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SUMMARY MINUTES

OF THE

GASTROENTEROLOGY AND UROLOGY DEVICES

ADVISORY PANEL

OPEN SESSION

July 29, 1999

**Room 020
9200 Corporate Blvd.
Rockville, Maryland**

**Gastroenterology and Urology Devices
Advisory Panel**

July 29, 1999

Panel Participants

Anthony N. Kalloo, M.D.
Panel Chair

Craig F. Donatucci, M.D.
Voting Member

Jenelle E. Foote, M.D.
Participant

Robert Hawes, M.D.
Voting Member

Joseph H. Steinbach, Ph.D.
Voting Member

Leonard L. Vertuno, M.D.
Voting Member

Richard E. Deitrick, M.D.
Consultant and Temporary Voting Member

Michael P. Diamond
Consultant and Temporary Voting Member

Patrick T. Hunter II, M.D.
Consultant and Temporary Voting

Naida B. Kalloo, M.D.
Consultant and Temporary Voting Member

Diane K. Newman, RNC, MSN, DRNP, FAAN
Consumer Representative

Alan H. Bennett, M.D.
Industry Representative

FDA Participants

Mary J. Cornelius
Executive Secretary
Gastroenterology and Urology Devices Panel

Thomas Gross
FDA

Dave Segerson
FDA

Donald St. Pierre
Branch Chief, Urology and Lithotripsy Devices Branch

Rao Nimmagadda
Urology and Lithotripsy Devices Branch

Hector Herrera
Urology Devices Branch

John Baxley
Urology and Lithotripsy Devices Branch

OPEN SESSION-JULY 29, 1999

Panel Chair Anthony N. Kalloo, M.D., called the session to order at 9: 18 a.m., noting that the voting members present constituted a quorum and asking the panel members to introduce themselves and give their areas of expertise.

Panel Executive Secretary Mary Cornelius read appointments to temporary voting status for Drs. Deitrick, Diamond, Hunter, and Kalloo. Ms. Cornelius also read the conflict of interest statement, noting that waivers had been granted for Drs. Vertuno, Diamond, Donatucci, and Hunter and for Ms. Newman. A limited waiver without voting privileges had been granted to Dr. Jenelle Foote. Ms. Cornelius listed future panel meeting dates as November 18-19, January 27-28, April 13-14, August 31-September 1, and November 30-December 1, 2000.

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Dr. Roger R Dmochowski of the American Urological Association (AUA), read a statement from the AUA in support of ongoing industry research for the development of new nonsurgical treatments for male and female urinary incontinence. He stated that the AUA supports development of the newest research frontiers, which include both bulking agents and various devices or injectable mechanisms.

Dr. Thomas Gross of the FDA gave the panel a presentation on postmarket surveillance and methods of postmarket evaluation at CDRH. He explained that medical devices have a definable life cycle, in which the clinical community has an important role to play in providing feedback during postmarket evaluation. He outlined the questions assessed in the postmarket period and described the Medical Device Reporting (MDR) Program, which provides limited but critical information to FDA about devices with

problems, and he listed the possible actions prompted by such a medical device report. Dr. Cross discussed the two postmarket authorities, postmarketing surveillance and postapproval authority, and outlined the criteria for a panel to suggest postmarketing surveillance as well as study designs used in postmarketing surveillance. He acknowledged the frustrations involved in monitoring the postmarketing period and challenged the advisory panel to ensure that a postmarketing study will be of primary importance, to specify the public health question it is to address, and to note what will be done with the data collected. He briefly outlined of the **future** for the MDR and Postmarketing Surveillance programs.

Mr. Donald St. Pierre, branch chief of the Urology and Lithotripsy Devices Branch, updated the panel regarding activities based on panel recommendations. At the October 29, 1998 panel meeting, the panel recommended as approvable with conditions a PMA Supplement from Cypress Bioscience, Inc. for the PROSORBA column. FDA issued an approval order for the device on March 15, 1999. The FDA also agreed with the panel recommendation from the July 30, 1998 meeting to **downclassify** extracorporeal shock wave lithotripters to class II and issued a proposed rule on February 8, 1999 for that down-classification. At the same time, FDA issued a level 1 draft guidance document for extracorporeal shock wave lithotripters as the panel had recommended. The final rule and final guidance document incorporating comments received are now being prepared.

