DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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To: Daniel Schultz. M.D.
Director, Center for Devices and Radiological Health

From: Aron Yustein, M.D.
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Date: December 22, 2005

Subject: Summary of Pediatric Advisory Committee Meeting
Clinical Trial Design Issues for Pediatric Obesity Devices
November 16, 17, 2005

Background

The prevalence of obesity in the United States has been steadily increasing over the past 20-30 years and in the opinion of some, has reached “epidemic” proportions. This is true for the adult population as well as the pediatric/adolescent populations. The Center for Devices and Radiological Health has a fair amount of experience in working with manufacturers and sponsor-investigators in designing trials for the evaluation of the safety and effectiveness of devices to treat obesity in the adult population. It also has recognized that it is likely, in the near future, there will be more interest on the part of device manufacturers and investigators to study such devices in the pediatric population. Therefore, the Center contacted the Office of Pediatric Therapeutics (OPT) in early 2005 to discuss the possibility of convening the Pediatric Advisory Committee (PAC) to discuss the clinical and ethical issues of such trials.

Meeting Preparation

Key individuals from CDRH and OPT met at frequent intervals to discuss the logistics of convening the PAC to discuss clinical trial design issues for pediatric obesity device trials. These included:

CDRH:

- Nancy Pluhowski
- Ron Yustein, MD
- Carolyn Neuland, PHD
- Kathleen Olvey
- Jeff Cooper, DVM
- Joanne Less
- Joy Samuels-Reid. MD

OC/OPT

- Diane Murphey, MD
- Sara Goldkind, MD
- BJ Gould
- Jan Johannssen
- Joanne Holmes (CDER)
- Ann Myers (CDER)
- Benson Silverman (CFSAN)

The group worked together to come up with a 2-day agenda for a meeting. The PAC would consist of the standing members plus consultants with expertise in pediatric subspecialties relevant to obesity (endocrinology, psychology, nutrition, surgery, cardiology, etc.). Among the endocrinologists would be sub-specialists in Type II diabetes and metabolic syndrome. Since obesity device trials endanger ethical issues, four members and consultants with background in pediatric ethics were chosen as well. Additionally, there were consultants with expertise in adult bariatric surgery. In addition, the group identified national experts to make presentations on the various aspects of obesity during the first part of the 2-day meeting in order to get all the panelists on the same page with regards to the status of pediatric obesity within the United States.

Meeting Details

The PAC meeting was held on November 16 and 17, 2005 at the Gaithersburg Hilton. The night before the meeting, an informal training session was held for the panel members to familiarize the consultants with device regulations and issues since the vast majority of the panelists were familiar with drug but not device issues or, because of their unique expertise, were new to an FDA panel.

The first day of the meeting was reserved for presentations to the panel to familiarize them with the issue at hand. Dr. Yustein from ODE gave the first presentation which was a summary of approved devices for the treatment of obesity, a general discussion of the trial designs typically seen for adult obesity device trials, and a summary of the questions which would be asked of the panel on the second day. This was followed by 5 presentations from national experts on various topics:

1. Discussion of Epidemiology of Pediatric Obesity – W. Dietz, MD, PhD - CDC
2. Pathophysiology of Obesity – Sandra Hassink, MD – Jefferson Medical College
3. Discussion of Assent and Consent – David Wendler, PhD – NIH
4. Discussion of Conservative Management of Pediatric Obesity – Deanna Hoelscher, PhD – Univ of Texas
5. Discussion of Surgical Interventions and Devices – Victor Garcia, MD – Univ of Cincinnati

The second day of the meeting was dedicated to Panel discussion of the 4 questions from FDA related to trial design. These focused on:

1. The appropriate patient population (eligibility criteria) to study.
2. The appropriate effectiveness and safety endpoints to measure
3. The appropriate trial designs for studying devices in this population including the ethical issues surrounding randomized controlled and sham controlled studies.
4. The long-term safety and effectiveness issues and the role of post-approval studies.

Open Public Sessions took place on both days.

