

FDA Executive Summary

Prepared for the
November 10, 2016 meeting of the
Microbiology Devices Panel of the
Medical Devices Advisory Committee

*Discussion and Recommendations for the Application of Procalcitonin
to the Evaluation and Management of Suspected Lower Respiratory
Tract Infections and Sepsis*

Gaithersburg, Maryland

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1. Introduction and Purpose of the Panel Meeting

The Division of Microbiology Devices (DMD) in the Office of In Vitro Diagnostics and Radiological Health (OIR), Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA) has regulatory oversight of diagnostic assays for infectious diseases. FDA is convening this Advisory Panel meeting to discuss and make recommendations regarding the application of procalcitonin (PCT) to the evaluation and management of Lower Respiratory Tract Infections (LRTI) and sepsis. This meeting will discuss meta-analyses of the peer-reviewed PCT literature conducted by bioMérieux in support of an expanded Indications for Use (IFU) claim for the bioMérieux VIDAS B·R·A·H·M·S PCT assay. FDA is seeking expert advice to discuss the benefits and risks of the proposed applications of PCT for clinical decision making and any limitations or risk mitigation strategies that should be considered based on the current scientific evidence.

FDA regulations applicable to *in vitro* diagnostic devices are based on the FDA classification of the device. Medical devices, including *in vitro* diagnostic devices, are classified on the basis of risk. An example of a risk most commonly seen in the context of IVDs is the risk to a patient stemming from actions taken based on a false-positive or a false-negative result (e.g., unnecessary surgery, treatment delay). There are three regulatory classes for device categorization which are based on the level of control necessary to assure the safety and effectiveness of a device. Currently, devices to detect and measure procalcitonin in human clinical specimens are regulated as Class II devices. Class I designation is primarily for devices of low risk, while Class III is generally for the high risk devices that ‘are of substantial importance in preventing impairment of human health’ or ‘for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of such device.’ During the upcoming November 10, 2016, meeting, the Microbiology Devices Panel will not be asked to vote on whether the modified Indications for Use proposed by bioMérieux should be cleared, but to discuss whether the modified IFU raises different questions of safety and effectiveness for this device compared to the predicate device and whether FDA can adequately evaluate the safety and efficacy of the new device without additional clinical studies.

2. Background

a. Regulation of *In Vitro* Diagnostic Devices

FDA regulates devices, including *in vitro* diagnostic devices (IVDs), by classifying devices based on the degree of regulation necessary to provide a reasonable assurance of their safety and effectiveness. Generally, IVDs are regulated by FDA according to their device classification regulation and FDA uses product codes to assist in the accurate identification and tracking of devices. Under the authority of the Medical Device Amendments of 1976,

FDA issues regulations that classify devices based upon the risk associated with the device. This act established regulatory controls for medical devices and devices may be further distinguished by whether they are pre-amendment or post-amendment devices, (i.e., whether they were marketed before or after 1976). All assays under discussion during this meeting are post-amendment devices.

- Class I: Devices of low risk for which general controls are sufficient to provide a reasonable assurance of safety and effectiveness of the device.
- Class II: Devices which require both general and special controls to provide a reasonable assurance of safety and effectiveness of the device.
- Class III: Devices for which insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness and for which premarket approval is necessary.

General controls are not unique to any specific device but controls that can be applicable to all devices in general. Examples of general controls include prohibition against adulteration or misbranding, good manufacturing practices (GMPs), 510(k) premarket notification requirement, registration of manufacturing facilities, listing of device types and record keeping. Special controls are generally incorporated into the classification regulation for Class II devices and may change with the technological and clinical considerations associated with the assay as the special controls, along with general controls, must provide a reasonable assurance of the device's safety and efficacy. Examples of special controls include specific device performance standards, labeling requirements, and the design of clinical and analytical trials to support safety and effectiveness.

Class III devices require 'pre-market applications' (PMA) for which additional materials are necessary at the time of regulatory filing by the sponsor/manufacturer, and the FDA review time is longer (180 days compared to 90 days for non-PMA devices). Other significant differences between a PMA and a 510(k) application include the following premarketing requirements: that selected sites from the pivotal clinical trials undergo FDA inspection for application integrity and sponsor quality/Good Clinical Practice; that inspections of a sponsor's manufacturing facilities occur; and that FDA review and approve the product labeling and marketing materials before approval. A Class III determination for an IVD carries with it greater oversight than a Class I or II device, including post-market clinical studies and/or monitoring, if indicated. FDA has limited authority to request post-market studies of Class II and III devices. Section 522(g) of the Federal Food, Drug and Cosmetic Act (Act) gives FDA the authority to require a manufacturer to conduct post-market surveillance of a class II or class III device that meets any of the following criteria:

- Its failure would be reasonably likely to have serious adverse health consequences
- It is expected to have significant use in pediatric populations

- It is intended to be implanted in the body for more than one year
- It is intended to be a life-sustaining or life-supporting device used outside a device user facility

New devices (i.e., post-amendment devices) are automatically classified as Class III under section 513(f) of the Act unless the new device is substantially equivalent to a legally marketed device (predicate) which has been classified into Class I or Class II. The ‘*de novo*’ regulatory pathway is a process in which new devices without a predicate can be classified as either Class I or Class II depending on whether there is sufficient information such that general controls or general controls in combination with special controls are needed to provide reasonable assurance of device safety and effectiveness. Devices placed into class II under this process are subject to any special controls ordered within the device regulation. A new device classified by FDA under this mechanism becomes a possible predicate device for future 510(k) submissions and would be subject to the same requirements as the predicate device if the new device is determined by FDA to be substantially equivalent to the predicate device.

As described on the FDA web site, “a claim of substantial equivalence does not necessarily imply that the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable.” The determination of ‘substantial equivalence,’ is therefore a multifaceted examination of the new device focused heavily on the intended use and not independent of the underlying technology.¹

The FDA is also responsible for categorizing diagnostic tests under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 (42 U.S.C. 263a) based on their complexity and reviewing requests for Waiver by Application to determine whether certain diagnostic tests are simple to use and have an insignificant risk of an erroneous result. CLIA categorization is determined after the FDA has cleared or approved a marketing submission. Diagnostic tests that are simple to use and have an insignificant risk of an erroneous result may obtain a certificate of waiver (CLIA waiver). CLIA requires that clinical laboratories obtain a certificate before accepting materials derived from the human body for laboratory tests, however, healthcare facilities may obtain a certificate of waiver and perform tests that have been CLIA waived. According to CLIA, ‘simple’ devices “employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible” or

¹ More detailed information regarding pre market applications under the 510(k) process is available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm>.