On February 12, 1998, the panel had discussed a product development protocol (PDP) for American Medical Systems' penile inflatable implants; this PDP was completed and given marketing approval on November 2, 1998.

Mr. St. Pierre also noted that on April 15, 1999, the agency approved a PMA supplement to expand the indications for Medtronic's previously approved Implantable Sacral Nerve Stimulator. The agency has also approved two humanitarian device exemptions (**HDEs**) for **NeuroControl** Corporation's **VOCARE** Bladder system, an implantable stimulator for bladder and bowel evacuation.

Mr. St. Pierre discussed two postapproval studies recommended by panel action. The first was on the relationship between lithotripsy and hypertension, which resulted in a labeling change of extracorporeal shock wave lithotripters to state that hypertension is not a long-term risk of lithotripsy. The second was a postapproval study on the long-term effects of EDAP Technomed's Prostratron microwave thermal therapy system for treating BPH in terms of durability and retreatment rates. The sponsor completed this study and modified labeling to include the five-year follow-up data.

There were no further requests to address the panel.

OPEN COMMITTEE DISCUSSION-PMA APPLICATION P980053

Sponsor Presentation

Karen Peterson of Advanced UroScience introduced the sponsor team members and described the Durasphere Injectable Bulking Agent for the treatment of stress urinary incontinence (SUI). She discussed the prevalence of urinary incontinence and the cause of SUI, as well as the device mechanism to treat it. She defined and described the device, noting that it is a sterile, injectable bulking agent composed of pyrolytic carbon-coated beads suspended in a water-based beta glucan carrier gel.

Mr. Richard Holcomb listed the three objectives of the IDE study, which was a multi-center, double-blinded, randomized, controlled trial of the device compared to the marketed control product Contigen. He explained measurement of the two primary efficacy endpoints, which were change in continence grade score over 12 months and pad weight measuring urine loss during a prescribed set of activities, and of safety endpoints, which were **evaluated** through morbidity analysis and complication rates. Mr. Holcomb listed five secondary endpoints and discussed sample sizes and statistical methods used to calculate summary statistics for all study variables. He noted that a maximum of four retreatments was allowed in the study, as consistent with device labeling.

Dr. Jeffrey Snyder showed a video of the actual injection procedure of Durasphere and presented the clinical study results. A total of 377 patients were injected with device or control at 10 investigational centers, of whom 355 patients were female. Male patients experienced less improvement than did the female patients in both device and control groups. There was no significant difference in the two primary efficacy endpoints between Durasphere and control, and no significant difference in the distribution of severity of events **between** device and control patients. Most adverse event categories showed no significant difference in incidence between Durasphere and control, with the exception of urgency and acute retention, which Dr. Snyder analyzed in detail. There were no significant **differences** in secondary endpoints as well, or in the difference in the number of treatments in each group.

Karen Peterson summarized that both of the primary efficacy endpoints were significantly improved from baseline to follow-up for the device, and the results were equivalent to that of control. Few differences were found between Durasphere patients

and control group in severity, incidence, duration, and resolution of adverse events and no significant differences in most secondary endpoints. She noted that results on durability of improvement were not significantly different **from** control but are suggestive of potential longer-term durability.

Panel Review

Dr. Jenelle Foote gave a clinical overview of incontinence, discussing its prevalence and health and cost implications. She listed three types of incontinence and three subtypes of stress incontinence. Citing an AUA study of different technologies to deal with stress incontinence, she discussed operations and injectable agents as curative or palliative methods.

FDA Presentation

Dr. Rao Nimmagadda, FDA lead reviewer, introduced the FDA presentation by listing the PMA contents. He described the device and listed the critical manufacturing points and biocompatibility testing performed. After a brief outline of the clinical study, Dr. Nimmagadda described discrepant skin sensitivity tests done in the United States and Costa Rica. He noted that effectiveness results at one year showed no statistically significant difference between device and control and that Durasphere was equally effective as Contigen when analyzed as a function of number of treatments; he then listed three effectiveness issues for panel consideration. On safety, Dr. Nimmagadda found no significant difference for most adverse events other than urgency and acute retention and he listed two issues for panel review.

