

Draft Questions for the Endotoxin Activity Assay:

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 being used in these calculations in this submission (CDC criteria and Clinical Evaluation Criteria) appropriate to support these terms or should alternative descriptive terms (% agreement, etc.) be used?

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 58% (...CI) adequate and acceptable for this assay?

Consider:

* the use of the device and how it affects patient management and treatment decisions.

* the varying prevalence of gram negative infection in different ICU populations.

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?

4. Did the endotoxin assay meet the primary objective of the MEDIC Study, i.e. to exclude the diagnosis of Gram negative infection in critically ill patients admitted to the ICU with suspected infection?

Consider:

* The bioavailability of endotoxin in the setting of gram negative sepsis. Some organisms shed more endotoxin than others.

* Binding of proteins to lipopolysaccharide (LPS) and clearance of endotoxin from the circulation.

* Limitations in the device's ability to detect endotoxin from non-hemogenous infection sites early in the course of infection.

5. What directions should be provided for use of this assay?

Consider:

* Appropriate populations for the indications for use.

* Labeling as it relates to warnings, limitations, and precautions for use.