“pose no unreasonable risk of harm to the patient if performed incorrectly.” (42 U.S.C. 263a(d)(3)). To support a CLIA waiver application to FDA, additional clinical and analytical studies that were not submitted in connection with the device’s marketing submission may be required to demonstrate that a device is simple and has an insignificant risk of an erroneous result. Clinical risks associated with erroneous results and device result interpretations are also considered when determining if a device is eligible for a CLIA waiver.²

b. Current Indications for Use of Procalcitonin Assays

Devices to detect and measure procalcitonin in human clinical specimens are regulated as Class II devices under the regulation 21 CFR 866.3215, reproduced as [Appendix One](#). The following is the current IFU statement for the VIDAS B·R·A·H·M·S PCT assay:

VIDAS[®] B·R·A·H·M·S PCT[™] (PCT) is an automated test for use on the instruments of the VIDAS[®] family for the determination of human procalcitonin in human serum or plasma (lithium heparinate) using the ELFA (Enzyme-Linked Fluorescent Assay) technique.

VIDAS[®] B·R·A·H·M·S PCT[™] (PCT) is intended for use in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock.

VIDAS[®] B·R·A·H·M·S PCT[™] (PCT) is also intended for use to determine the change in PCT level over time as an aid in assessing the cumulative 28-day risk of all-cause mortality in conjunction with other laboratory findings and clinical assessments for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission.

Procalcitonin (PCT) is a biomarker associated with the inflammatory response to bacterial infection that aids in the risk assessment of critically ill patients on their first day of Intensive Care Unit (ICU) admission for progression to severe sepsis and septic shock. The percent change in PCT level over time also aids in the prediction of cumulative 28-day mortality in patients with severe sepsis and septic shock.

PCT levels on the first day of ICU admission above 2.0 ng/mL are associated with a higher risk for progression to severe sepsis and/or septic shock than PCT levels below 0.5 ng/mL.

A PCT level that declines $\leq 80\%$ from the day that severe sepsis or septic shock was clinically diagnosed (Day 0) to four days after clinical diagnosis (Day 4) is

² More detailed information on CLIA waiver applications is available on FDA’s website at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079632.htm>.

associated with higher cumulative 28-day risk of all-cause mortality than a decline > 80%.

The combination of the first PCT level (≤ 2.0 ng/mL or > 2.0 ng/mL) at initial diagnosis of severe sepsis or septic shock with the patient's clinical course and the change in PCT level over time until Day 4 provides important additional information about the mortality risk.

The PCT level on Day 1 (the day after severe sepsis or septic shock is first clinically diagnosed) can be used to calculate the percent change in PCT level at Day 4 if the Day 0 measurement is unavailable.

c. Proposed Revisions to Indications for Use of Procalcitonin Assays

bioMérieux has proposed the following changes to the IFU of the VIDAS B·R·A·H·M·S PCT. If FDA were to clear this 510(k) for a device with this IFU, then the proposed IFU by bioMérieux would become an eligible predicate for current and future devices of this type.

VIDAS[®] B·R·A·H·M·S PCT[™] (PCT) is an automated test for use on the instruments of the VIDAS[®] family for the determination of human procalcitonin in human serum or plasma (lithium heparinate) using the ELFA (Enzyme-Linked Fluorescent Assay) technique.

Used in conjunction with other laboratory findings and clinical assessments, VIDAS[®] B·R·A·H·M·S PCT[™] is intended for use as follows:

- To aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock*
- To aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission, using a change in PCT level over time*
- To aid in decision making on antibiotic therapy for inpatients or outpatients, with suspected or confirmed lower respiratory tract infections (LRTI) defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)*
- To aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis*

3. Proposed Clinical Applications of Procalcitonin

The sponsor, bioMérieux, has proposed that existing studies and clinical experience with PCT is sufficient to support clinical decision making for sepsis de-escalation and LRTI antibiotic management. LRTI has been defined in this context as community-acquired pneumonia (CAP), acute exacerbations of chronic obstructive pulmonary disease (AECOPD), and acute bronchitis; ventilator-associated pneumonia is not included within the scope of the proposed IFU expansion of PCT. For LRTI, blood and sputum culture may identify a likely pathogen in only approximately 30% of cases, although typical clinical symptoms and characteristic findings on chest x-ray are felt to be indicative of a bacterial process. Diagnostic uncertainty, coupled with an empiric therapeutic approach and perceived risks of under-treatment, have likely contributed to use potentially unnecessary antimicrobial use for LRTI, particularly in outpatient settings. Compared to pneumonia and bronchitis, AECOPD presents further management challenges due to the chronic nature of the underlying disease and difficulty distinguishing bacterial infectious exacerbations from chronic symptoms or other causes of acute worsening, although in the ICU setting, antibiotic use for severe COPD exacerbations has been associated with consistent benefits, including reduced hospital stay and mortality. (Vollenweider, Jarrett, Steurer-Stey, Garcia-Aymerich, & Puhan, 2012) The evidence in support of antimicrobial use for COPD is less supportive in non-ICU inpatient and outpatient settings, as some meta-analyses have suggested fewer and less frequent relapses in patients treated with antibiotics. (Arenas & Rada, 2015; Ni et al., 2015; Saint, Bent, Vittinghoff, & Grady, 1995; Vollenweider et al., 2012).

