

SUMMARY MINUTES

**MEETING OF THE GASTROENTEROLOGY AND UROLOGY DEVICES
ADVISORY PANEL**

OPEN SESSION

January 17, 2003

**Gaithersburg Hilton
Gaithersburg, MD**

Gastroenterology and Urology Devices Advisory Panel Meeting

January 17, 2003

Attendees

Chairperson

Karen L. Woods, M.D.
Baylor College of Medicine

Executive Secretary

Jeffrey Cooper, D.V.M.
Food and Drug Administration

Voting Members

Sami R. Achem, M.D.
Mayo Clinic, Jacksonville, FL

Abdelmonem A. Afifi, Ph.D.
School of Public Health, UCLA

Brian M. Fennerty, M.D.
Oregon Health Sciences University

Mark Ferguson, M.D.
University of Chicago Pritzker School of
Medicine

Mary E. Gellens, M.D.
St. Louis University Health Sciences Center

Michael J. Manyak, M.D.
George Washington Univ. Medical Ctr.

Nicholas Shaheen, M.D.
University of North Carolina–Chapel Hill

Industry Representative

Andrew Balo
DexCom, Inc.

Consumer Representative

Christine Moore
Baltimore, MD

Food and Drug Administration Representative

Nancy C. Brogdon
Director, Division of Reproductive,
Abdominal, and Radiological Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Food and Drug Administration Speakers

Carolyn Neuland
Kathleen Olvey, ODE
Katharine Merritt, Ph.D., OST
Ron Yustein, M.D., ODE
Melvin Seidman, OSE
S. Lori Brown, Ph.D., MPH, OSB

CALL TO ORDER

Panel chair Karen L. Woods, M.D., called the meeting to order at 8:33 a.m. She noted that the panel members present constituted a quorum. **Panel Executive Secretary Jeffrey Cooper, D.V.M.**, then asked the panel members to introduce themselves.

Carolyn Neuland, Chief, Gastroenterology Branch, Office of Device Evaluation, introduced the Gastroenterology Branch members with whom the panel may be working over the next few years. She then updated the panel on the status of two devices reviewed by the panel. The lap band adjustable gastric banding system, a silicone band implanted around the stomach for use in weight reduction in severely obese patients, was approved on June 5, 2001, with requirements for 2 years of postapproval follow-up. The Acticon neosphincter, a fluid-filled silicone cuff device used to treat severe fecal incontinence in adults age 18 and older, was approved on December 18, 2001, with conditions of revised physician and patient labeling, revised indications for use, development of a physician training program, and 12 months postmarket follow-up.

Dr. Cooper read the appointment to temporary voting status, which stated that Nicholas Shaheen, M.D., and Mark Ferguson, M.D., were appointed as temporary voting members for the meeting. Dr. Cooper noted that Abdelmonem Afifi, Ph.D., Brian Fennerty, M.D., and Michael Manyak, M.D., were granted conflict-of-interest waivers for their current or past interests in firms at issue for matters that were not related to the day's agenda. Drs. Achem, Fennerty, Shaheen, and Woods were granted conflict-of-interest waivers for their past or current involvement in firms at issue for matters related to the day's discussions. All panel members' waivers allowed them to participate fully in the day's session.

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No comments were made.

SPONSOR PRESENTATION

Alan Stein, Ph.D., president and chairman, Enteric Medical Technologies, provided an overview of his company and summarized the development of the Enteryx device. He noted that Enteryx is indicated for endoscopic injection into the lower esophageal sphincter for the treatment of gastroesophageal reflux disease (GERD). The device consists of a biocompatible polymer in a liquid solvent with a radiopaque marker. The polymer, EVOH, is a copolymer of polyethylene and polyvinyl alcohol; it is extensively used for orthopedic implants and vascular embolization. The solvent is DMSO, which has a variety of medical applications. Tantalum, the radiopaque marker, is extensively used as a coating for devices including stents and beads for radiographic localization. The material was first used for vascular embolization in 1996 and has a good track record of patient tolerance, stability, and lack of migration.

Enteryx is injected into the lower esophageal sphincter (LES) via endoscope; on contact with fluid, EVOH and tantalum precipitate as a spongy material. The mechanism of action is unknown, but Dr. Stein stated that the device works through modification of compliance of the LES due to the volume and mechanical properties of the Enteryx material and fibrous encapsulation of the material. The decreased distensibility of the cardia thus prevents sphincter shortening during gastric distension.

