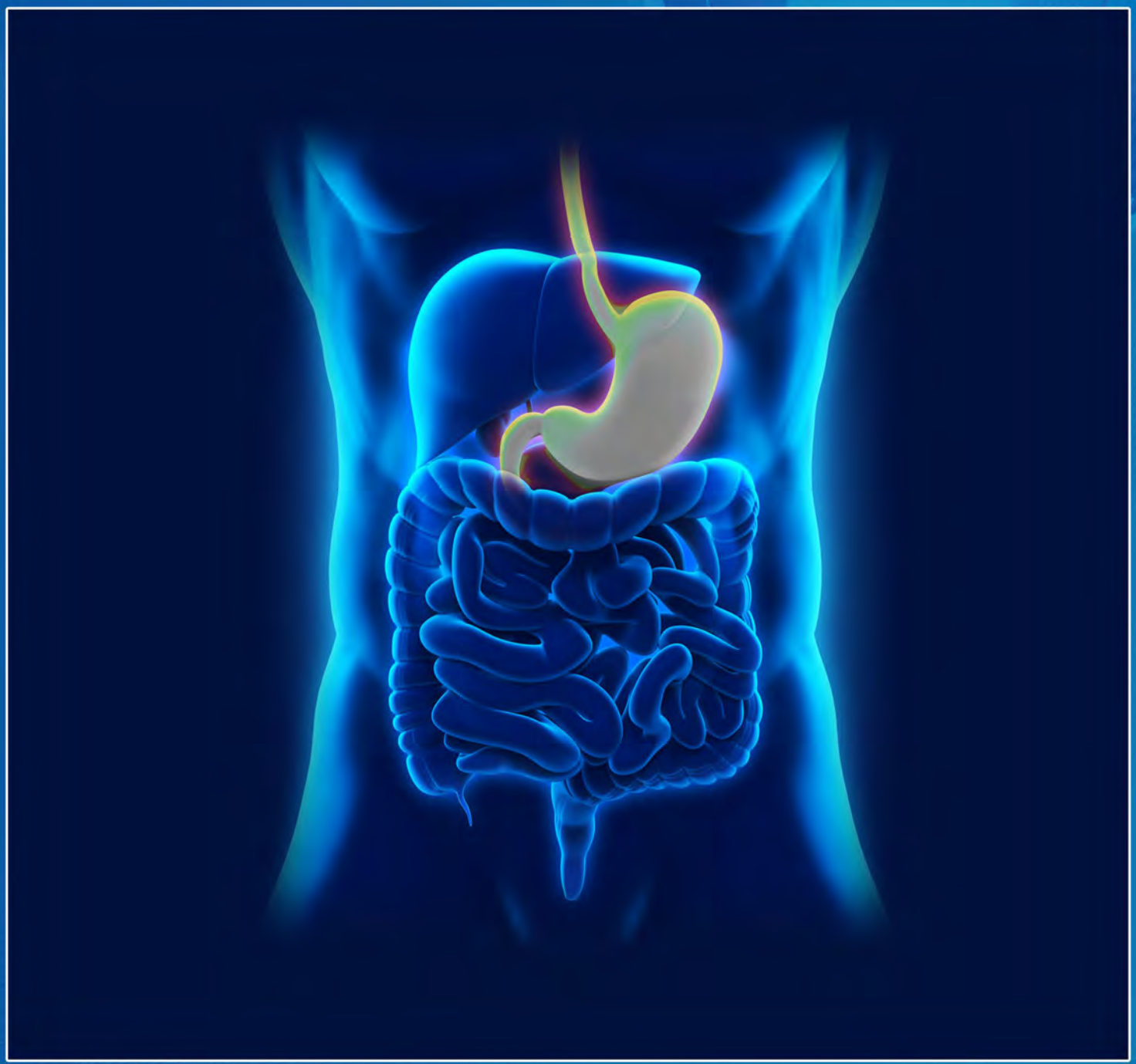
U.S. FOOD & DRUG ADMINISTRATION

Discussion Paper:

Consideration of Benefit-Risk Approaches for Weight-Loss Devices



Discussion Paper: Consideration of Benefit-Risk Approaches for Weight-Loss Devices

Disclaimer: This discussion paper is for discussion purposes only and does not represent draft or final guidance. It is not intended to propose or implement policy changes regarding the evaluation of devices intended for weight loss.