In February, 2016, the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) was released, modifying the definition of sepsis to life-threatening organ dysfunction due to a dysregulated host response to infection. It is believed bacterial infection is the cause of the majority of sepsis episodes,, although distinguishing sepsis from non-infectious etiologies remains challenging. In a critically ill patient, risks from inappropriate antibiotic use are usually far outweighed by morbidity from untreated infection. Similar to LRTI, low yield from traditional diagnostics have led to the empiric management of presumed bacterial infection in most patients. At the present time, there are no precise guidelines to define adequate therapy in the absence of an identified infectious etiology and there are no FDA cleared/approved diagnostics to aid in determining the duration of antibiotic treatment and/or treatment efficacy of a therapeutic agent for any infection or infectious syndrome. Determining the duration of antibiotic therapy is typically informed by clinical assessment, in which the circumstances of each individual patient's presentation, underlying host characteristics, laboratory test results and hospital course are considered in determining the recommended duration of antibiotic therapy. In the absence of an identified pathogen, the perceived risks of under-treatment in a critically ill patient may lead to prolonged antimicrobial treatment. For these patients, procalcitonin may serve as

supplemental information to help guide clinical decision making and provide reassurance when determining the appropriate timing of antimicrobial de-escalation.

4. Current Guidelines

A number of professional societies, including the Infectious Disease Society of America (IDSA), Society for Healthcare Epidemiology (SHEA), have reviewed the scientific evidence concerning the application of procalcitonin to LRTI and sepsis. Recommendations have also been published from other groups such as the U.S. Agency for Healthcare Research and Quality (AHRQ) and UK's National Institute for Health and Care Excellence (NICE). Most groups evaluated antibiotic discontinuation and initiation separately, and a brief summary of their recommendations is provided below.

a. LRTI

IDSA has developed separate guidelines for community-acquired pneumonia (CAP) and hospital-acquired (HAP) or ventilator-associated pneumonia (VAP). For CAP, IDSA does not incorporate PCT into their recommendations. However, PCT was endorsed as an aid to guide discontinuation of antibiotics for HAP/VAP (weak recommendation, low-quality evidence), based primarily upon VAP data. IDSA also commented that the duration of antibiotic therapy in the control groups may exceed the standard of care in some hospitals and questioned the potential benefit for facilities where shorter baseline antibiotic regimens are used. However, IDSA also concluded that the overall benefits outweighed the potential risks for antibiotic discontinuation, despite uncertainty regarding the magnitude of benefit and generalizability from existing data. For antibiotic initiation in patients with suspected HAP/VAP, they concluded that PCT was not recommended (strong recommendation, moderate-quality evidence). IDSA based this recommendation on a pooled analysis of PCT sensitivity and specificity, which failed to meet the *a priori* performance criteria identified as sufficient to recommend use of PCT for antibiotic initiation decisions in patients with HAP/VAP. IDSA concluded that “the frequency of such undesirable consequences due to misleading PCT results was unacceptable, and, therefore, recommended not using PCT to guide antibiotic initiation.”

In contrast, AHRQ reviewed the available evidence and concluded that there was a high strength of evidence that PCT-guided therapy reduces antibiotic duration and moderate strength of evidence that PCT-guided therapy does not increase adverse outcomes. Although the AHRQ noted that data from antibiotic initiation, discontinuation and change of antibiotic therapy was not easily separated, they did not limit their recommendation to either discontinuation or initiation, or distinguish between PCT-guided therapy in inpatient or outpatients.

NICE independently reviewed published studies on procalcitonin and recommended use of PCT only in the setting of community-acquired pneumonia. The NICE guidance found that PCT assisted antibiotic prescribing may reduce the initiation of antibiotic therapy without influencing mortality or morbidity (moderate to very low quality evidence). Ultimately, NICE concluded that PCT testing appeared to offer “little additional benefit” over clinical judgment in identifying patients with pneumonia, but there did appear to be a significant reduction in overall antibiotic prescription rates. Further, in CAP patients undergoing monitoring, PCT significantly reduced the duration of antibiotic therapy without an increase in mortality or treatment failure; however, they observed that the overall duration of antibiotic therapy was significantly longer in the control group of the PCT studies than is typical for UK clinical practice.

b. Sepsis

Recommendations regarding the application of PCT to antibiotic management in patients presenting with sepsis are more limited. The Surviving Sepsis Campaign (SSC) guidelines advocate for early antimicrobial intervention, similar to other published guidelines. The SSC 2012 Guidelines concluded that procalcitonin could be used to assist in antibiotic discontinuation in patients who initially appeared septic (grade 2C; weak recommendation), but noted that clinical experience was limited and that there was no evidence that the practice would reduce rates of antimicrobial resistance or *C. difficile* infections. (Dellinger et al., 2013). Similarly, the 2016 IDSA/SHEA antibiotic stewardship guidelines describe serial PCT measurements to decrease antibiotic use in intensive care units but also as a weak recommendation based on moderate quality evidence. Due to the limited U.S. experience with PCT-guided algorithms, the IDSA/SHEA guidelines note that stewardship programs should develop internal guidelines to assist clinicians in interpreting and responding appropriately to results, and determine if this intervention is the best use of local resources.

AHRQ concluded that there is high quality evidence that procalcitonin-guided antibiotic discontinuation reduces antibiotic use without evidence of increased mortality (moderate quality evidence); in contrast, the 2015 NICE guidelines conclude that there is insufficient evidence to recommend the adoption of PCT to stop antibiotic treatment in patients who present with suspected or confirmed sepsis. In their discussion, the NICE guidelines note that antibiotic stewardship programs may be poorly standardized between countries, and the clinical practice continues to evolve: on this basis the NICE committee noted that results observed in the literature may not be generalizable to other patient populations and that further research was needed before they could endorse procalcitonin for antibiotic decision making.

5. Device Description

Procalcitonin (PCT) is a 116 amino acid protein precursor to calcitonin, secreted by a variety of human cells in response to bacterial infection and other stressors. In general, viral infections, allergic reactions, autoimmune diseases and other non-infectious clinical conditions are not believed to lead to significant PCT elevation. PCT levels increase with the severity of bacterial infection, i.e., sepsis. PCT is released 2–6 hours after bacteria are present and has a serum half-life of approximately 24 hours. Levels generally decrease daily by around 50% if the bacterial infection is controlled by the immune system supported by effective antibiotic therapy. The VIDAS B•R•A•H•M•S PCT assay is an enzyme-linked fluorescent assay (ELFA) that measures procalcitonin in human serum or plasma (lithium heparinate) on the VIDAS[®] instruments. There are three instruments in the VIDAS family: VIDAS, VIDAS3 and miniVIDAS. The sample volume used per test is 200 µL and the test incubation time is 20 minutes. The analytical measuring range is 0.05-200 µg/L.

