DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Brief Summary of the Microbiology Devices Panel Meeting – November 10, 2016

Introduction:

On November 10, 2016, the Panel met to discuss and make recommendations regarding the 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 regarding the application of procalcitonin (PCT) to the evaluation and management of inpatients and outpatients with suspected Lower Respiratory Tract Infections (LRTI) and sepsis. The panel engaged in a very robust discussion of the benefits and risks for the new indications. The committee also commented on the clinical study design and limitations of the meta-analysis. There was one presentation entitled "*Challenges in Studying Rapid Diagnostic Tests in Outpatient Respiratory Tract Infections"* by guest speaker Dr. Ebbing Lautenbach, M.D., MPH, MSCE, representing the Antibacterial Resistance Leadership Group (ARLG).

Open Public Hearing Speakers:

1) Sean-Xavier Neath, MD, PhD (University of California)
2) Michael Broyles, BS, Pharm, RPH (Five Rivers Medical Center)
3) Bryant Nguyen, MD, MS (Loma Linda University Medical Center)
4) Volker Leidenberg, MD (Thermo Fisher Scientific)
5) George Sakoulas, MD (University of California School of Medicine)
6) Devendra Amin, MD (Medical Director Baycare eCARE)
7) James Newton, MD (Washington Regional Medical Center, California)
8) Michael Mansour, MD (Massachusetts General Hospital)
9) Dr. Lance Price, PhD (Antibiotic Resistance Action Center, George Washington University)

Deliberations:

The panel deliberated the benefits and risks of the proposed IFU for LRTI, addressing statistical methodology, specific clinical subpopulations, such as COPD and outpatients, and practical testing considerations. The panel arrived at a consensus recommendation that the data presented supported the safe and effective use of PCT-guided discontinuation in the setting of sepsis. In the setting of LRTI, the panelists' general consensus was that the benefits of procalcitonin (PCT) as an aid in the management of LRTI outweighed the risks for inpatients and the patients in the emergency department (ED). Based on the data presented, the panel did not recommend the use of PCT-guided management in an outpatient setting for patients with LRTI. The panelists also discussed potential limitations and additional analyses that could be conducted to further mitigate potential risks.

A number of panelists noted that the data presented was insufficient to determine if the benefits outweighed the risks in outpatient settings beyond the ED. The panel questioned the practicality of testing in outpatient clinics and potential practical complications, such as patients not returning for follow-up testing. It was repeatedly emphasized that the current test is currently performed in moderate to high complexity clinical laboratories and that discussion of PCT use in CLIA-waiver settings was beyond the scope of the meeting. Subgroup analysis of the outpatients with community-acquired pneumonia (CAP), acute bronchitis and COPD was presented by bioMérieux in response to panel questions. The subgroup analysis did not demonstrate a significant difference for antibiotic duration, exposure or mortality in outpatients, but the sample size was acknowledged to be relatively small by bioMérieux and the panel. Several panelists emphasized that AECOPD is a uniquely difficult population to assess and additional data analysis is needed.

As potential risk mitigations, the panel discussed the role of labeling and education for clinicians. The panel stressed that education of the clinicians is critical for the success for the proposed modifications. bioMérieux presented a detailed educational plan describing their plans to provide training for their users. The panel felt that the proposed educational plan would help to mitigate some risks associated with PCT-guided management. It was repeatedly emphasized that PCT would be used as an aid in the management of LRTI and sepsis. The panel's general consensus was that the proposed use in inpatient settings and ER settings presented considerably less risk, as other diagnostic tests would be conducted and multiple clinicians could be available to determine the appropriate clinical implementation of PCT on a case-by-case basis.

The package insert was also discussed as a major source of risk mitigation. Panelists recommended that specific clinical limitations be included in the device labeling, such as immunocompromised subjects, pediatrics and specific potential clinical situations, such as hypoperfusion, atypical bacterial respiratory infections and chronic kidney disease. The panel also emphasized that the specific testing frequency should be included in labeling to guide implementation by clinical laboratories and avoid over-testing. The open public comments emphasized that the test is currently used for the proposed indications by some clinicians. Future clinical trials were also discussed, but the panel felt it was not necessary to wait for these studies to be completed to implement the proposed indications.

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