The objective of this discussion paper is to obtain public comment and early input on initial thoughts regarding a concept that FDA is considering to aid in assessing tolerability of risk in light of varying degrees of benefit for devices intended for weight loss. Please submit your comments regarding this discussion paper to https://www.regulations.gov, Docket No. FDA-2019-N-4060 within 90 days. FDA will consider all comments submitted to this docket (FDA-2019-N-4060) before issuing draft guidance that will be developed and published for additional public comment to identify the parameters FDA considers important to assess the safety and effectiveness of weight-loss devices. Additional information can be found on FDA's webpage, https://www.fda.gov/medical-devices/products-and-medical-procedures/weight-loss-and-weight-management-devices.

Introduction

Obesity is a major public health epidemic in the United States and is associated with many health problems such as heart disease, diabetes, and stroke[1]. Not all treatment options work for all patients due to the complexity of the disease, and not all options are available due to patient comorbidities; therefore, having a variety of weight-loss options increases the number of patients who could benefit from therapy. Several medical interventions are available when lifestyle changes alone have not been effective. Weight-loss devices serve as an option for patients who have not responded to more conservative medical interventions, such as drugs, but who want an alternative to bariatric surgery.

The Center for Devices and Radiological Health (CDRH) is responsible for assuring the safety and effectiveness of devices intended for weight loss. To date, CDRH has approved nine (9) devices through premarket approval applications (PMAs) for weight loss (Table 1). Of the nine (9) approved weight-loss devices, five (5) were approved in 2015-2016, and one was approved in 2019. FDA continues to receive a high volume of pre-submissions from industry requesting feedback about the necessary data to support pivotal clinical studies and marketing applications for a wide variety of device designs intended for weight loss.[2]

[1] National Institutes of Health (1998). "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults - The Evidence Report." Obesity Research **6**(S2): 51S-179S.
[2] See FDA guidance entitled "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program", available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program

Table 1. FDA approved devices intended for weight loss (*in reverse chronological order*)

Device Name	Device Type	Marketing Application	Date Approved
Transpyloric Shuttle	Intragastric implant	P180024	April 16, 2019
Obalon Balloon System	Intragastric implant	P160001	September 8, 2016
AspireAssist	Aspiration therapy system	P150024	June 14, 2016
Orbera Intragastric Balloon System	Intragastric implant	P140008	August 5, 2015
ReShape Integrated Dual Balloon System*	Intragastric implant	P140012	July 28, 2015
MAESTRO Rechargeable System**, #	Neuromodulator	P130019	January 14, 2015
REALIZE Adjustable Gastric Band*	Restrictive band	P070009	September 28, 2007
LAP-BAND Adjustable Gastric Banding System	Restrictive band	P000008	June 5, 2001
Garren Gastric Bubble*	Intragastric implant	P840025	September 17, 1985

* voluntarily removed from the market; ** no longer commercially distributed; # also known as ReShape vBloc

FDA has actively engaged stakeholders regarding how we can best ensure patients have access to safe and effective devices intended for weight loss. This discussion paper continues FDA's efforts to be transparent and informative about how we regulate these devices. Past activities include[3]:

- On October 16-18, 2011, the 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)[4]."
- On May 10-11, 2012, the Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee discussed general issues related to obesity treatment devices and provided clinical study design recommendations to better evaluate the safety and effectiveness of obesity treatment devices[5].
- In 2013, FDA proposed a benefit-risk assessment model to help manufacturers in developing clinical studies that could provide valid scientific data on the safety of obesity treatment devices[6].
- In 2015, FDA worked with the Research Triangle Institute Health Solutions (RTI-HS) to carry out the first national benefit-risk preference study to provide information on patient risk tolerance for weight-loss devices[7].
- FDA held a listening session on June 28, 2018, with patients who have used FDA-approved weight-loss devices.

[3] See also https://www.fda.gov/medical-devices/weight-loss-and-weight-management-devices/fda-activities-weight-loss-and-weight-management-devices
[4] http://www.obesitydevices.org/
[5] https://wayback.archive-it.org/7993/20170113191551/http:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/ucm286235.htm
[6] Lerner, H., J. Whang and R. Nipper (2013). "Benefit-risk paradigm for clinical trial design of obesity devices: FDA proposal." Surg Endosc **27**(3): 702-707.
[7] Ho, M. P., J. M. Gonzalez, H. P. Lerner, C. Y. Neuland, J. M. Whang, M. McMurry-Heath, A. B. Hauber and T. Irony (2015). "Incorporating patient-preference evidence into regulatory decision making." Surg Endosc **29**(10): 2984-2993.

