

## **CALL TO ORDER**

Panel Chair Michael Wilson, MD, called the meeting to order at 9:47 AM. The Panel Executive Secretary Freddie Poole read the conflict of interest statement and noted that waivers had been granted to Drs. Ng and Nachamkin, which allowed their full participation in today's meeting. Further, matters of past interest had been considered for Drs. Baron, Carroll, Nolte, Reller and Sanders and their full participation was allowed. Dr. Wilson then asked the panel members and consultants to introduce themselves.

## **NEW BUSINESS**

### **PRESENTATION OF THE PREMARKET APPROVAL APPLICATION**

**Sepsis Inc, Endotoxin Activity Assay (EAA) P 0100226.** *An in vitro diagnostic device for the determination of endotoxin activity in human blood samples, to rule out Gram negative infection.*

### **SPONSOR'S PRESENTATION**

**Paul Walker, MD, Ph.D.**, President & CEO, Sepsis Inc., introduced the Endotoxin Activity Assay (EAA) and described the interactive review process and presented the intended use, to rule out the presence of gram negative organisms – a shift in diagnostic paradigm strategies.

**R. Phillip Dellinger, MD**, a Site Investigator, Director, Critical Care Medicine, Rush Presbyterian St. Luke's Medical Center, explained the proposed use of EAA in the decision making process for infections in the intensive care unit. In their pivotal study, the MEDIC Trial, 18% of the patients had confirmed infection and 8% had gram negative infection. He concluded that because there is now general consensus that endotoxemia occurs in absence of gram negative infection these findings can be used with negative blood cultures to tailor patients' treatment.

**Alex Romaschin, Ph.D.**, Scientific Director, Sepsis Inc., and Associate Professor of Laboratory Medicine and Surgery, University of Toronto, described the technology of

the chemo-luminescent assay. The antibody used in this assay has high specificity and sensitivity to the Lipid A molecule found in endotoxins. Gram positive bacteria, pathogenic fungi and their cell walls or disruptive membrane products do not react in this assay. Lipopolysaccharide binding proteins, which are problematic in the LAL assays, did not confound this reaction. He concluded that the unit dosage format of the assay, and the reproducibility with which it could be performed, and that the assay is completed in one hour, makes this assay a good indicator for the absence of gram negative infection.

**Debra Foster, BSc.** Clinical Project Manager, Sepsis Inc., presented the clinical investigative plan for the Multi-center Endotoxin Detection in Critical Illness (MEDIC) Trial. Ten centers in four different countries (US, Canada, Belgium and UK) participated in the study. The inclusion criteria were all ICU patients suspected of having an infection. These patients had at least one set of blood cultures and were followed for seven days. The CDC criteria were initially used to interpret gram negative infection. A clinical evaluation committee (CEC) was later employed to adjudicate the interpretation of the data.

**John Marshall, MD,** Principal Investigator, Research Director Medical-Surgical ICU, Toronto General Hospital, discussed the pivotal trial in which 408 evaluable patients were enrolled from intensive care units and tertiary care facilities. He further explained the necessity of the CEC and the shortcomings of using only CDC interpretive criteria. Eighteen per cent of the evaluable patients showed gram-negative growth in their blood specimens. Thirteen percent met the CEC criteria and 8% met the CDC criteria for infection. The specificity and sensitivity of these tests were similar between the two criteria, roughly 33% and 80% respectively. If the blood culture and the assay were drawn on the same day and were negative, there was a 94% negative predictive value (NPV) (likelihood that the patient did not have a gram negative infection) with the CEC criteria and 91% NPV with the CDC criteria..

**Dr Paul Walker** summarized the presentation by noting Sepsis Inc. has proposed EAA as an adjunct test with blood culture in ruling out gram negative infection in patients admitted to the ICU, at risk of or suspected of having an infection.

**Dr. Wilson** invited the panel members to question the sponsor. The panel wanted to know the effect of polymorphonuclear leukocytes, albumin, antibiotics, and

corticosteroids and immunosuppression response on the assay. The firm responded that there were no effects. Other questions asked were: Did fungal infection and gram positive infection lead to false positives? What would a clinician do differently with a positive or negative assay? The sponsor responded that they were not making claims for a positive EAA test result; however a negative test would infer that the patient did not have a gram negative infection. How much weight did this test have on its own merit? The firm responded that it was an added piece of information. The negative predictive value was based on an erroneous assumption that a negative culture meant that the patient did not have infection. Another panel member commented that the pretest probability was 83-87, or maybe 92, but with the EAA the probability is 91 percent.

