

## **NEW BUSINESS**

Panel Chair Dr. Wilson called the second session to order at 4:07 PM.

### **AGENDA: PREMARKET NOTIFICATION SUBMISSION K 011043**

*An in vitro diagnostic device for detecting and measuring urinary tract infection by semi-quantitative analysis of volatile compounds released from urine samples.*

### **SPONSOR PRESENTATION**

**James White, CEO**, Osmetech introduced the Osmetech team then gave a brief description of the history of the company and the chronology of their interactions with the FDA. He noted that their 501K application was submitted in April 2001.

**John Plant**, Healthcare Projects Team Leader, Osmetech, presented the description of the device and the technology, and its' intended use. The Osmetech Microbial Analyzer, Urinary Tract Infection Detector is an automated in vitro diagnostic device for use as an aid in the detection of bacteria found in urinary tract infection (UTI). By means of a semi-quantitative analysis of volatile compounds in the headspace above a urine sample, the OMA-UTI indirectly measures a urinary tract infection. A positive OMA-UTI would send the sample on to culture. He stated that the Osmetech would not replace culture, as it did not provide organism identifications. He also discussed the calibration procedure and classification thresholds and concluded with a summary of the study conducted in London.

**Patrick Murray, Ph.D.**, Site Investigator, Director, Clinical Microbiology Laboratories, University of Maryland Medical Center, Baltimore, presented an overview of the clinical studies. He stated that the standard microbiology cultures were considered as the Gold Standard. Three Centers in the US and UK evaluated 1038 samples that resulted in a sensitivity of 81%, a specificity of 83%, and a negative predictive value of 96% and a positive predictive value of 44%. The overall accuracy was 83%. The false negative rate may be explained in part by antibiotic use. Since informed consent was not obtained from the patients, the information on disease state, antibiotic use, or patient

descriptions could not be determined. This test was compared with other similar tests used in detecting urinary tract infections. An agreement of 93% with a Kappa of 0.86 was obtained between the two US sites.

**Dr. Wilson** then invited the panel to question the sponsor. The panel had several questions for the sponsor.

**Dr. Nachamkin** asked whether the urine samples were refrigerated while transporting to the laboratory and whether boric acid preservatives were used.

**Dr. Durak** asked if yeast were excluded from the study, and further if any bacteria were particularly difficult to detect. **Dr. Murray** replied that yeasts were included in the test, but no claim was made about them in the study results. Escherichia were the most difficult organism to detect in this study. **Mr. Travers** replied that boric acid was used in the bench trial of the test and cleared the machine with no problem, however it was not recommended for use. **Dr. Carroll** was concerned about the number of missed Group B Streptococci because of its implications for pregnant woman. **Dr. Nolte** raised the question of antibiotics influencing the out come of the test. **Dr. Beavis** expressed concern about the number of false negative specimens.

**Dr. Charache** questioned the study design and asked about the distribution of species and the appearance that there were many contaminants one site. **Dr. Reller** asked about the effect of boric acid on the assay. **Mr. Travers** responded that with the levels of boric acid used as a preservative, no effect was noted on the assay. **Dr. Reller** asked about screening asymptomatic pregnant women, diabetics, etc.. **Anthony Schaeffer, MD** answered that if such a woman had a negative screening test and culture, the clinician would not have to re-culture her. Subsets of patients will have to be considered, such as, patients with a history of urinary tract infections or uretero-vesical reflux.

**Dr. Baron** asked if the four polymers in the test detected different metabolites. **Mr. Plant** replied that two polymers focus on one metabolite, while the second two polymers respond to the other marker analytes. **Dr. Janowski** asked for information on the cause of the system failures and whether the firm had any data on subgroup analysis.. **Dr. Durak** asked about sensor systems drift and recalibrations. **Mr. Travers** stated that

in the trial study, the machine was recalibrated twice. Dr. Wilson then ended the questions and invited the FDA to present.

## **FDA PRESENTATION**

**Marian Heyliger**, Senior Scientific Reviewer, Bacteriology Branch, briefly summarized the technology of the device, as compared to previous urine screening devices reviewed by the FDA, the positive/negative rates, the performance characteristics and the discrepant results. She also provided some theoretical reasons for false positive and false negative results.

**Dr. Wilson** invited the panel to question the FDA. **Dr. Charache** commented on the use of device as a screening test in light of the number of organisms missed. **Dr. Nachamkin** worried about using this device in a screening test when the results show a positive predictive value of 44%. **Dr. Baron** was concerned about the effect of catalase in the test. **Dr. Reller** was concerned with the negative predictive value of the test because there are patient populations, elderly, pregnant women, diabetics, who should be screened by culture.

## **OPEN PUBLIC HEARING**

Dr. Wilson then opened the meeting. No one came forward so he closed the Open Public Hearing segment.

## **OPEN COMMITTEE DISCUSSION**

The FDA questions were read and the panel members commented on each item.

**Question #1: Please comment on the adequacy of these data to support the use of this device as an aid in the detection of bacteria associated with urinary tract infection.**

**Dr. Durack** believed that the package insert appeared to differ in intended use with what was presented by the sponsor. **Dr. Gutman** stated that he believed the sponsor's intended use for this device was to rule out infection. FDA would work with them on the labeling, the panel could state if additional data was required and the types. **Dr. Charache** recommended that the patient population be described so that clinicians would know how the device worked. **Dr. Baron** suggested that the data to be broken down into age, gender, site, etc. **Dr. Nachamkin** suggested that data broken down into asymptomatic and symptomatic patients.

**Question #2: Results of the OMA-UTI when compared to standard culture showed a high number of false positive results. Given confounding factors such as reduction in bacterial numbers due to antibiotic use or production of high levels of metabolites with some bacteria, are there any other comparative methods that may be more appropriate?**

**Drs. Baron** and **Nachamkin** did not have problems with the comparative method used because of the number of false positives and because it was a screening test.

**Question #3: The detection threshold of the OMA-UTI has been set to detect levels of volatile metabolites found in specimens with bacterial counts  $1 \times 10^5$  CFU/ml for either single colonies or mixed colonies containing at least one predominant organism  $1 \times 10^5$  CFU/ml. Should the package insert address bacterial counts below  $1 \times 10^5$  CFU/ml? If so, how?**

Dr. Charache stated that contamination is always a problem especially from *E. coli*. Using  $10^5$  as the cut off point, the company should analyze the results of contaminated specimens separately. She also suggested certain type specimens, such as suprapubic aspirations, be excluded and use only for clean catch specimens. **Dr. Baron** stated that in a routine lab  $10^4$  was considered positive for many symptomatic patients whereas  $10^5$  may be a good cut for asymptomatic patients.

**Question #4: Please comment on the warning, limitations and precautions in the labeling.**

**Dr. Baron** said that discrepancies in labeling needed to be corrected; in particular, the time to complete the test. It was stated as 12 hours and 24 hours.

**Dr. Nachamkin** stated that the labeling should state the specimens should be refrigerated. **Dr. Durak** suggested that there was no data to support use in asymptomatic patients. **Dr. Charache** noted that in the warning section G2, #2 the last sentence should recommend culture, not retesting. **Dr. Reller** suggested that the confidence intervals be included, and he urged the FDA to raise the scientific bar in order to better serve the public health. **Dr. Carroll** added that this device represents new technology that is being compared with predicated devices. She added that perhaps other volatile sources emitted by organisms should be studied.

**Dr. Wilson** thanked the panel for their discussion, the FDA for its presentation and the sponsor for all their work. Since there were no further comments, the meeting was adjourned at 6:20 PM.