Reagents for the assay are ready-to-use and pre-dispensed in the sealed reagent strips. Dependent on the instrument, the sample is either manually pipetted or transferred by the instrument into the wells containing anti-procalcitonin antibodies labeled with alkaline phosphatase (conjugate). All of the subsequent assay steps are performed automatically by the instrument. The VIDAS B•R•A•H•M•S PCT kit contains two calibrators and two controls. At the end of the assay, results are automatically calculated by the instrument in relation to two calibration curves corresponding to the two detection steps. A fluorescence threshold value determines the calibration curve to be used for each sample. Dependent on the instrument, 12-30 samples can be run simultaneously. For the mortality risk assessment, results can be returned with a reference to the online BRAHMS PCT calculator to assist in interpreting assay results. A video demonstrating the analytical principles of the VIDAS automated immunoanalyzer is available online.³

6. Sponsor Interpretation of Published Literature

a. LRTI

In support of the proposed LRTI claim, the sponsor conducted multiple analyses of peer-reviewed literature, including an analysis of data extracted from the published manuscripts (study-level data) and analyses of raw dataset from some studies (patient-level data), which utilized the raw patient data from a subset of available studies. The study-level meta-analysis consisted of 11 randomized controlled trials enrolling 4,090 subjects (2,050 subjects in the control arm and 2,040 subjects in the PCT-guided arm).

³ <https://www.youtube.com/watch?v=ZFRuJYynLwkResults>

The patient-level meta-analysis included 13 randomized controlled trials and included 3,142 subjects, with 1,606 subjects in the control arm and 1,536 subjects in the PCT-guided arm. In the study-level meta-analysis, the sponsor concluded that PCT-guided clinical management resulted in a 74% reduction in the odds of antibiotic initiation without any associated increase in mortality, complications or length of hospital stay. They estimated that the absolute reduction in antibiotic duration, defined as number of days of antibiotic therapy in patients who were initiated on treatment, was 1.25 days. Total antibiotic exposure, defined as number of days of antibiotics regardless of initiation, was found to decrease by 2.79 days. The patient-level meta-analysis found a 73% reduction in the odds of antibiotic initiation, with a 2.9 day reduction in antibiotic duration and a 3.6 day reduction in total antibiotic exposure. Subgroup analysis of the patient-level data found decreased rates of antibiotic initiation and duration as reported in Table 1.

Table 1^a

LRTI Patient-Level Data Subgroup Analysis	Standard Therapy	PCT-guided Therapy	Adjusted OR or Difference (95% CI) ^b
Overall	1606	1536	
Initiation of antibiotics, n(%)	1420 (88.7)	1096 (71.4%)	0.27 (0.22, 0.33)
Duration of antibiotics in days, median (IQR) ^c	10 (7, 12)	7 (4, 10)	-2.9 (-3.3, -2.5)
CAP	1028	999	
Initiation of Antibiotics n(%)	1019 (99%)	898 (90%)	0.07 (0.03, 0.14)
Duration of Antibiotics in days median (IQR)	10 (8, 14)	7 (5, 10)	-3.34 (-3.79, -2.88)
Bronchitis	282	249	
Initiation of Antibiotics n(%)	185 (66%)	61 (25%)	0.15 (0.10, 0.23)
Duration of Antibiotics in days median (IQR)	7 (5, 8)	7 (4, 9)	-0.38 (-1.21, 0.46)
AECOPD	296	288	
Initiation of Antibiotics n(%)	216 (73%)	137 (48%)	0.32 (0.23, 0.46)
Duration of Antibiotics in days median (IQR)	8 (6, 10)	6 (3, 9)	-1.58 (-2.33, -0.82)
Inpatients	1139	1106	
Initiation of Antibiotics n(%)	1039 (91.2%)	881 (79.7%)	0.35 (0.27, 0.46)
Duration of Antibiotics in days median (IQR)	10 (8, 14)	7 (4, 10)	-3.26 (-3.72, -2.79)
Outpatients	467	430	
Initiation of Antibiotics n(%)	381 (81.6%)	215 (50%)	0.13 (0.09, 0.19)
Duration of Antibiotics in days median (IQR)	7 (6, 10)	6 (4, 8)	-1.75 (-2.28, -1.21)

^a Modified table from Table 15, Figures 11 and 12 in the bioMérieux executive summary and Section 26.3 of ‘Clinical Performance Characteristics.’

^b Multivariable hierarchical model adjusted for age and diagnosis and trial as a random effect; For the subgroup by type of LRTI, diagnosis was not included in the model.

^c Duration includes subjects who were initiated on antibiotics

b. Sepsis

In support of the proposed sepsis de-escalation claim, bioMérieux conducted study-level and patient-level analyses of the peer-reviewed literature, specifically focusing upon studies who examined antibiotic de-escalation, rather than initiation. The study-level meta-analysis consisted of 10 randomized controlled trials and enrolled 3,489 subjects with 1,754 subjects enrolled in the control arm and 1,735 subjects enrolled in the PCT-guided arm. The patient-level meta-analysis included five randomized controlled trials and 598 subjects, with 311 subjects in the control arm and 287 subjects in the PCT-guided arm. The study-level meta-analysis found a 1.5 day reduction in antibiotic duration, while the patient-level meta-analysis demonstrated a 3.2 day reduction in antibiotic exposure (12 days in standard therapy and 8 days for PCT-guided therapy). No increase in mortality, length of stay or ICU length of stay was observed in either the study-level or patient-level analysis. Specific patient subpopulations were not examined, and the majority of clinical studies were conducted in intensive care units.

7. Discussion

a. LRTI

The sponsor's modified IFU statement proposes that PCT can be used for LRTI antibiotic decision making, a concept which encompasses initiation and discontinuation of therapy for both inpatients and outpatients with CAP, AECOPD and acute bronchitis. The study-level and patient-level meta-analyses performed in support of the proposed IFU demonstrate a reduction in antibiotic use without increased mortality or other serious adverse events. However, there are design and analysis limitations that should be considered when assessing the quality of the completed meta-analyses.