Dr. Stein then described preclinical testing, including tests on Yucatan minipigs that were endoscopically injected with Enteryx. No complications were observed. All pigs continued to thrive, ate without difficulty, gained weight, and had no behavior or other changes.

Panel members asked for clarification on the volume of material injected for vascular indications versus GERD indications, possible effects of transmural injections, toxicity of

DMSO, and sloughing of the Enteryx material. Dr. Stein answered the questions to the panel's satisfaction.

Lucas Brennecke, DVM, DACVP, director, medical device pathology, Pathology Associates, presented information on the histopathology of samples from animals sacrificed at 2 weeks, 3 months, 6 months, and 12 months. Early and persistent fibrous encapsulation of the Enteryx material was observed at 2 weeks. A normal progression from acute to chronic inflammatory response occurred. The tantalum was stable: None was found in blood or lymph. Minimal calcification occurred in the tissue, with no increase over time as inflammation became chronic. The inflammatory responses were consistent with those observed with other permanent implant materials.

Panel members asked for clarification on the extent of the material distributed through the LES, the correlation between the amount of material injected and histological changes, the extent of the calcifications and their etiology, and the effects of the histological changes and the injections on the nerves in the esophagus. Dr. Brennecke answered the questions to the panel's satisfaction.

Glen Lehman, M.D., professor of medicine and radiology, Indiana University Medical Center, Indianapolis, summarized the clinical study results. The Enteryx procedure was conducted on an outpatient basis using standard endoscopic technique with fluoroscopic guidance. The study used a prospective design in which well-characterized GERD patients served as their own controls; a total of 85 patients were enrolled. Baseline pretreatment parameters were compared with posttreatment outcomes through 12 months. The hypotheses was that treated patients would experience clinically significant reduction in proton pump inhibitor (PPI) usage. Secondary objectives consisted of improvements in the GERD-HRQL symptom

score, the SF-36 Health Survey, pH values, and manometry. Significance was determined by the Sign test and the Wilcoxon Signed Rank test. Only PPI-dependent patients were eligible for the study; exclusion criteria were erosive esophagitis greater than Savary grade 3, hiatal hernia 3 cm or larger, Barrett's esophagus, esophageal body motility disorder, esophageal or gastric varices, body mass index (BMI) of 35 or greater, and prior GERD or gastric surgery. Ninety-three percent of the participants were Caucasian, 58 percent were male, and the mean age was 49.6. Average BMI was 28.3.

After listing several deviations from the protocol for specific patients, Dr. Lehman noted that analysis of the data with and without those subjects resulted in no statistically significant changes in primary and secondary objectives; the subjects were therefore included in the analysis.

No serious device- or procedure-related adverse events occurred, and all device-related and procedure-related adverse events were anticipated in the protocol. Device-related adverse events included retrosternal chest pain (92%), transient dysphagia (20%), fever (12%), belching/burping (7%), bloating/flatulence (6%), body odor or bad taste (5%), rib pain (1%), and flu syndrome (1%). All adverse events were resolved without sequelae. By 14 days, 75 percent of patients experienced resolution of their pain; by 3 months, all patients had resolution of their pain. No mortalities were observed in the study population.

Panel members expressed concern over the study design and endpoints, but Dr. Lehman noted that the endpoints had been worked out with FDA. Panel members also wanted more information on how the amount of implant material not sloughed was calculated; Dr. Lehman said that the amount was determined visually through imaging. The deeper the material is placed, the less it sloughs. Some patients sloughed all material but still had a good clinical outcome.

Panel members asked for clarification on the study design, which John Kennedy, a statistical consultant for the sponsor, provided. Panel members asked about patient selection criteria for retreatment; Dr. Lehman replied that if at 30 days the patient's quality-of-life score was below a certain level, he or she qualified for retreatment. In some cases, the patient felt better even though the implant had sloughed out. Panel members wanted to know whether fluoroscopy was required; Dr. Lehman stated that the procedure could be done without it.

David Johnson, M.D., professor of medicine, Eastern Virginia Medical School, presented data on the effectiveness study. At 6 months, 74 percent of patients were off all PPIs, and 10 percent had reduced their dose by more than half. At 12 months, 70 percent of patients were off PPIs, and 10 percent had reduced their PPI dose by more than half. At 12 months, 73 percent of patients had GERD-HRQL heartburn scores less than or equal to 15, and 92 percent had regurgitation scores less than or equal to 11. Most patients (82%) experienced at least a 20 percent improvement in at least one pH parameter. No significant changes from baseline were found in LES pressure, peristaltic amplitude, or postswallow residual LES pressure at 6 or 12 months. Endoscopy results at 12 months showed that 72 percent of patients demonstrated improvement or no change compared to baseline esophagitis scores on PPIs. Residual implant volume demonstrated good stability by 3 months.