During development of this discussion paper, FDA considered the observed benefit and procedure/device related adverse events of recently approved weight-loss devices reported in the clinical studies used to support FDA's regulatory decisions. To supplement FDA's discussions, we also worked with FDA's Network of Experts[8] to obtain outside expertise on our initial thoughts regarding the potential benefit-based categorical indications (Table 3), adverse event classification concept (Table 4), and Evaluation Matrices (Figure 1). Internal and external subject matter experts considered published medical society guidelines[9] and other peer-reviewed clinical literature when providing their perspectives on a potential benefit-risk concept for weight-loss devices under consideration by FDA.

When impacted stakeholders (e.g., FDA, patients, healthcare professionals, industry) have a common understanding of the factors that contribute to the benefit-risk profile, such would hopefully translate into improving the predictability, consistency and transparency of the review process for all stakeholders in the weight-loss device space while improving patient access to quality therapy.

After considering public comments submitted to docket FDA-2019-N-4060, FDA intends to issue draft guidance which would include a proposal for a concept to aid in assessing tolerability of risk in light of varying degrees of effectiveness for devices intended for weight loss. This discussion paper is not draft or final guidance and is not intended to propose or implement policy changes regarding the benefit-risk of weight-loss devices. Rather, the intent of this discussion paper is to obtain public comment on a concept (benefit, risk, and Evaluation Matrices) for weight-loss devices that FDA is considering proposing as part of a draft guidance.

Benefit-Risk

The Federal Food, Drug, & Cosmetics (FD&C) Act specifies that FDA will review medical device applications to determine if they provide a "reasonable assurance of safety and effectiveness" by "weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use," [10] among other considerations. To aid in this process, device applicants submit valid scientific evidence, including one or more clinical investigations, where appropriate, and/or nonclinical information, which FDA reviews to determine 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."[11]

[8] https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/ucm289534.htm
[9] See Jensen, M. D., Ryan, D. H., Apovian, C. M., *et al* (2013) 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults. *Circulation.* 125(25):S102-S138
[10] In addition to Section 513(a) of the FD&C Act, the criteria for establishing safety and effectiveness of a device are set forth in 21 CFR 860.7
[11] Section 513(a)(3)(A) of the FD&C Act.

In recent years, FDA has issued a series of guidance documents to articulate a more flexible, patient-centric, and transparent benefit-risk framework to evaluate devices in both the pre- and post-market settings [12, 13, 14]. The initial framework guidance identified the principal factors FDA considers when making benefit-risk determinations during the premarket review of PMAs and De Novo classifications. When assessing 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. When assessing risks of devices, FDA considers severity, types, 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 include uncertainty[15] surrounding the benefit and risk, patient-centric assessments and patient-reported outcomes, characterization of the disease or condition, patient perspectives[16], availability of alternate treatments, risk mitigation, device-type post-market data, and novel technology for addressing unmet medical needs.

Specific to weight-loss devices, important considerations, which have been publicly-discussed previously[17] and are currently considered for assessing benefit-risk, include the factors listed in Table 2.

[12] See FDA guidance entitled "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications", available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de

[13] See FDA guidance entitled "Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions", available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-investigational-device

[14] See FDA guidance entitled "Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions", available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-regarding-benefit-risk-medical-device-product-availability-compliance-and

[15] See FDA guidance entitled "Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions", available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/consideration-uncertainty-making-benefit-risk-determinations-medical-device-premarket-approvals-de

[16] See FDA guidance entitled "Patient Preference Information - Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling", available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications

[17] See May 10-11, 2012, Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee discussions available at https://wayback.archive-it.org/7993/20170113191551/http:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/ucm286235.htm

Table 2. Factors for consideration as part of the weight-loss device benefit-risk evaluation

Factor	Example(s)
Benefits Assessed in a Clinical Study	
Weight loss	amount of weight loss, proportion of patients experiencing weight loss, and durability of weight loss
Changes in comorbidities	clinically significant reduction in HbA1c[18], hypertension, and/or hyperlipidemia
Risks Determined from a Clinical Study	
Adverse events	severity, types, numbers, rates, duration of adverse events in a clinical study
Long-term effects of the device	permanent implantation, anatomic changes, restriction of future treatment options, reversibility limitations
Clinical treatments/procedures related to the device	expected concomitant medications or therapies, rate of early device removal, risks related to placement/removal procedures
Additional Factors	
Uncertainty	uncertainty resulting from study design, study conduct, potential for sham effect, and range of confidence intervals
Additional clinical data	studies from outside of the United States, feasibility studies, real-world evidence
Additional considerations	availability of alternative therapies, risk mitigation measures, patient preference information

There is a wide range of approaches being attempted for weight-loss devices. These different approaches include variations in technology and techniques which 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 weight-loss devices with plans to market such devices to the US population, FDA would like to provide greater clarity on how it is contemplating the consideration of risk in light of varying degrees of benefit (specifically extent of weight loss and duration of device use) for legally marketing weight-loss devices.