As noted by previous analyses, including those conducted by the IDSA, AHRQ and NICE groups, distinguishing between the different subpopulations and the definitions of antibiotic exposure used in the PCT clinical trials is challenging. PCT-guided clinical trials are not diagnostic trials, but pragmatic trials in which treatment superiority for duration, initiation or de-escalation can be demonstrated, but diagnostic accuracy for the underlying condition (i.e., LRTI, sepsis) cannot be established. Endpoints included: 'total antibiotic days,' percentage of patients on antibiotics at pre-specified dates (e.g., Day 3, 5 or 10), total antibiotic use over the varying follow-up periods, or frequency of antibiotic treatment. Antibiotic initiation and antibiotic duration were the most common endpoints used. Although 11 RCTs met the criteria for inclusion in the LRTI meta-analysis, determination of antibiotic duration was based upon only three studies and antibiotic exposure was based upon only five studies. In addition, it has not yet been proven that reductions in antibiotic duration will produce a meaningful reduction in antimicrobial

resistance, nor is it clear that the reduction in duration of antibiotic use observed in the published studies is associated with a meaningful reduction in adverse events.

Another consideration is the strength of data for subpopulations within the different disease entities. Although ‘all’ LRTI outpatients have been analyzed, subgroup analysis for outpatients with CAP, AECOPD and acute bronchitis was not conducted, although further post-hoc analyses may be underpowered to detect meaningful differences in these populations, particularly for safety in outpatient subpopulations in which mortality is likely to be uncommon and later onset *C. difficile* infection would not be captured. The combined analysis provides additional statistical power, but may overstate the estimation of effectiveness and magnitude of benefit to the different subpopulations, e.g., the 73% reduction of antibiotic initiation may not reflect performance in patients with severe COPD exacerbations requiring admission or outpatients with acute bronchitis. FDA is interested in discussing the most appropriate format by which performance estimates and limitations could be reported to users and clinical laboratories, so that informed decisions regarding the utility of PCT to their patient population can be made, or whether additional analyses are necessary.

For AECOPD, previous meta-analyses have concluded that antibiotics may reduce recurrences and morbidity in severely ill patients, but the evidence of benefit is inconsistent in outpatients. (Vollenweider et al., 2012). Neither the sponsor’s patient-level nor study-level meta-analysis identified an increase in disease recurrence or morbidity associated with PCT-guided reduction of antibiotic use for AECOPD. Eight of the ten studies which enrolled subjects with COPD in the study-level meta-analysis were conducted with inpatients. Two studies enrolled subjects managed as outpatients, but only 1-5% of the enrolled subjects had AECOPD with other LRTIs (e.g., rhinosinusitis, CAP, bronchitis) comprising the majority of enrolled patients. (Briel et al., 2008; Burkhardt et al., 2010). Thus, the estimations of mortality and complications for AECOPD are primarily based upon inpatients who are presumably more seriously ill than outpatients and at higher risk for adverse events or mortality. It is unclear if additional studies in outpatients would reveal a clinically significant safety concern that was not observed in inpatients. However, it should be noted that the pathophysiology of COPD exacerbations may vary between patients. Recent reviews of COPD exacerbations noted some patients present with a ‘frequent exacerbator phenotype’ who may be at increased risk for recurrences at baseline which could affect long-term pulmonary function and quality of life. (Agusti A, 2014; Santos et al., 2016) As the outpatient population that may benefit from antibiotics is under further investigation, it is unknown if the current evidence is sufficient to establish safety for all patients with AECOPD.

The median age of subjects in the patient-level meta-analysis was 66 years for LRTI PCT-guided therapy. Subgroup analysis of the effects of age was conducted for patients

over 65 years of age and did not identify a difference in safety or effectiveness. However, some observational studies have suggested that the elderly have elevated baseline levels of PCT, particularly if underlying chronic kidney disease (CKD) is present. A 2012 review of afebrile adults >75 years found that the baseline PCT concentration ranged from 0.02 to 1.02 ng/mL with a median value of 0.057 ng/mL and that PCT concentration was inversely related to eGFR in the elderly. (Chenevier-Gobeaux et al., 2012). Another study also found that PCT baseline values were elevated with a mean value of 0.90 ng/mL in elderly patients with CKD without sepsis (Buglio et al., 2016); however, a third study found that 79% of PCT values were less than 0.1 µg/L in the elderly. Although this study did not provide the range of PCT values that were observed or variability associated with CKD, the authors concluded that PCT dynamics in the elderly were similar to younger patients. (Dwolatzky et al., 2005). The possible association of higher baseline PCT values in elderly patients with CKD may represent a significant concern for clinical use.

The subject of variability between local standards of care should also be considered. Among the studies that enrolled outpatients, significant reductions in the initiation and duration of antibiotic therapy were observed. (Briel et al., 2008; Burkhardt et al., 2010). However, the majority of studies included in the meta-analysis were conducted outside the US, and differences between geographic locations were also not analyzed. It is unclear if the magnitude of benefit observed in other countries would be transferrable to the US. At least one multi-center RCT examining the effects of PCT-guided antibiotic therapy, the ProAct trial, is currently being conducted in the U.S. (ClinicalTrials.gov ID#NCT02130986), and additional studies, such as the ARLG's TRAP study⁴ are underway to look at PCT use in outpatients. Results from these studies are anticipated to be available in approximately five years. Also, as discussed by both the IDSA and NICE committees, the reduction of antibiotic therapy duration may not be observed in hospitals or other settings where baseline duration of antibiotic therapy is already low. Although not a randomized controlled study, an observational study of procalcitonin-guided antimicrobial stewardship for inpatient community and hospital-acquired LRTIs outside of the ICU observed a much smaller reduction in antibiotic use than reported in most clinical trials. (Bignardi, Dhar, Heycock, Bansal, & Majmudar, 2006). However, as reductions in both inpatient and outpatient antibiotic use have been identified as a goal for U.S. healthcare organizations, it seems that there may be a net benefit, particularly in hospitals without robust antimicrobial stewardship programs. It should also be acknowledged that antibiotic use often differs between individual clinicians; future studies of U.S. populations are unlikely to be representative of the full spectrum of

⁴ <http://arlg.org/studies-in-progress>

clinicians, some of whom may be greatly reassured by supplemental laboratory information to assist in antibiotic decision making.