Recommendations from Panel

Led by the Panel Chair, "Skip" Nelson, M.D., the panel engaged in a robust and thoughtful discussion of the issues presented by FDA. This meeting was planned as a pro-active discussion and as such, was attempting to deal with a topic which has been largely overlooked or inadequately addressed/studied by the medical community to this point. Due to the novelty of some of the issues as well as the paucity of data and ethical issues, CDRH did not anticipate that the Panel would be able to reach full consensus on all or even many of the questions. Although remaining split or uncertain as to how to deal with certain issues, the panel was able to reach majority consensus on several. In general, the panel recommended the following:

- Devices, especially implants, should not be studied in the pediatric population until enough data has been gained from adult study and use.

- 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.

- In general, long-term implant devices should be studied in patients with significant disease which would be:
    - Subjects in the 99th percentile for BMI for age
    - Patients with at least one significant comorbidity to include such as
        - Sleep apnea
        - Diabetes
        - Pseudotumor Cerebri
        - NASH (Non-Alcoholic Steatohepatitis)

  Some panel members expressed concern about allowing patients with depression into the studies as a comorbidity as treating obesity may not improve their depression symptoms.

- Patients should be screened for known genetic causes of obesity and for Prader Willi, and if included in the study, should be evaluated separately.

- Change in BMI for age would be an appropriate assessment tool for the primary effectiveness. For purposes of sample size calculation, a 5-7 point reduction in BMI would be a clinically meaningful reduction.

- Comorbidity reduction or resolution would be an important secondary effectiveness endpoint although the study would need to be powered appropriately to evaluate such changes. Some panel members felt this should be the primary endpoint but recognized the limitations involved in defining reduction and sizing studies appropriately.

- The panel recognized that each device would have its own risk profile and potential benefit profile and as such, the study design may need to be adjusted accordingly.
    - For devices where the adult data shows an obvious clinical benefit, a non-randomized study with concurrent or matched controls might suffice.
    - For devices with borderline effectiveness in adults, a randomized study would be ethical and an option

- A dissent clause should be included in the protocol.

- Since some device trials may span 2-5 years, provisions for reconsenting the subjects should be made as new data becomes available or as the children transition from assent to consent.

- Premarket data should be collected for 2 years although patients should be consented/assented for 5 years.

- Studies should have DMC or DSMB

- 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. Although the panel agreed on the need for such, a concensus was not reached on the duration (1 or 2 months versus 6 months). The panel felt that for true emergencies, a lead-in period may not be required.

- Studies should be done in Centers where a multi-disciplinary team with pediatric expertise is available.

- It is important to standardize dietary and behavioral components between centers involved in the study.

- Data from Outside the US is less desirable than US data but may be considered.

- Post-approval data should be collected through 5 years

- Parties should be encouraged to have registries for long-term implants which follow patients for 5-10 years. This would include collection of data such as:
    - Height and Weight
    - Device Removal or Revisions
    - Infections
    - AEs including infection and device AEs
    - Obesity specific comorbidities such as HbA1c, arthritis scales
    - Pregnancy/Reproduction Issues
    - Nutritional Status
    - QoL – employment and marital status

Next Steps

The PAC Meeting was the culmination of the efforts of many staff members from across Centers within the agency. The meeting stands out for:

- The high level of and very successful cooperation between two groups (CDRH/ODE and OC/OPT) which have not worked together extensively in the past.
- The first major device issue brought to the PAC which has traditionally dealt with drug issues.
- The proactive nature of the agency in attempting to be prepared to address a significant public health issue which is only now coming to the forefront.

CDRH felt that the information gained from the Advisory Panel's discussions will be useful as it moves forward with its interactions with various sponsors and device manufacturers who wish to pursue clinical studies to support a pediatric indication for obesity devices.

ODE staff will consider drafting a concept paper to support a guidance document. In the meantime, the major points discussed by the panel will be used when discussing potential clinical studies with sponsors. Since the transcript is a public document, it will be readily available to sponsors and manufacturers on CDRH's website.

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