In advance of issuing draft guidance, FDA would like to obtain public comment on the following concept to assess the safety and effectiveness data for weight-loss devices.

The concept discussed in this paper focuses on how to consider the extent of weight loss in relation to the extent of adverse events for weight-loss devices, a subpart of the totality of the benefit-risk determination. To reiterate, this assessment would be considered in conjunction with the factors described above in Table 2 as part of FDA's benefit-risk assessment of a new weight-loss device. In this discussion paper, we propose a concept or tools to address the following considerations from a clinical study, which may affect the benefit-risk assessment for weight-loss devices:

1. Benefit: consider the extent of weight loss and duration of device use;
2. Risk: categorization (prevalence and severity) of adverse events; and

[18] HbA1c is a term commonly used in relation to diabetes - the higher the HbA1c, the greater the risk of developing diabetes-related complications

3. Evaluation Matrices: a potential additional decision aid for use by FDA review staff for considering benefit and risk as defined in #1 and #2 above. As noted, such would be in addition to other considerations and benefit-risk tools[19] for FDA's benefit-risk determination.

Initial Thoughts for Consideration

Considerations for Benefit

Evidence denoting clinical benefit for a device that supports its conditions of use are directly relevant when making a benefit-risk determination. Within the technical space of weight-loss devices, FDA is considering proposing the placement of each device into one of four benefit 'categories' based on the amount of weight loss demonstrated in a clinical study and the duration of device use (*See* Table 3). Given the diversity in device technologies and to promote further consistency and transparency in potential 'general indication' language within the weight-loss device space, FDA is considering proposing the concept identified in Table 3 as relevant to describe clinical benefit and as noted below is specifically seeking feedback regarding the proposed concept.

Table 3. Benefit categories under consideration for weight-loss devices

General Indication	**Demonstrated Weight Loss**		**Duration of Device Use**
	Superiority Margin % TBWL Over Control	**Responder Rate** % patients achieving ≥5% TBWL	
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

TBWL = total body weight loss

Additional considerations and specificity FDA is contemplating from a clinical study design perspective for weight-loss devices as best practices approaches, include the following aspects:

- Demonstration of weight loss would typically include comparison with a control arm, which contains a sham device or sham procedure, when appropriate. Although it is appreciated that a sham control may not be appropriate in all circumstances, a sham control in a clinical study can provide an important baseline comparator from which to compare the efficacy of device therapy. A sham control may also be beneficial to reduce the uncertainty regarding the treatment effects demonstrated by weight-loss devices.

- Consistency in treatment conditions during the study to assure that both treatment and control subjects follow the same diet, exercise, and/or behavioral modification program which often are used in conjunction with weight-loss devices.

[19] See Appendices B and C in FDA's guidance entitled "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications", available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de

- Demonstrated weight loss would be based on percent total body weight loss (%TBWL), which is typically captured in a clinical study with co-primary effectiveness endpoints that include (1) a hypothesis with a pre-specified superiority margin over control and (2) a performance goal for a responder rate.

    - For the pre-specified superiority margins, we are considering proposing two minimum values over the control arm, as part of the proposed benefit categories (Table 3): devices demonstrating at least 5% superiority margin would be in a "weight loss" category; devices with at least a 2% superiority margin would be in a "limited weight loss" category.

      Note: The 2% and 5% minimum superiority margins are consistent with the benefit demonstrated for FDA approved devices intended for weight loss that are currently on the market. To calculate the margin, the mean %TBWL of the control group is subtracted from the mean %TBWL of the device group. The lower bound of the 95% confidence interval of the difference of the means would need to equal, or exceed, the superiority margin specified for the benefit category identified in Table 3.

    - For the responder rate, we are considering proposing that for all categories ("weight loss" or "limited weight loss"), at least 50% of treated subjects achieve ≥5% TBWL; this endpoint would be independent of the weight loss achieved in the control group.