As a non-microbial biomarker that measures the host response to infection, PCT is not linked to a particular microorganism or family of microorganisms. While it generally increases in association with bacterial infections, some exceptions have been identified. Some strains of influenza, such as H1N1 and H7N9, have been associated with elevations in PCT measurement. (Guervilly et al., 2010; Paiva et al., 2012; Shi et al., 2013). A meta-analysis of PCT levels in H1N1 influenza without bacterial co-infection found the median value of PCT to be 0.56 $\mu\text{g/L}$ (IQR 0.18 – 3.33). (Pfister et al., 2014) In contrast, not all bacterial infections appear to trigger significant PCT elevations. A study of 106 patients with viral and atypical bacterial infections found the median PCT value to be 0.09 ng/mL (IQR 0.06 – 0.17). (España et al., 2012). Other studies of atypical organisms have suggested also that PCT values can be low or only mildly elevated compared to typical bacterial infections. (Kruger et al., 2009; Masia et al., 2005). The lack of specificity for viral and atypical pathogens may represent a further confounding factor for the clinical utilization of PCT.

The PCT algorithm used for initiating and discontinuing antibiotic use varied in the studies selected for meta-analysis. The sponsor (bioMérieux) proposes to recommend that initiation of antibiotics for LRTI should be discouraged when initial PCT levels are $\leq 0.25 \text{ ng/mL}$, and antibiotic therapy may be discontinued when PCT levels drop to $\leq 0.25 \text{ ng/mL}$ or have declined by $>80\%$ from the peak concentration. Obviously, serial PCT measurements would be necessary to determine if patient has experienced a drop of 80%. For inpatients, serial measurements could be obtained without difficulty. However, setting aside the current technological limitations, repeat PCT measurements in outpatients could require a significant shift in clinical practice in the U.S., where outpatients do not typically receive daily surveillance labs, particularly if clinically improving. To obtain the maximal benefit for outpatients, it is likely that a CLIA waiver would be necessary to allow for better access to testing. However, for patients obtaining testing in a facility operating with a CLIA waiver, clinicians may have limited access to supplemental diagnostic tools, such as additional laboratory or radiological testing, and PCT may be the sole supplement to clinical judgment.

In section 2.3 of the sponsor's executive summary, the negative predictive value for the diagnosis of bacterial LRTI for PCT is reported to be 0.94 with sensitivity of 0.84 and specificity of 0.98. (Stolz et al., 2006) Although the sponsor cites this study that identified strong performance for the diagnostic accuracy of PCT, there are multiple peer-reviewed published studies that suggest that PCT has limited ability to discriminate between bacterial and viral infections. (Chan et al., 2004; Holm et al., 2007; Indino et al., 2008; Ip et al., 2007; Kherad et al., 2010; Ruiz-Esteban et al., 2012; Steichen et al.,

2009). Previously published literature has provided a range of sensitivities from 0.31 – 0.94 and specificities from 0.71 – 0.98. (España et al., 2012; Falsey et al., 2012; Ip et al., 2007; Nseir et al., 2008; Stolz et al., 2006). Literature has suggested that the determination of diagnostic accuracy is hindered by the fact that pathogens are not detected in the majority of patients with respiratory disease.(Jain et al., 2015). The IDSA concluded that PCT did not meet pre-specified performance goals for sensitivity and specificity and concluded that PCT should not play a role in the initiation of antibiotic therapy for HAP/VAP. However, an accurate calculation of sensitivity and specificity for biomarkers such as PCT may not be possible. As discussed above, diagnostics for LRTI have significant limitations in their ability to identify a specific infectious etiology for the majority of symptomatic patients. As a result, the comparator method to determine sensitivity and specificity can vary widely between studies and performance estimations are inherently flawed in the setting of an imperfect comparator method. Performance may further vary with the PCT cut-off selected in each study. Thus, FDA has concerns that it does not appear that a reliable determination of the diagnostic accuracy of PCT, or other non-microbial biomarkers, is realistic and that clinical outcomes studies are the best possible determination of assay performance for clinical practice.

b. Sepsis

While the LRTI meta-analyses examined multiple subpopulations in support of the proposed IFU, the proposed use of PCT for sepsis de-escalation does not include specific clinical subpopulations. Accordingly an analysis of subpopulations of septic patients in support of the proposed antibiotic de-escalation claim was not conducted and fewer questions regarding clinical generalizability are raised. Most PCT clinical trials excluded subjects who were immunocompromised, had an infection requiring long-term antibiotics (e.g., chronic osteomyelitis, endocarditis, *Pseudomonas aeruginosa*, *S. aureus*, etc.), or pregnancy. Surgical patients were not excluded, with two studies specifically examining the utility of PCT in the surgical ICU and a third study enrolling 40% of its study population from post-operative patients. (Hochreiter et al., 2009; Layios et al., 2012; Schroeder et al., 2009).

As discussed above for LRTI, the primary limitation associated with the sepsis meta-analysis was the lack of U.S. clinical trial sites. All studies identified for inclusion in both the study-level and patient-level meta-analyses were conducted in Europe, Asia or Latin America. As a result, the magnitude of potential benefit to U.S. patients is uncertain, since U.S. antibiotic stewardship practices and baseline duration of therapy may differ from international sites. It should be acknowledged that antibiotic duration for the control groups in the sepsis analyses ranged from 10-14 days, which is consistent with current Surviving Sepsis recommendations. However, a study performed in centers with low baseline durations of antibiotic therapy did not observe a significant decrease in antibiotic use associated with PCT-guided therapy. (Layios et al., 2012). The sponsor excluded

antibiotic initiation studies based on the proposed IFU, which is limited to de-escalation. One prospective randomized controlled trial that demonstrated no survival benefit with increased lengths of stay was also excluded from the meta-analysis. (Jensen et al., 2011). Jensen et al. tested asymptomatic patients, and identified an “alert procalcitonin” that was used to trigger additional clinical evaluation and antibiotic initiation. Although approximately 70% of patients in both arms of the study were ultimately determined to have an infection, the manuscript does not comment on what clinical signs and symptoms of infection, if any, that were associated with the “alert procalcitonin” values.