## **FDA PRESENTATION**

**Marian Heyliger, MS**, Senior Scientific Reviewer, Bacteriology Devices Branch, presented an overview of the spectrum of sepsis and laboratory diagnosis. She pointed out the differences in the false negative rates using CDC and CEC criteria. The EAA sensitivity of 80%, was based on gram negative infection, however, there was no evaluation of false positive rates due to a lack of specificity of endotoxin production. It is well documented that endotoxins arise from other sources than gram negative infection. She stated that FDA would like to know if the false-positive results should be included in the evaluation of the assay. She described the organisms isolated and the various sites of infection in the false negative population. She noted EAA is limited by non-hematogenous and remote sites of infection, and false positive bacterial cultures due to colonization. In closing, she raised two questions: 1) could infection outcomes be better measured beyond Day 1 and 2) does the negative predictive value (NPV) of 91% and 94%, as found in this study, indicate a role for this assay in clinical laboratory diagnosis?

**John Dawson, MS, JD**, Mathematical Statistician, Division of Bio-statistics, Office of Surveillance and Biometrics, presented the FDA's statistical perspective on the application. He explained that negative predictive value (NPV) requires a gold standard for unbiased evaluations. When there is no gold standard, NPV stands on its own. Since

the NPV takes prevalence into account, it is more accurate to interpret negative predictive value as a probability, that is, probability a patient would have a negative test, if he had been in the study.

**Dr. Wilson** then invited the panel to ask questions of the FDA. The panel had questions concerning the validity of the confidence level in such a small study, the meaning of a negative culture, the threshold level between positive and negative cases, the composition of ICU patients that is, proportion of medical and surgical patients and species bias, (did EAA miss Serratia, Pseudomonas and E. coli?) Other concerns expressed were the EAA 0.4 cutoff vs. 0.3; and criteria used by the CEC.

## **OPEN PUBLIC HEARING**

Dr. Wilson opened the meeting for comments from the public. There were no comments from the public. The Open Public Hearing session was then closed.

## **FDA Questions**

**Question #1: The performance parameters used to describe this assay included sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Are the diagnostic endpoints used in these calculations (CDC criteria and Clinical Evaluation Criteria) appropriate to support these terms or should alternative descriptive terms (% agreement, etc) be used?**

**Dr. Nachamkin** felt that there was no compelling evidence presented with this limited data for the ability of the test to rule out infection. A report of endotoxin present, is not a safe method of reporting an assay. He believes that the sponsor might not have taken the clinician decision making into account. **Dr. Charache** thought that the values are expressed as predictive values and are stated as predictive of infection, when in fact there is no documentation that it is. If you look at percent agreement then you have to add all your false positives and false negatives. If the goal of the test is to get a no answer then you should look only at the negative tests. **Dr. Nolte** wondered how the difference in CDC and CEC data influenced the clinical outcome. He didn't think there is any choice but not to use conventional parameters of sensitivity and specificity. **Dr. Durak** suggested that FDA consider using a quasi-gold standard. **Dr. Reller** stated that the test did not give sufficient confidence to dictate appropriate clinical action. **Dr. Solomkin** advised the sponsor to look at each gram-negative infection on a site by site basis, since infections such as meningitis would probably have low levels of endotoxin, whereas a gram-negative pneumonia infection would have high levels of endotoxins.

**Question #2: The sponsor stated that the NPV is the key parameter in the EAA assay. Is the NPV of 91% (84 to 96% CI) adequate and acceptable for this assay? Is the PPV of 15% (11 to 20% CI) adequate and acceptable for this assay? Consider: 1) the use of the device and how it affects patient management and treatment decisions, and 2) the varying prevalence of gram negative infection in different ICU populations.**

**Dr. Baron** thought the sponsor should re-look at the threshold of positivity and apply the larger pool of results to the ROC, which might improve the NPV. **Dr. Nachamkin** was not comfortable with the wide confidence interval for the negative predictive value, and thinks the negative predictive value is an unacceptable test for predicting infection. **Dr. Charache** worried about a test that missed 25% of the true culture positive patients.