      Note: A 50% responder rate of ≥5% TBWL is consistent with the benefit demonstrated for FDA approved devices intended for weight loss that are currently on the market.

For the benefit categories proposed in Table 3, FDA explains that 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 defined as 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. 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 8 months of daily use, then the duration would be 8 months.

It should be noted that as part of the concept being proposed in this discussion paper, FDA is not considering devices with a duration of use less than six months.

For example, consider a device that is 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 6 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 6 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 proposal in Table 3, this benefit would be considered "short-term limited weight loss."

FDA is seeking feedback on the following questions related to the proposed benefit categories (Table 3):

- **Is it appropriate to categorize benefit based on superiority of weight loss relative to a control arm, responder rate, and duration of device use?**
- **Are the proposed minimum superiority margins of 2% and 5% TBWL clinically meaningful?**
- **Are the proposed categories of duration of device use appropriate?**

Considerations for Risk

To assist FDA's assessment of known or probable risk, FDA has previously sought to categorize adverse events associated with weight-loss devices[20] We are considering whether an adverse event classification modeled after the Clavien-Dindo Classification of Surgical Complications,[21] where the severity of each adverse event is graded based on the treatment used to address the event, would be appropriate for weight-loss devices (*See* Table 4). The Clavien-Dindo Classification was chosen as a framework for consideration due to its wide use among physicians as a reliable and reproducible system for reporting surgical complications. Modifications are being proposed to the Classification system to make it more relevant for weight-loss device complications.

Table 4 proposes a modified Clavien-Dindo Classification for consideration for weight-loss devices.

[20] Lerner, H., J. Whang and R. Nipper (2013). "Benefit-risk paradigm for clinical trial design of obesity devices: FDA proposal." Surg Endosc **27**(3): 702-707.

[21] 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. *Ann Surg*. 240:205–213

Table 4. Adverse event classification concept under consideration for weight-loss device 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 of a patient

FDA is highlighting the differences from the original Clavien-Dindo Classification as well as relevant considerations in the following summation:

- Grade I was adapted to include all 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 was not included, since practices vary between medical centers and unexpected hospitalization typically occurs in combination with other therapies that are captured by the classification.

- 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.

- As part of discussions related to the proposed adverse event classification scheme, FDA considered whether it would be acceptable to classify all surgical, endoscopic, and radiological interventions within a single grade, Grade III, especially considering that such interventions encompass a wide range of risks, from the risks of a minimally invasive approach to those of open surgery. As discussed below in the proposed Evaluation Matrices decision aid for weight-loss devices (*See* Figure 1), since there did not appear to potentially be an additional impact in 'shading', at this time, FDA is proposing the Grade III as stated in Table 4.

- Regarding Grade II, we note that the 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 require additional treatments defined as Grade III or Grade IV, and the grades of those additional treatments would also be captured.

It should be noted that the proposed classification scheme for weight-loss devices identified in Table 4 focuses on deviations from the normal treatment course for a device. For example, the normal treatment course for a weight-loss device may include use of concomitant medications, and additional therapy (e.g., anti-emetics, pain medication, etc.) typically provided as part of the practicing physician's treatment plan. While concomitant medications are not being proposed as adverse events per this proposed classification scheme, FDA does intend to consider such as part of the overall benefit-risk determination for a device, as described in Table 2.

It should also be noted that 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). It is intended that 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 intended to be of approximately equal severity/risk to the patient.

FDA is seeking feedback on how to best classify adverse events for weight-loss devices. Please consider the caveats and explanations which have also been provided in this discussion paper.

- **Is the proposed classification scheme appropriate for the anticipated adverse events associated with weight-loss devices?**
- **Are there any adverse events which are not captured or clearly classified by the proposed classification scheme?**

Evaluation Matrices

As part of FDA's decision-making to support marketing authorization of a device, we decide whether the benefits of the device outweigh the risks of the device. To assist with this assessment, FDA is considering whether the use of Evaluation Matrices (*See* Figure 1) as proposed are helpful in considering acceptable levels of risk for a given amount of weight loss, which is only one part of the overall benefit-risk determination performed by the FDA (*See* Table 2) for weight-loss devices.

Figure 1. Proposed Evaluation Matrices under consideration as an additional decision aid during the premarket review of weight-loss devices

Reminder: The matrices are provided as 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. Please refer to the accompanying text when using the proposed Evaluation Matrices.

