FDA Perspective

Session 1. Introduction

- Epidemic of Obesity - Aronne
- Challenges and Opportunities - Kaplan
- Medical Device Therapy for Obesity and Metabolic Disease - The Current Landscape - Rothstein
- Medical Device Development and Regulatory Challenges - Lerner
FDA Perspective— what we heard

• Obesity epidemic exists - (Obesity is a disease which causes other diseases) - growing burden on health care system
• Causes of Obesity are multifactorial – (diet, lack of physical activity; endocrine disruption ; lack of sleep; ambient temperature, medication related, stress and distress, etc. )
• Need to take into consideration physiology and GI signals and how to mimic effects of bariatric surgery with medical device– plateau wt set pt
• Many devices under development – short term use and long term use, surgical and non surgical (endoscopic; space occupying, sewing tools; duodenjl; stimulators, and Notes)
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Session 2. Optimization of Clinical Trial Design: Controls and Blinding

• Sham-controlled Trials - Ethical and Policy Considerations - Miller
• Case studies - Machineni
• Practical Considerations in Sham-controlled Device Trials - Rothstein
FDA Perspective- what we heard

• Sham controlled trials are possible for surgical procedures
• Sham trials may be justified if clinically relevant; methodologically necessary to produce valid results; and the risks are not excessive
• Sham control reduces bias. Can show actual benefit of device from noise. Attention to maintaining blind is key. Finding the true effect of treatment is important.
• Crossover trials keeps patients in the study
• 2X2 Factorial design can help sort out effects
Concerns with sham – may under represent treatment effect;

If you want to see if the procedure contributes to a treatment effect, you need a sham;

What if the sham is a viable treatment? – you can do a three arm study (treatment vs sham vs SOC – but risks must be low); longer term studies may be needed to prove sham does not work – sham effect may be short lived;

Patient Unmasking – not a problem if due to good therapy or slide effects
FDA Perspective- what we heard
Panel Discussion Session 2

• Life style modifications/counseling as part of study – various concerns – pros and cons – if in both arms - may require a larger trial; but there my be a positive synergistic effect of diet with the device, or the device may require a restrictive diet and this is how device will be used in clinic; may keep patients in the trial

• FDA requires patients have failed diet and exercise prior to enrollment; trial designs very regarding counseling during the trial

• Comparison to meta-analysis – some concerns
Session 3. Inclusion Criteria and Outcome Targets

- Tying Outcome to Risk - Introduction – Kaplan
- Defining Study Outcomes - Comorbidities – Beaston
- Defining Outcomes – Weight loss - Aronne
- Outcomes for Wt Loss Device Trials - Nipper
- Assessing Device Risk/Benefit - Lerner
- Stratification of Devices by Risk and Expected Outcome – Proposal - Kaplan
FDA Perspective—what we heard

• Session focused on tying outcomes to risks;
  Three components for determination of risk
  ➢ Device/procedure characteristics
  ➢ Risk of substantially similar devices/procedures
  ➢ Outcomes of pivotal trials

• Comorbidities – obesity is a chronic disease with many comorbidities – many complex and difficult to assess success (Cardiovascular or metabolic syndrome); Type II Diabetes Mellitus (most linked to obesity)
FDA Perspective—what we heard

• Weight loss = good
• Weight loss + improvement in complications of obesity = better
• Weight loss + improvement in many complications of obesity = even better
• Risk must be assessed and balanced against benefit
• Stratification scheme for device risk and expected outcomes proposed
Devices for cosmetic use – minimal or moderate wt loss on a temporary basis would need to be carefully balanced against the risks of device and procedure, as well as the lack of improvement in health outcomes.

Dr. Ginsburg - ASGE – PIVI White paper on Obesity devices – also a tiering (anatomy altering versus non-anatomy altering with minimal threshold weight loss; bridge therapies; preemptive obesity category, etc)

BMI vs Met life Tables – majority prefer BMI (23-25)
FDA Perspective—what we heard
Panel Discussion Session 3

• %EWL vs Total Wt loss – due to problems with skewing of data when BMI<30, most preferred %Wt change
• Clinically meaningful weight loss?
  • Mathematical models could be developed
  • Complexity of proposed stratification - make more complex and have layers and add numbers like FMEA
  • Drugs – 5% Total wt loss -but very large trials
  • Trending should be for improvement in all events
  • Clinically meaningful should depend on risks
• Obesity is a chronic disease – duration of response should relate to risk, but risk may change over time; don’t forget risks of not treating a disease

• Reversibility of removing the device – where does that fit into risk/benefit?
• Time of removal also plays a role
• Delta for effectiveness – what is best?
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Panel Discussion Session 3

• Responder analysis? Studies vs patients—Predictors of response over time is needed
• What about procedures being done at Centers of Excellence – none for endoscopic procedures – how by about credentialing by Medical societies at hospitals?
• Advisory panels are just that – advisory FDA makes final decisions
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Session 4. Device Development Strategies and Regulatory Considerations

• Combination Products – Lauritsen
• Regulatory Considerations in Device Development 1: Overview - Kahan
• Regulatory Considerations in Device Development 2: Role of OUS Studies and Mechanistic Studies – Venkataraman-Rao
• Regulatory Considerations in Device Development 3: Post-marketing Surveillance - Yustein
FDA Perspective-what we heard

• Overview of various regulatory issues:
  • Combination products
  • Post market studies
  • OUS trials
  • Mechanistic studies
  • Other issues
FDA Perspective—what we heard
Panel Discussion Session 4

- Panel Discussion:
Treatment of Obesity is a very complex disease and we heard extensive discussion on many of the critical issues.

We received preliminary responses to many of our questions; we note that everyone has the same questions, plus many more.

We will review in more depth information provided in this workshop and continue the discussions internally and at an advisory panel in 2012.
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• Population
  • What is the best measure of obesity?
  • How is “Ideal” weight defined?
  • Who should be eligible for these devices?
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• Clinically Meaningful Weight Loss
  • Does weight loss alone predict the prevention or reversal of comorbid conditions?
  • How long should weight loss be maintained?
    • For temporary devices, how long should the effects be maintained?
    • When should the devices be explanted?
  • How much risk is acceptable for certain amounts of weight loss?
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• Study Design
  • How important are randomized controlled trials?
    • Is there a need for a diet/exercise/behavior modification control?
    • Does one need to fail this to be eligible for a bariatric device?
  • Should a sham control be required?
  • Should temporary devices be compared to permanently implantable devices?
• Endpoints
  • Should primary endpoint be responder rate, mean percent excess weight loss or a combination of these?
  • Should the same study goals (%EWL, % weight loss, patient population) apply to permanent and temporary devices?
  • Is weight loss alone an adequate endpoint, or should there be an associated improvement in comorbidities?
  • How much better should a device be over sham (if applicable)?