Classification was chosen due to its wide use among physicians as a reliable and reproducible system for reporting surgical complications. Modifications to the Classification system were adapted to make it more relevant for weight loss device-related complications.

We highlight the differences from the original Clavien-Dindo Classification as well as relevant considerations in the following summation:

- Grade I was adapted to include over-the-counter medications and non-narcotic prescription pain medications.
- Grade II includes all other prescription medications and the administration of intravenous fluids.
- Like the original Clavien-Dindo Classification scheme, length of hospital stay is not included, since practices vary between medical centers and unexpected hospitalization typically occurs in combination with other therapies that are captured by the classification. However, FDA intends to consider seriousness and the need, duration of, and reason for hospitalization when making our overall benefit-risk determination for these devices.
- Diagnostic procedures, such as diagnostic endoscopies, are not included, because an adverse event discovered by a diagnostic procedure would be classified by the treatment needed for the adverse event. However, FDA intends to consider the risk of diagnostic procedures that may be used to diagnose device- or procedure-related adverse events when making our overall benefit-risk determination for these devices.
- Regarding Grade II, a study participant's need for blood transfusions and total parenteral nutrition (TPN) would be indicative of more serious adverse events in comparison to prescription medication use; however, the associated adverse events are likely to include

[84] Dindo, D., Demartines N., Clavien P.A. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery*. 240(2):205–213. doi: 10.1097/01.sla.0000133083.54934.ae

additional treatments defined as Grade III or Grade IV, and the grades of those additional treatments would also be captured.

- Devices can electively be removed prior to the end of their intended course of therapy for reasons other than adverse events included in the Adverse Event Classification described in Table 2. These reasons could be at the study participant's request. These events are not captured in the Adverse Event Classification, but FDA intends to consider early device removal when making our overall benefit-risk determination for these devices.

C. Balancing Weight Loss and Adverse Events for an Indication of Weight Loss

FDA's assessment of tolerability of adverse events in light of varying degrees of weight loss for devices specifically with a weight loss indication have been developed considering:

- Outcomes from the 2012 Gastroenterology-Urology Devices Panel on general issues related to obesity treatment devices;[85]
- Feedback from external experts, including clinicians; and
- The public comments submitted to Docket No. FDA-2019-N-4060 in response to a discussion paper outlining concepts discussed below.

As described in Sections IV.M(2) and IV.M(7), indications for weight loss depend on the extent and duration of weight loss demonstrated in a clinical study. For devices used for less than six months, or having less benefit than that outlined in Table 5, a weight management indication may be appropriate. An obesity treatment indication should be supported by clinical benefits in addition to weight loss alone.

Table 5 summarizes four weight loss indication categories based on the amount of weight loss observed in a clinical study and the duration of device use.

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[85] 2012 Materials of the Gastroenterology-Urology Devices Panel can be accessed at https://wayback.archive-it.org/7993/20170113191551/http:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/ucm286235.htm.

Table 5. Weight loss indication categories

Indication	**Demonstrated Weight Loss: Superiority Margin** **% TBWL Over Control**	**Demonstrated Weight Loss: Responder Rate** **% Participants achieving ≥5% TBWL**	**Duration of Device Use**
Short-Term Limited Weight Loss	≥2% and <5%	50%	6 months to <12 months
Limited Weight Loss	≥2% and <5%	50%	≥12 months
Short-Term Weight Loss	≥5%	50%	6 months to <12 months
Weight Loss	≥5%	50%	≥12 months

For the categories in Table 5, the duration of device use depends on the characteristics of device use. It may depend on the time period over which the device is used and/or the time period over which weight loss is measured, as follows:

- For an implantable device, the duration of device use is the total time that the device is inside the body. For example, for an intragastric balloon that is in the stomach for 6 months and then removed, the duration of device use would be 6 months.
- If the device is used transiently and results in changes to the anatomy and/or physiology that persist after use, the duration of device use is the terminal time point at which weight loss is measured within a clinical study. For example, for a device that is used temporarily but permanently reduces the size of the stomach, if the change in total body weight was assessed at 12 months post-device use, then the duration would be 12 months.
- For devices that are used on a recurring basis, the duration of device use is the course of time the device is used before measuring the results. For example, for a device that is used daily, if the change in total body weight is assessed after eight months of daily use, then the duration would be eight months.