**Question #3: The primary outcome of the MEDIC Study was the documentation of gram negative infection. The difficulty of determining gram negative infection was shown by the implementation of a Clinical Evaluation Committee (CEC) to provide a second evaluation of a patient's infection status. Should device performance be evaluated using the CDC criteria, the CEC criteria or both? Is use of clinical and laboratory information from Day 1 of the study an appropriate endpoint to characterize performance?**

**Dr. Wilson** asked the panel to focus on the second part of the question since the first part had already been discussed. **Dr. Durak** commented that it was important to distinguish clinical value and performance, since they may not be the same. **Dr. Baron** wanted to know what happened to the endotoxin levels on Day 2 and Day 3, so that the clinician could make an informed decision. **Dr. Nolte** asked about the interval for using the test. Would the test be used on admission and then daily? **Dr. Danner** wanted to know about repeat testing; how many tests have to be done before one positive test result is obtained because endotoxemia may be intermittent. There may not be any performance criteria that could describe this in the labeling.

**Question #4: Did the endotoxin assay meet the primary objective of the MEDIC Study, to exclude the diagnosis of gram negative infection in critically ill patients admitted to the ICU with suspected infection? Consider: 1) The bio-availability of endotoxin in the setting of gram negative sepsis. Some organisms shed more endotoxin than others; 2) Binding of proteins to liposaccharide (LPS) and clearance of endotoxin from the circulation; and 3) Limitations in the device's ability to detect endotoxin from non-hematogenous infection sites early in the course of infection.**

**Dr. Baron** reiterated that the study had ten false negative patients, and only 33 that were excluded. This did not appear to meet the primary objective..

**Question #5: What recommendations and suggestions should be provided to improve the labeling of this assay?**

**Dr. Nachamkin** stated that the package insert should include the fact that only one company supplied all the tubes for this test, therefore any other tube should be evaluated before use. **Dr. Durak** thought antibiotics and other drugs such as aspirin and cardio-active drugs, which could possible be interfering substances, should be added to the list in the labeling. **Dr. Baron** stated that since EAA works better with sepsis than pneumonia, the labeling could list which types of infectious diseases EAA rules out. **Dr. Nachimkin** disagreed, and stated that because the numbers are so small, no generalizations can be made about the type of infection. **Dr. Reller** suggested that we defer this question until one had a product to label.

## **OPEN PUBLIC HEARING**

Dr. Wilson opened the Open Public Hearing session. No one came forward to speak. He therefore closed the session.

## **SPONSOR RESPONSE**

**Dr. Dellinger** noted that using a panel of experts to decide if a patient was infected provided the best possible predictability. **Dr. Romaschin** stated that the overall precision found in the trial study was 11% for all centers weighted by the number of patients. **Dr. Romaschin** added that fluctuations in endotoxin were not observed over time with extensive repeat tests. Dr. Walker stated that Sepsis Inc. has not found a drug that interferes with this assay.

## **FDA RESPONSE**

The FDA had no further comments.

## **VOTE AND RECOMMENDATIONS**

The Executive Secretary **Freddie Poole** read the names of the voting and temporary voting members. She then explained the voting options for premarket approval that the panel could recommend. A motion was made and seconded, and the Panel voted that the PMA was not approvable.

VOTE: The panel voted unanimously for not approval of the PMA. The panel provided the reasons for their vote. Comments related to numbers being too small in the study, no clinical role for the test, and possible use in the research setting.

The panel then provided suggestions as to how the sponsor could make the device approvable. They recommended that the sponsor should consider increasing the sample size, which should increase the confidence in the negative results. The test as it was had no clinical role in clinical management. The study design should be revised to obtain meaningful outcomes irrespective of differences between patients, sites and personal characteristics. Endotoxemia does not equate with infection. The false positives may provide further information on what the test is detecting. The gold standard issue and the negative predictive value must be resolved.

**Dr. Wilson** thanked the panel members for their participation and the sponsor for its presentation

**Dr. Wilson** adjourned the meeting at 3:37 PM.