Questions for the Pediatric Advisory Committee on Development of Trials to Assess the Safety and Efficacy Relevant to Scientific and Ethical Issues Surrounding Trials for Pediatric Devices for Weight Loss

A. Introduction

FDA has four complex questions involving scientific and ethical components. For each question we are providing a summary of the issues and focusing on areas for which we specifically need your guidance. Broadly, we are seeking your advice on the following:

1. The appropriate pediatric population for inclusion in device trials including issues of assent
2. The appropriate pediatric endpoints that determine success and the timing of that assessment
3. The appropriate trial design including issues of assent
4. Recommendations on long term safety and effectiveness assessments

B. Questions

1. Appropriate Pediatric Population

Inherent differences in adult and pediatric populations make the selection of the appropriate patients for device treatment more problematic for the younger age group. Whereas most adults have reached physical, emotional, and sexual maturity by the time they seek aggressive weight loss management, the pediatric population may not have. In addition, since many adults have been overweight or obese for years, medical co-morbidities such as hypertension, diabetes, and dyslipidemia have had more opportunity to develop and manifest when compared to the pediatric population. Furthermore, adult patients have usually failed multiple attempts at conservative and/or supervised treatment regimens whereas children may not have had adequate supervised attempts at weight loss.

This makes the selection of appropriate patients for studies of devices which may require invasive surgery or which may permanently alter certain functions or anatomy more challenging. Although the selection of patients certainly would be influenced by the relative risk/benefit ratio of the particular device, this will not always be known prior to initiating a study.

As such, FDA would like recommendations from the committee for selecting an appropriate candidate population for device study in general – recognizing that in certain situations, flexibility will be required.

In responding to this question, it would be helpful to consider the following seven patient characteristics in your discussion and attempt to prioritize these characteristics as absolute requirements or preferred but not mandatory.

a. Age requirements.
b. Weight requirements
    i. BMI-for-Age percentile
    ii. Weight-for-Age percentile
    iii. Absolute Weight
    iv. Absolute BMI
    v. Only overweight or should at-risk for overweight be considered for enrollment as well?
c. Developmental milestone requirements
    i. Tanner Stage
    ii. Bone Age
d. Medical co-morbidity requirements
    i. Diabetes Mellitus
    ii. Hypertension
    iii. Dyslipidemia
    iv. Sleep Apnea
    v. Renal Disease
e. Failure to respond to more conservative/less invasive therapy including diet, exercise, and behavioral modification.
f. Psychiatric/psychological requirements.
g. Any diagnoses or existing conditions which should definitely be excluded.

In addition, issues of assent and parental permission are paramount when selecting permanent and irremovable, permanent and removable, or temporary. ***Please discuss this issue including how well children can assess the risk-benefit ratio for devices that will require significant compliance with a diet regimen and that may have a component of permanence to them.***

2. Appropriate Endpoints and Timing of Assessments

Traditionally, the most effective therapy for obesity in the adult patient population has been surgery. Many surgical studies have used percent excess weight loss (%EWL) as the primary effectiveness assessment for the treatment. However, other assessments have been used when reporting results of surgical and non-surgical treatments including weight loss as a percentage of the initial body weight, absolute weight loss (in pounds or kilograms), change in BMI, change in anatomical measures such as hip or waist circumference, and change in medical co-morbidities.

The time at which endpoints are measured in adult obesity studies varies significantly – from one or two months to several years.

As such, FDA would like recommendations from the committee on what the appropriate study endpoints for device trials in this setting might be and when they should be assessed – again recognizing that in certain situations, flexibility will be required.

In responding, it would be helpful to consider the following questions in your discussion

a. What is the most appropriate primary effectiveness endpoint and when might be the most appropriate time for it to be assessed?
b. What are appropriate secondary effectiveness endpoints?
c. What is the role for Quality of Life (QoL) assessments in these studies and which questionnaires are most informative?
d. What is the role of comorbidity improvement/resolution as an endpoint?
e. Besides monitoring for device- and procedure-related adverse events, what other safety endpoints should be considered?

In addition, length of the trial may raise certain ethical issues. ***Please discuss parameters for guiding the need for re-assenting patients in a long-term trial, or the need for modification of the "informed consent process" as patients transition from assent to consent.***

3. Trial Design and Assent Issues

The design of the clinical study protocol is crucial to the assessment of the safety and effectiveness of any medical device. Yet, the very nature of medical devices makes the well-known and preferred placebo-controlled trials pursued with pharmacological agents, more difficult. Blinding (masking) patients or evaluators may be difficult to impossible in many situations where the device requires surgical implantation or causes an abnormal sensation from its physical presence or action. As devices are often mechanical or electrical products which may not be easily turned off or removed, or may permanently alter the structure or function or an organ, there may be more of a safety concern compared to drugs where the product can simply be stopped if a significant adverse event is noted.

In addition, there are many other factors which could affect outcome in an obesity trial including personal and family motivation, concurrent medications, exercise, diet, behavioral therapy/changes and the like.

As such, FDA would like recommendations from the committee on what the appropriate study design(s) for device trials in this setting might be – again recognizing that in certain situations, flexibility will be required.

In responding to this question, it would be helpful to consider the following in your discussion:

a. Are randomized controlled trials (RCT) the preferred trial design and if so, what would be an appropriate choice for control group treatment? In your discussion, please comment under what circumstances and for what types of devices this might be appropriate or best suited. In addition, please consider the role of a *sham* treatment/procedure in your discussion. Furthermore, please discuss how the issue of blinding/masking should be addressed.
b. What are other appropriate and acceptable study designs? Please include in your discussion, comments on the use of single arm studies (patients as own control), concurrent non-randomized studies, and studies using historical controls.

c. How should other confounding factors such as concurrent diet, exercise, and behavioral modification therapy be addressed in the study design?
d. What is the most appropriate duration of a pre-market study? In your discussion, please discuss what you believe to be an ethical duration for a sham-controlled group (including the situation where the device is surgically or procedurally placed but not activated), and a conservative interventions control group (diet, exercise, behavior modification).

In addition, various trial designs raise multiple ethical issues besides adequate assent and parental permission. ***Please discuss pertinent ethical considerations of placebo-controlled trials and sham procedures.***

4. Long-term Assessment

Since many devices are intended to serve as long-term or permanent implants, not all information regarding the device's safety and effectiveness can be reasonably expected to be obtained in the pre-market or short-term arena.

As such, FDA would like recommendations from the committee on what long-term safety and effectiveness issues are important and how should they be evaluated and addressed.

In your discussion, please consider the following items:

a. The effect of the device and weight loss on future growth and development
b. The effect of the device and weight loss on future comorbidities
c. How important is it to demonstrate maintenance of weight loss and for what period of time. This discussion will require you to make recommendations on what would be considered "maintenance."
d. What type of information you believe would be important to collect and analyze as part of a post-approval study (PAS) if the device were a Class III PMA product as well as the duration of such a study.
e. What role do you anticipate for registries in the post-market arena?

In addition, Data Monitoring Committees may be an important method of human patient protection in long-term trials as well as other trial designs. ***Please discuss DMCs as well as any other suggestions for human subjects protection.***