In a hypothetical example, a device was temporarily placed in the stomach. A clinical investigation included two groups: a treatment group that had the device placed via an endoscopic procedure; and a sham group for the control arm, which underwent an endoscopic procedure, but no device was placed. After six months, devices were removed from the treatment group and the change in weight was measured for both groups, so the duration of this device use is six months. The results showed that at least half (50%) of the treatment group lost at least 5% of their starting body weight. The results also showed that the treatment group lost more of their starting body weight than the sham group did, with a superiority margin of 3% more weight lost. Thus, the device successfully met co-primary effectiveness endpoints of 50% responder rate and at least 2% TBWL over sham when measured at device removal 6 months post implant. Based on the recommendations in Table 5, this weight loss would be considered "short-term limited weight loss."

FDA intends to use the weight loss indication categories (Table 5), the Adverse Event classification (Table 2), and the Evaluation Matrices decision aid (Figure 1) to compare the weight loss demonstrated with the adverse event classification profile as part of the benefit-risk assessment of a weight loss device (Table 4).

1. There are four proposed Evaluation Matrices (numbered 1-4 in Figure 1). There is one Evaluation Matrix corresponding with each of the four weight loss indication categories described in Table 5. An Evaluation Matrix is selected for a device based on the amount of weight loss demonstrated in a clinical study and the duration of device use, consistent with Table 5.
2. Within each Evaluation Matrix, there are five columns for the five grades of adverse events described in Table 2. For each grade of adverse event, if there is a participant in the clinical study with that adverse event, then a lettered cell is intended to be selected based on the percentage of participants who experienced that grade of adverse event. The letter of the cells is for reference purposes only.
3. The shading of each cell indicates the possible consideration for the device based on the corresponding grade of adverse events (the column the cell is in). White indicates that the weight loss to adverse event profile appears favorable. Light gray shading indicates that the weight loss to adverse event profile is uncertain. Dark gray shading indicates that the weight loss to adverse event profile appears unfavorable.
4. The Evaluation Matrix for a specific device may include some combination of cells with different shading. The overall risk of the device depends on the cell of greatest risk; thus, the cell with the darkest shading suggests the outcome of the decision aid.
5. The outcome from the Evaluation Matrix is considered as part of the totality of the benefit-risk determination (Table 4).
6. The matrices are provided as a decision aid, which is only one part of FDA's assessment when evaluating whether probable benefit outweighs probable risk for the device for its conditions of use.

Weight loss to adverse event profile appears favorable
Weight loss to adverse event profile is uncertain
Weight loss to adverse event profile appears unfavorable

Reminder: The matrices are a decision aid, which is only one part of FDA's assessment of whether benefit outweighs risk for the device for its conditions of use.

1. Short-Term Limited Weight Loss

Rate of Adverse Events	Severity of Adverse Events: Grade I	Grade II	Grade III	Grade IV	Grade V
≥25%	A	F	K	P	U
10-24.9%	B	G	L	Q	V
5-9.9%	C	H	M	R	W
1-4.9%	D	I	N	S	X
>0-<1%	E	J	O	T	Y

2. Limited Weight Loss

Rate of Adverse Events	Severity of Adverse Events: Grade I	Grade II	Grade III	Grade IV	Grade V
≥25%	A	F	K	P	U
10-24.9%	B	G	L	Q	V
5-9.9%	C	H	M	R	W
1-4.9%	D	I	N	S	X
>0-<1%	E	J	O	T	Y