Dr. Hector Herrera, clinical reviewer, discussed demographic issues, which included the small number of men and under-representation of African Americans

compared to the U.S. population. He summarized effectiveness and safety comparisons and listed treatment options for stress urinary incontinence. He listed several advantages of the device, and stated that his main concern is that the durability of the implant's effectiveness beyond one year is not well characterized. In assessing risks and benefits, he noted **that** the device showed an equivalent effectiveness and similar **safety** profile to control, although with an increased risk of urgency and acute retention. Dr. **Herrera** observed that the device can be injected as an outpatient procedure in a familiar injection procedure. The beads are not absorbable, but long-term effectiveness is yet to be demonstrated. Dr. **Herrera** stated that he thought skin testing unnecessary and that the device showed no apparent risk of long-term immunological complications. He read five questions for panel discussion.

In general discussion, panel members raised questions on whether reproductive toxicity had been tested and on effects of skin testing on other racial and ethnic groups.

Dr. Roy Ritz, a consultant to the sponsors, discussed the skin test results, which he thought were not an issue of significant concern.

FDA Questions

On exclusion of men or patients under the age of 21, the panel recommended an indication for use in patients over the age of 21 with no specific exclusion for children, men, and women of reproductive age. The panel did recommend a labeling comment on the absence of data on children and paucity of data on men and the lack of specific safety data on pregnant women and women of reproductive age.

The panel agreed that the risk/benefit profile of the device is favorable. Members thought the post-approval study outlined was adequate, but there was a feeling that more

data should be included on effectiveness for grade three incontinence and on safety in children, women of reproductive age, and men.

The majority of the panel recommended that the labeling require users to be familiar with therapeutic endoscopy, but there was dissension. Some members wanted documented physician training in cytoscopy and injection therapy.

The panel thought the directions for use were accurate and comprehensive, but it was noted that the patient education booklet should address the question of pain.

OPEN PUBLIC HEARING

There were no requests to address the panel.

There were no additional comments from sponsors or FDA personnel.

Panel Recommendations and Vote

Panel Executive Secretary Mary Cornelius read the panel voting instructions and options. A motion was made and seconded to recommend the PMA as approvable subject to the following conditions: 1) The labeling should be revised to indicate use in patients over the age of 21, with a notation that there are minimal data on men, children, and women of reproductive age. 2) **Labeling** should require that device users be familiar with therapeutic endoscopy. 3) The postapproval study should include more data on effectiveness for grade three incontinence and safety in men, children, and women of reproductive age.

The motion passed by a vote of seven to one. Those in favor voted for the motion because they thought the demonstration of safety and effectiveness was adequate. Dr. Diamond, who opposed the motion, agreed in principle but could not approve allowing

use in males with no reasonable assurance of effectiveness in that group. He would have preferred that use to be off-label.

OPEN COMMITTEE DISCUSSION - REVISIONS TO DRAFT GUIDANCE ON TESTICULAR PROSTHESES

John H. Baxley of the Urology and Lithotripsy Devices Branch presented FDA recommendations for revisions to the Draft Guidance for Preparation of PMA applications for testicular prostheses.

Mr. Baxley explained the regulatory history of these class III devices and described the March 1993 guidance document and the April 1995 final regulation. He noted that these documents contained detailed testing recommendations specific to the silicone gel-filled design, which was then the predominant implant on the market. Since 1995, however, manufacturers have ceased production of testicular prostheses. Some companies have since proposed clinical investigations of new models that do not contain silicone gel, but these are difficult to test, given the heavy emphasis of the March 1993 guidance on silicone gel-filled designs.

Mr. Baxley outlined the clinical study recommendations of the March 1993 guidance in terms of material -related adverse events, effectiveness endpoints, study design, postapproval follow-up, and **epidemiological** studies. He discussed development of design-specific clinical recommendations for solid elastomer implants **and saline-filled** designs, as well as elastomer shells **filled** with silicone gel. Mr. Baxley's second general recommendation was **PMA reliance** on the literature regarding the surgical technique **and** short-term risks **and** benefits; he noted that such information could be included in each

PMA as supplementary information to confirm clinical results. His final general recommendation was that patients should serve as their own control.