The level of risk may be acceptable for the given amount of weight loss as part of the benefit-risk assessment

The level of risk will be further weighed against the given amount of weight loss as part of the benefit risk-assessment

The level of risk may not be acceptable for the given amount of weight loss as part of the benefit-risk assessment

***Lettering within the matrices is included for reference purposes only to aid in discussion of specific cells. For example, the cell corresponding to a Grade V adverse event (death) occurring at a rate of more than 25% of the time is lettered "E".**

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

As further explanation of Figure 1, please note the following for the proposed Evaluation Matrices decision aid to assist with risk assessments:

- There are four proposed Evaluation Matrices (identified as numbers 1-4 in Figure 1). It should be noted that there is one Evaluation Matrix proposed which is intended to correspond with each of the four 'benefit categories' as described in Table 3. The corresponding 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, in accordance with Table 3.

- Within each Evaluation Matrix, there are 5 columns identified, which are for the 5 grades of adverse events described in Table 4. For each grade of adverse event, if there is a patient in the clinical study with that adverse event, then a lettered cell is selected based on the percentage of patients who experienced that grade of adverse event.

- The shading of each cell indicates the possible outcome for the weight-loss device based on the corresponding grade of adverse events (the column the cell is in). White indicates that the level of risk may be acceptable for the given amount of weight loss as part of the benefit-risk assessment. Light gray shading indicates that the level of risk will be further weighed against the given amount of weight loss as part of the benefit-risk assessment. Dark gray shading indicates that level of risk may not be acceptable for the given amount of weight loss as part of the benefit-risk assessment.

- The Evaluation Matrix for a specific device may include some combination of cells which fall within areas of different shading. In such scenarios, the overall risk of the device would depend on the area of greatest risk; thus, the cell with the darkest shading would provide the decision outcome for the risk of the weight-loss device.

- The Evaluation Matrix decision outcome would be considered as part of the totality of the benefit-risk determination (Table 2).

As an example considering the above tenets, suppose that in a clinical investigation, a device successfully met co-efficacy endpoints of 50% responder rate and a superiority margin of 3% TBWL over sham control when measured at device removal 6 months post implant. Based on Table 3, this benefit would be considered "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, 3% of subjects had Grade II adverse events, which corresponds to the white cell I in Matrix 1 of Figure 1. Additionally, 1% of subjects 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 determined by the events of greatest risk, i.e. the 1% Grade IV adverse event rate, where the dark gray cell indicates that the level of risk may not be acceptable for the given amount of weight loss as part of the benefit-risk assessment. The low rate of adverse events in Grade II (the white cell) does not undo the risk associated with the rate of adverse events in Grade IV (the dark gray cell).

FDA would consider information from the proposed Evaluation Matrices along with other factors identified in Table 2, e.g., permanent implantation, anatomic changes, restriction of future treatment options, uncertainty etc., to make a final determination regarding whether the benefits of the device outweigh the risks of the device.

FDA is seeking feedback as to whether the proposed Evaluation Matrices decision aid may be a beneficial tool[22] to systematically compare benefits and risks for devices intended for weight loss.

- **Specifically, please address whether the proposed shadings of the cells provide the appropriate assessment of rates of adverse events for different levels of benefit, i.e., should the shading of any of the cells change from how currently being proposed?**
- **Are there any general suggestions on ways to improve the proposed Evaluation Matrices?**

Additional Comments

The previously FDA-approved weight-loss devices (Table 1) are all indicated for "weight loss." However, under the concept being proposed in this discussion paper, future medical devices intended for weight loss may have indications that are more specific to the measured benefit, e.g., "short-term limited weight loss" (Table 3). These more specific indications would provide additional information about the intended use of the device and promote further transparency and consistency in expectations of performance. The proposed concept in this discussion paper is not intended to reflect a new level of performance necessary to support marketing approval for weight-loss device technologies.

The previously approved weight-loss devices, which fit into different matrices based on demonstrated benefit, all fall into the light gray category of "*The level of risk will be further weighed against the given amount of weight loss as part of the benefit risk-assessment*."

Anticipated Outcomes of Discussion Paper

FDA intends to consider all comments submitted to docket FDA-2019-N-4060 within 90 days. FDA intends to consider such comments before issuing draft guidance that will be developed and published for additional public comment in identifying the parameters which FDA considers important to assess the safety and effectiveness of weight-loss devices.

[22] In addition to the worksheet in Appendix B in FDA's guidance entitled "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications", available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de