Panel members noted a possible decline in the primary endpoint at each evaluation. Dr. Johnson replied that no major differences were observed at 6 and 12 months. Panel members also asked what proportion of patients were still defined as having GERD on the basis of pH results. Dr. Johnson noted that people do not normalize pH with standard PPIs and that normalization was not required to meet efficacy criteria. Panel members expressed concern that the device's mechanism of action is not known and that the methods for assessing residual implant volume

were not precise. Dr. Stein said that the company's use of tantalum in the product is to provide guidance during the implant procedure and that x-rays were used only to assess any gross loss of material, not volume. The sponsor is using spiral CT to quantify the residual in some patients.

Dr. Stein concluded the company's presentation by noting that in addition to the patients in the study, approximately 400 patients have been treated with the Enteryx device in more than 40 institutions in the United States, Canada, and Europe. The safety and effectiveness of the device worldwide is consistent with that reported in the sponsor's clinical trial. The sponsor plans to conduct a postmarket evaluation study involving 3-year follow-up on 300 patients. Finally, Dr. Stein described the procedure for training physicians to use the device.

FDA PRESENTATION

Kathleen Olvey, Lead Reviewer, Office of Device Evaluation, summarized the regulatory history of Enteryx and reviewed the proposed indication for use. She described the device and noted that it would have a 3-year expiration date. The sponsor's short- and long-term testing were in compliance with ISO standards.

Katharine Merritt, Ph.D., Office of Science and Technology, reviewed the preclinical data. She noted that in all three animal studies described by the sponsor, initial acute inflammation progressing to chronic inflammation was found. Some fibrous encapsulation was found at 6 and 12 months. Mineralization may be a problem, and persistent inflammation may cause loss of the material from the site, requiring repeat injections.

Ron Yustein, M.D., Office of Device Evaluation, presented the clinical data review. He summarized the results of two feasibility studies that were conducted prior to the IDE as well as the results of the pivotal trial. Although patients experienced improvements in some endpoints, other outcomes were problematic. For example, at 12 months more than 60 percent of patients

failed to normalize intraesophageal pH, and 54 percent had lower LES pressure than at baseline. In summary, effective treatment for GERD should address both the symptoms and signs of the disease as well as the prevention of complications. The data suggest potential beneficial effects for treating the symptoms of GERD, such as reduction in medication use and improvements in validated quality of life measures. However, the data appear less convincing for treating the signs of GERD and for preventing complications, as shown by intraesophageal pH data and esophagitis rates.

Melvin Seidman, Office of Surveillance and Biometrics, presented the FDA's statistical review. He noted the potential for bias when a study has many protocol deviations or much missing data. In this case, the sponsor assumed that the missing data would be no different from that for patients who completed the study, an assumption that may not have been valid. The pivotal trial had many protocol deviations: 13 at entry and 31 listed as study method deviations. These deviations, along with the missing data, suggest that the conclusions from the analysis of all secondary endpoints could be biased. However, conclusions from the primary endpoint appear to be conclusive. Missing data are not a factor, and protocol deviations were either explained or analyzed for the primary endpoint.

S. Lori Brown, Ph.D., MPH, Office of Surveillance and Biometrics, presented general information on the FDA's reasons for requiring postmarket assurance. Issues of concern for Enteryx are that the clinical study is too small to detect rare or potentially common adverse events and that the duration of follow-up was too short to provide evidence of long-term efficacy or safety. In addition, repeat application of Enteryx was required for 22 percent of the cohort, and the pivotal study provided little information on the safety and efficacy of repeat applications. Dr. Brown noted that the sponsor is proposing a 3-year follow-up study that would involve 150

to 200 patients from 10 to 20 institutions in addition to the patients recruited for the pivotal study and its extension, for a total of about 300 patients. She concluded by listing some questions concerning the study for the panel to consider (see Question 10 below).

PANEL DISCUSSION

Dr. Fennerty, lead panel reviewer, noted that up to 25 percent of people in the United States have GERD. The pathophysiology is not singular; GERD is many diseases wrapped into one symptom complex. Standard therapies (i.e., PPIs) have set a high bar: 80 to 90 percent symptom relief over 3 years. This study assesses a novel endoscopic application. It is important for the panel to consider what it is going to accept for new therapies for reflux disease. What is the minimum standard for trials?