3. Short-Term Weight Loss

Rate of Adverse Events	Severity of Adverse Events: Grade I	Grade II	Grade III	Grade IV	Grade V
≥25%	A	F	K	P	U
10-24.9%	B	G	L	Q	V
5-9.9%	C	H	M	R	W
1-4.9%	D	I	N	S	X
>0-<1%	E	J	O	T	Y

4. Weight Loss

Rate of Adverse Events	Severity of Adverse Events: Grade I	Grade II	Grade III	Grade IV	Grade V
≥25%	A	F	K	P	U
10-24.9%	B	G	L	Q	V
5-9.9%	C	H	M	R	W
1-4.9%	D	I	N	S	X
>0-<1%	E	J	O	T	Y

Figure 1. Evaluation Matrices for comparing weight loss indication categories (Table 5) and adverse events classification.[86]

In a hypothetical example, suppose that in a clinical investigation, a device successfully met co-primary effectiveness endpoints of 50% responder rate and a superiority margin of 3% TBWL over sham control when measured at device removal six months post implant. Based on Table 5, the weight loss indication category would be "short-term limited weight loss," so the device would be evaluated via Evaluation Matrix 1 in Figure 1. In the assessment of the clinical study:

- 50% of participants had Grade I adverse events, which corresponds to the light gray cell A in Matrix 1 of Figure 1;
- 3% of participants had Grade II adverse events, which corresponds to the white cell I in Matrix 1 of Figure 1;
- 0% of participants had Grade III adverse events; and

[86] Lettering within the matrices is included for reference purposes only. For example, the cell corresponding to a Grade IV adverse event occurring at a rate of more than 25% of the time is lettered "P."

- 1% of participants had Grade IV adverse events, which corresponds to the dark gray cell S in Matrix 1 of Figure 1.

Overall, the risk of the device is characterized by the prevalence of greatest risk observed in the study, i.e., the 1% Grade IV adverse event rate, where the dark gray cell indicates that the weight loss to adverse event profile may not be favorable for the given amount of weight loss as part of the overall benefit-risk assessment. The low rate of adverse events in Grade II (the white cell) and Grade I (the light gray cell) may not negate the risk associated with the rate of adverse events in Grade IV (the dark gray cell).

In another hypothetical example, suppose that in a clinical investigation, a device successfully met co-primary effectiveness endpoints of 50% responder rate and a superiority margin of 10% TBWL over sham control when measured at device removal 12 months post implant. Based on Table 5, the weight loss indication category would be "weight loss," so the device would be evaluated via Evaluation Matrix 4 in Figure 1. In the assessment of the clinical study:

- 70% of participants had Grade I adverse events, which corresponds to the light gray cell A in Matrix 4 of Figure 1;
- 10% of participants had Grade II adverse events, which corresponds to the white cell G in Matrix 4 of Figure 1;
- 0.5% of participants had Grade III adverse events, which corresponds to the white cell O in Matrix 4 of Figure 1; and
- 2% of participants had Grade IV adverse events, which corresponds to the light gray cell S in Matrix 4 of Figure 1.

Overall, the risk of the device is characterized by the prevalence of greatest risk observed in the study, i.e., the 2% Grade IV adverse event rate and 70% Grade I adverse event rate, where the light gray cells indicate that the weight loss to adverse event profile is uncertain given the amount of weight loss as part of the overall benefit-risk assessment. The low rate of adverse events in Grade II and Grade III (the white cells) may not negate the risk associated with the rate of adverse events in Grade I and Grade IV (the light gray cells).

During the review of a marketing submission, FDA intends to consider information from the proposed Evaluation Matrices, along with all other applicable factors identified in Table 4, to make a final determination regarding whether the probable benefits of the device outweigh the probable risks of the device.

Guidance History	Date	Description
Level 1 Final Guidance	March 2026	See Notice of Availability for more information.**
Level 1 Draft Guidance	September 2023	See Notice of Availability for more information.**

**The Notice of Availability is accessible via the Search for FDA Guidance Documents webpage.