The appropriate cut-off to guide antibiotic de-escalation in sepsis was not consistently defined in the published literature. Although the LRTI studies converged around a single diagnostic algorithm, the sepsis literature uses more varied cut-off values, percent changes from baseline, and monitoring strategies. The sponsor proposes to use a cut-off of ≤ 0.5 ng/ml or $>80\%$ reduction in PCT level to guide antibiotic de-escalation, but incorporated safety and efficacy data from other studies despite the different cut-off scores. However, the majority of subjects in both the patient-level and study-level analyses were enrolled using the recommended PCT algorithm. It should be noted that the majority of subjects in the patient-level analysis came from a single study with poor adherence to the PCT algorithm. (Bouadma et al., 2010). The observed reduction in antibiotic use, despite poor compliance, indicates a robust treatment effect, but also suggests that the safety analysis may be biased by clinicians opting to override the algorithm in patients they felt needed longer courses of antibiotics. Algorithm adherence data was only available for four of the ten studies in the study-level analysis and two of the five patient-level studies; however, the studies that reported adherence enrolled the majority of patients in both the study-level and patient-level analyses. It should be noted that the largest clinical trial of sepsis de-escalation reported less than 50% adherence to the recommended PCT algorithm. (de Jong et al., 2016) The study authors did observe differences in the baseline characteristics in patients for whom the clinicians disregarded the algorithm stopping advice, and the authors concluded that PCT can be used to support antibiotic decision making in “stable” patients. Although the safety analysis could be biased by poor algorithm compliance, incorporation of studies with low adherence may more accurately reflect the likely real-world use of the PCT assay. The sponsor has not addressed the added contribution of PCT to existing commonly used laboratory tests, such as WBC or CRP, or other diagnostic evaluations, such as chest x-ray. FDA is interested in panel discussion regarding the effect of PCT algorithm compliance on the safety analysis.

c. Statistical Considerations

Meta-analyses provide a quantitative synthesis of research by combining and integrating available published information on an effect of interest. Although generally regarded as a high level of evidence, meta-analyses are not without limitations and shortcomings. Meta-analyses may be subject to publication bias, the tendency of published studies in a research area to be unrepresentative of all of the completed studies in that area. (Rothstein HR, 2005; Song, Eastwood, Gilbody, Duley, & Sutton, 2000). Funnel plots and statistical tests are available for evaluating a meta-analysis for publication bias. (Begg & Mazumdar, 1994) The studies included for a meta-analysis may exhibit heterogeneity in design, conduct, and analysis, creating difficulties in interpretability and generalizability of the statistical inference. (Oakes, 1993). For example, randomized trials can vary in enrollment criteria, study endpoints, length of follow-up, available data, treatment arm (e.g., PCT algorithm used for making anti-biotic use recommendations), control arm, rate of compliance (e.g., adherence to PCT algorithm recommendation), measurement procedure (e.g., PCT assay), effect estimator, etc. Additionally, a meta-regression evaluating relationships between variables across studies using study-level data summaries can be subject to aggregation bias (ecological fallacy), the phenomenon that a relationship across studies does not reflect the relationships within studies. (Harbord & Higgins, 2008; Higgins, Thompson, Deeks, & Altman, 2002). In particular, FDA has concerns that subgroup analysis is susceptible to aggregation bias unless patient-level data are used.

The results from meta-analysis showed a significant reduction in antibiotic use using PCT guidance without adversely affecting safety endpoints, such as mortality. However, the similarity of safety outcomes between PCT guided group and control group may be due in part to low frequency of the events. The randomized controlled trials selected for meta-analysis used the so-called marker strategy design in which patients are randomly assigned to an experimental treatment arm that uses a marker to guide treatment selection or to a control arm that does not. The design is an attempt to evaluate if marker-guided treatment selection can improve clinical outcomes, although statistically, the design, as noted by Bossuyt, Lijmer, & Mol, 2000; Freidlin, McShane, & Korn, 2010 and Simon, 2010, is not as compelling as some other designs in at least two respects. (Bossuyt, Lijmer, & Mol, 2000; Freidlin, McShane, & Korn, 2010; Simon, 2010).

First, in a marker-strategy design, the effectiveness of the treatment selection strategy cannot be separated from variation in treatment effect unrelated to the treatment strategy. For example, in the trials considered here, if a random strategy for discontinuing antibiotic use overlaps with subgroups in which discontinuation is indeed preferential, then the random strategy will tend to show improvement in certain outcomes (e.g., antibiotic related complications) compared with the control of never discontinuing antibiotics. Also, effectiveness of the strategy cannot be distinguished from a

homogenous treatment effect. As an extreme example, if antibiotic use has no effect on anyone in a trial population, then any strategy for selecting a subgroup for antibiotic discontinuation will be preferred over never discontinuing antibiotic use. If a ‘prolonged’ course of antibiotics (i.e., a course longer than is biologically necessary) does not improve outcome, even in patients with bacterial infection, then PCT-guided therapy may not have a meaningful effect on clinical outcomes or morbidity/mortality, despite a true correlation with clinical outcome. In this scenario, PCT may be serving as ‘reassuring’ laboratory evidence justifying a shorter course of treatment relative to an unnecessary longer course (though similarly PCT use could prolong antibiotic use for some patients).

Second, a proportion of patients in a marker-strategy trial will receive the same treatment in either arm, diluting between-arm differences in outcomes. In the trials considered here, differences in hospital length of stay, complications, and 30-day mortality between the PCT algorithm arm and the control arm will be diluted by subgroups of patients in the arms for which PCT algorithm recommends the same antibiotic use as in the control arm. In the PCT trials, differences in outcomes between arms are also diluted by lack of adherence to the PCT algorithm recommendation in the PCT algorithm arm. Some patients in the PCT guided arm will receive the same treatment as they would have in the control arm because the physician did not adhere to the PCT recommendation. An adherence adjusted outcome analysis was therefore requested by FDA and performed by the sponsor. Finally, a marker-strategy design is open label. That is, physicians are not masked (blinded) to the treatment arm to which subjects are randomized. The possibility exists that knowing the treatment arm may cause physicians to (consciously or unconsciously) manage subjects differently in the PCT arm than in the control arm, apart from the PCT algorithm result, i.e., a Hawthorne effect.