For solid elastomer prostheses, Mr. **Baxley** recommended that manufacturers submit data on 50 patients followed for a minimum of six months to confirm that the device requires similar surgical technique and has a comparable short-term adverse event profile to those already in the literature. One-year follow-up data on 50 patients should be collected to assess incidence of adverse events such as erosion or migration.

For saline-filled implants, the FDA is recommending that PMA approval would be based on a minimum of 100 patients followed for six months to confirm the same objectives but also to show higher statistical confidence, given potentially different rates of rupture or other adverse events. Manufacturers should collect five-year follow-up data on 100 patients or maintain a patient registry to assess long-term adverse event rates such as primary rupture and revision.

For silicone gel-filled implants, Mr. Baxley recommended that PMAs should contain the results of 100 patients followed for 12 months because of the **additional risk** of rupture with associated potential material-related adverse events. **After** approval, manufacturers should either follow 250 patients for ten years to document long-term adverse events or maintain a patient registry. The objectives and follow-up duration for the postapproval recommendations are designed to evaluate the rate of rupture and effects of release of silicone gel into the **body** and are consistent with postapproval study recommendations for breast implants.

The FDA recommended that effectiveness of the implant would be evaluated by physician assessment of the cosmetic effect and assessment of patient satisfaction. Safety

would be assessed through analysis of all reported adverse events. Recommendation on the design of epidemiological studies would be removed **from** the guidance because they are impractical given the limited numbers of patients involved.

Panel Review

Dr. Naida Brooks Kalloo provided a status report on the management of testicular implants. She discussed the history of testicular implants over time, indications for use, surgical procedure involved, and complications. She noted that **after** an AUA position paper against the use of silicone-gel testicular prostheses, production was suspended.

OPEN PUBLIC HEARING

A **representative of the AUA** applauded the FDA for its thoroughness in considering the need to ensure patient safety. He noted that any study would have to be a multicenter, multiyear study and questioned whether there would be enough sales to **justify** such a study. He offered to ask the AUA to reevaluate its position in light of the emotional benefits for the patients involved.

In answer to a panel question, Dr. **Baxley** clarified that this is a low-demand device, similar to an orphan drug situation in that there are few patients who need it but those who do would benefit emotionally **from** its availability. In answer to another panel question, a **representative from the Mentor Corporation** stated that there is industry interest in producing such devices if the **guidance** can be revised.

FDA Questions and Panel Recommendations

The panel agreed that the proposed stratification scheme for clinical testing recommendations for testicular prostheses is sound. The majority of the panel thought that

the adult and pediatric populations could be pooled, although one member thought children might stress the implants more. The majority of the panel thought the pre and postapproval follow-up recommendations are sufficient, with the comment that a postapproval study seemed excessive and a registry was sufficient. One member suggested a study with a control group for measurement of psychosocial effectiveness. It was moved, seconded, and unanimously approved that the FDA revisions to the Draft Guidance for Preparation of PMA Applications for Testicular Prostheses be accepted as discussed in the meeting and as revised in the questions noted above.

Executive Secretary Mary Cornelius read into the record a **letter from Dr. Stanley Kogan, Liaison to the Urology Section to the American Academy of Pediatrics**, who noted the need for legally marketed testicular implants and asked the FDA to facilitate making these implants available.

Panel Chair Dr. Anthony Kalloo thanked the panel on behalf of the FDA and adjourned the meeting at 3: 10 p.m.

I **certify** that I attended the Open Session of the Gastroenterology and Urology Devices Advisory Panel Meeting on July 29, 1999, and that this summary accurately reflects what transpired.


Mary J. Cornelius
Panel Executive Secretary

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


Anthony N. Kalloo, M.D.
Panel Chair

Summary minutes prepared by
Aileen M. Moodie
9821 Hollow Glen Pl.
Silver Spring, MD 20910
301-587-9722