- 1. The device, once injected, is intended as a permanent implant. Please discuss whether the current data provides adequate assurance of safety. Within your discussion, please specifically address the 12-month histology findings (persistent inflammation and mineralization) from the animal data.**

The panel agreed that the sponsor had adequately addressed short-term safety issues, but long-term follow-up is needed. Postmarketing studies involving placebos are indicated. Additional work is needed on foreign body reactions and calcifications as well as on the effects of retreatment. The observed inflammation is clinically irrelevant but warrants observation.

- 2. Tantalum was added as a component to the device to aid in visualization under x-ray and to assess indirectly the residual volume of implant at follow-up. Please comment on the degree to which the data in the PMA demonstrates that the amount of *tantalum* visualized on x-ray directly correlates with the amount of *polymer* remaining implanted.**

The panel concurred that it did not have enough information to answer the question. No data demonstrate that the amount of tantalum correlates with the amount of polymer implanted; clinicians should rely on CT scans, rather than x-rays, to determine the residual volume of implant. The issue is of minor importance.

- 3. Over 40% of evaluable subjects had a $\geq 25\%$ reduction in residual implant volume (as assessed by measurement of residual tantalum) at 6 and 12 months when compared to baseline at 1 month. Please**

discuss this finding and whether it poses any safety or effectiveness concerns. In addition, please comment on whether the conclusion that the “missing” material sloughed into, and was passed out of, the GI tract is reasonable and supported by the data.

The data are not precise, and the sponsor provided no evidence that the material is excreted in feces. More important is whether the material is still in the body and, if so, whether it is harmful. The sponsor has not adequately demonstrated where the missing material has gone; however, the consequences do not seem to be negative. Panel members noted that the main issue is not safety but whether loss of the implant material has an effect on device effectiveness. Patients who had less than 5 or 6 mL of product left were more likely to be treatment failures. The panel concluded that with the current data, it is not possible to tell where the material went.

- 4. . . . Please discuss the significance of the results from the intra-esophageal pH, esophagogastroduodenoscopy (EGD), and manometry procedures, and whether they support the use of Enteryx™ as a safe and effective treatment for GERD. Within your discussion, please comment on whether you believe that these results suggest patients may be at continued risk for developing complications of GERD including erosive esophagitis, strictures, and/or Barrett’s Esophagus despite symptom improvement while off their PPI medications.**

Many panel members noted that with a slowly degrading treatment effect over time, many subjective measures come into play. How much of the outcome is due to the placebo effect? Other plausible explanations involve nerve damage or interference with transient relaxations. The mechanism of action is unknown; a sham trial would help determine it. Minimal data are available to answer the last part of the question. The primary endpoint is too subjective.

Dr. Fennerty took the panelists to task for their criticism. He agreed that reduction in PPI use is not the primary endpoint that he would want, but it is what FDA and the sponsor agreed to. The accepted standard today is symptom improvement, and PPI use is a marker for symptom improvement. Secondary outcomes are important, but they are still secondary. Barrett’s esophagus is a complication of GERD, and esophagitis is not. Nearly 40 percent of patients neutralized their acid exposure after treatment; that result is not a placebo effect. The panel concurred that the sponsor had met the primary endpoint agreed to by the FDA.

5. **Based on your deliberations to this point, please discuss whether the overall benefits, including improvement in symptom as well as objective measures, outweigh any risks associated with use of this device.**

The target patient population is already having effective therapy, and the device offers an alternative that may not be as effective. Many issues remain unknown. The safety has been demonstrated, but the side effect profile is of concern. The panel concurred that the device should not be viewed as permanent. The sponsor has demonstrated short-term benefits, but the long-term efficacy and benefit outside the study population are not clear, and the effects of retreatment are unknown.

6. **Nineteen of the 85 patients underwent re-injection within the first 3 months. Please discuss whether sufficient data has been presented to support re-treatment with Enteryx™. If you believe the data is adequate, please comment on whether you believe any of the following should be recommended:**
- maximum number of repeat procedures (if so, what number);**
 - maximum number of repeat injections per procedure (if so, what number);**
 - maximum implantable volume at each procedure and overall (if so, what volumes); and**
 - timing of retreatment procedures relative to the initial treatment (if so, the length of time).**

The panel concurred that the data are inadequate to answer the question even generally, let alone specifically. Retreatment appears to be safe, but it would be speculative to answer the question.