As use of the PCT algorithm in studies has been designed to reduce antibiotic use, the outcome that both duration of antibiotic use and total exposure of antibiotics were reduced in the PCT-guided arm relative to the control arm is not surprising. This result is highly likely provided that the algorithm is followed for some patients in the PCT arm. As an alternative to evaluating efficacy (and within efficacy, different durations of use) and safety endpoints separately, a composite approach such as a desirability of outcome ranking (DOOR) is constructed based on the multiple endpoints. For antibiotic stewardship trials, a version of DOOR called response adjusted for duration of antibiotic risk (RADAR) accomplishes this by breaking ties between patients in a clinical outcome ranking based on duration of antibiotic use and incorporating safety into the rankings. (Evans et al., 2015). Trial arms may be compared on a DOOR composite endpoint using methods for analysis of rank data such as the Mann-Whitney test. Studies employing the DOOR/RADAR methodology have yet to be completed, but a proposed study is in late stage development for procalcitonin.

8. Potential Benefits and Risks of Procalcitonin

Multiple published studies, despite varying enrollment criteria, patient populations, and study designs have consistently demonstrated reductions in antibiotic duration associated with PCT-guided de-escalation of antibiotic therapy, without an associated rise in mortality or adverse events detected. The former is not unexpected as this is a fundamental property of these study designs. The overall clinical benefits of this strategy remain uncertain, although evolving clinical trial designs (such as DOOR/RADAR) may better define individual benefit. It is unlikely that any prospective study could address public health benefits such as a reduction in antibiotic resistance in the general population. Ongoing studies separate from PCT have identified changes in individual microbiomes secondary to antibiotic exposure, and these may provide additional insight into benefits from reduced antibiotic use that may be possible to extrapolate more broadly. A decrease in antibiotic prescriptions, rather than reduction in days of therapy, may better represent evidence of potential benefit. However, the safety analysis may not be adequately powered to detect a meaningful difference in the outpatient subpopulations most eligible for withholding antibiotic. The majority of enrolled subjects were enrolled as inpatients, although data regarding the proportion of inpatients is not available across the clinical subpopulations. The overall safety analysis of all subjects did not identify a difference in mortality or hospital length of stay.

Although signs and symptoms of infection are often nonspecific and shared by non-infectious processes, non-microbial biomarkers, such as PCT, may be useful to aid the clinical decision-making process. While numerous biomarkers have been investigated for a variety of diseases and clinical applications, PCT represents a widely studied analyte with much clinical evidence and experience. However, clinical judgment will always remain the most valuable tool when making decisions regarding the use of antibiotics. The optimal use of PCT (as true for all diagnostic tests) is likely to be in patients for whom a significant degree of clinical uncertainty remains, i.e., consistent with Bayes theorem an imperfect test is most useful when it alters prior probability to a level where the treatment decision is affected; this is less likely with high prior probabilities.

9. Question to the Panel

During your deliberations, please specifically discuss the rationale for each your recommendations. In your recommendation, please be certain to consider that the test is intended for use in U.S. populations, and that efficacy must be considered in the context of the sponsor's. This includes the sponsor's proposed cutoff values, settings use, and the recommendation for single versus serial measurements in the expanded Instructions for Use.

- 1) Please discuss the potential advantages and disadvantages of using this test as proposed in the IFU. In your discussion, please note whether the current submission addresses any

potential new risks from the modified IFU, if so please describe those risks. Please address each aspect of the modified Indications for Use independently including (a) as an aid in antibiotic decision making for inpatients or outpatients, with suspected or confirmed lower respiratory tract infections (LRTI) defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD), and (b) as an aid in decision making for antibiotic discontinuation for patients with suspected or confirmed sepsis.

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11. Appendix 1

Regulation: 21 CFR 866.3215

Device Type: Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis.

Class: II (special controls)

- (a) Identification: An in vitro device intended for the detection and qualitative and/or quantitative measurement of one or more non-microbial analytes in human clinical specimens to aid in the assessment of patients with suspected sepsis when used in conjunction with clinical signs and symptoms and other clinical and laboratory findings.
- (b) Classification. Class II (special controls). A device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis must comply with the following special controls:
 - 1) Premarket notification submissions must include the device's detailed Indications for Use statement describing what the device detects and measures, the results provided to the user, whether the measure is qualitative and/or quantitative, the clinical indications for which the test is to be used, and the specific population(s) for which the device use is intended.
 - 2) Premarket notification submissions must include detailed documentation of the device description, including (as applicable), all device components, software, ancillary reagents required but not provided, explanation of the device principle and methodology, and for molecular devices include detailed documentation of the primer/probe sequence, design, and rationale for sequence selection.
 - 3) Premarket notification submissions must include detailed documentation of applicable analytical studies, such as, analytical sensitivity (Limit of Detection, Limit of Blank, and Limit of Quantitation), precision, reproducibility, analytical measuring range, interference, cross reactivity, and specimen stability.
 - 4) Premarket notification submissions must include detailed documentation of a prospective clinical study or, if appropriate, results from an equivalent sample set. This detailed documentation must include the following information: a. Results must demonstrate adequate device performance relative to a well-accepted comparator. b. Clinical sample results must demonstrate consistency of device output throughout the device measuring range likely to be encountered in the Intended Use population. c. Clinical study documentation must include the original study protocol (including predefined statistical analysis plan), study report documenting support for the proposed Indications for Use(s), and results of all statistical analyses.

- 5) Premarket notification submissions must include evaluation of the level of the non-microbial analyte in asymptomatic patients with demographic characteristics (e.g., age, racial, ethnic, and gender distribution) similar to the Intended Use population.
- 6) As part of the risk management activities performed under 21 CFR 820.30 design controls, you must document an appropriate end user device training program that will be offered as part of your efforts to mitigate the risk of failure to correctly operate the instrument.
- 7) A detailed explanation of the interpretation of results and acceptance criteria must be included in the device's 21 CFR 809.10(b)(9) compliant labeling, and a detailed explanation of the interpretation of the limitations of the samples (e.g., collected on day of diagnosis) must be included in the device's 21 CFR 809.10(b)(10) compliant labeling.