7. **The sponsor has proposed the following Indication for Use for Enteryx™: *The Enteryx™ procedure kit is indicated for endoscopic injection into the lower esophageal sphincter (LES) for the treatment for gastroesophageal reflux disease (GERD).* Please discuss whether this Indication for Use accurately reflects the data obtained during the clinical trial.**

The panel expressed concern that the indication was too general and suggested that the sponsor should add “in patients responsive to PPI therapy” and “treatment of symptoms due to GERD.”

8. **The proposed labeling lists portal hypertension as the only contraindication for use. Please discuss any other clinical conditions for which you believe the labeling of the device should include specific contraindications, warnings, or precautions. In your discussion, please include comments on the following:**
- patients with Barrett’s Esophagus;**
 - patients with erosive esophagitis;**
 - patients with esophageal ulcers;**
 - patients with esophageal strictures; and**
 - patients with GERD symptoms refractory to proton pump inhibitors.**

The panel concurred that the only contraindication for use is portal hypertension; the conditions in the question should be listed as precautions.

9. Please discuss whether you believe the Physician and Patient Labeling brochures, as written, are adequate or whether certain *major* additions, deletions, or revisions should be made.

Panel members expressed concern about use of the term “permanent” to describe the device. The booklets need to address the fact that patients had side effects related to the device and note the length of the study. In addition, the recommendations concerning bland foods and prophylactic antibiotics can be deleted from both the physician and the patient information booklets. Panel members concurred that the physician labeling should include recommendations regarding the use of fluoroscopy and describe how to ensure that the material is injected correctly. The sponsor should ensure that the materials are compatible with all scopes currently in use.

10. Please comment on the sponsor’s proposed post-market evaluation of the device. Please specifically comment on and make recommendations concerning the

- a. study design;**
- b. number of patients;**
- c. length of follow-up; and**
- d. endpoints to be evaluated.**

The panel concurred that the postmarket evaluation plan would be improved if it included a randomized sham procedure and examined the effects of retreatment. Several panel members thought that a patient registry would be helpful and that 5-year follow up would be ideal. Panel members suggested that FDA should work with manufacturers to ensure that they provide sufficient follow-up data at the time of PMA submission that the panel can make better decisions. The panel concurred that the FDA staff and the sponsor could work out the details of the study.

11. Please comment on the sponsor’s proposed physician training program and whether you believe it is adequate for proper use of the device.

Panel members concurred that the training program is adequate.

OPEN PUBLIC HEARING

No comments were made.

VOTE

Dr. Cooper reviewed the voting options and noted that Dr. Fennerty had to leave to catch his flight home. The panel unanimously approved the device with the following conditions:

1. The sponsor must conduct the postmarketing study described in the PMA; the study must include placebo controls.
2. The indications should state that the device is intended for endoscopic injection into the region of the LES for treatment of symptoms due to GERD requiring and responding to pharmacologic therapy.
3. As part of the postmarket study, a registry of treated patients should be created to help study the indications for and results of retreatment.
4. Analysis of the data from the postmarket study should take into account longitudinal effects.
5. The labeling should add “esophageal stricture” and “symptoms unresponsive to pharmacologic therapy for GERD symptoms” to the list of precautions.
6. The sponsor should delete from the labeling the statements concerning prophylactic antibiotics, prophylactic pain medications, and dietary modifications and insert additional information explaining when fluoroscopy should be used to guide injection and when to use single versus multiple injections.
7. The information in the patient information brochure should be brought into line with the information in the physicians brochure. The patient information brochure should make it clear that patients who are not responsive to PPI are not candidates for treatment.
8. The labeling should state that the effects of retreatment are unknown.
9. The labeling should note that the device is a permanent implant.

10. The patient information brochures and the product labeling should reword the sentence containing the word “lifelong” to state that the device is a “minimally invasive alternative to drug use or antireflux surgery.”

In stating the reasons for their votes, panel members stated that they felt that the benefits of the device outweigh the risks to the consumer and that the sponsor has demonstrated short-term efficacy and freedom from complications. The panel concurred that the device is safe and effective.

ADJOURNMENT

Dr. Woods thanked the participants and adjourned the meeting at 4:26 p.m.

I certify that I attended this meeting of the Gastroenterology and Urology Devices Advisory Panel Meeting on January 17, 2003, and that these minutes accurately reflect what transpired.

Jeffrey Cooper, D.V.M.
Executive Secretary

I approve the minutes of this meeting
As recorded in this summary.

Karen L. Woods, M.D.
Acting Chairperson

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