Statement of the American Association for Clinical Chemistry
FDA Public Workshop - Mass Spectrometry in the Clinic: Regulatory Considerations Surrounding Validation of Liquid Chromatography-Mass Spectrometry Based Devices

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My name is Yan Victoria Zhang and I am an Associate Professor at the Department of Pathology and Laboratory Medicine at the University of Rochester Medical Center, and one of my clinical responsibilities is to serve as the Director of the Clinical Mass Spectrometry and Toxicology overseeing the development and implementation of clinical mass spectrometry assays for clinical diagnostics, prognosis, and therapeutic treatments. I am here today on behalf of the American Association for Clinical Chemistry to share our perspective on the validation considerations for LC-MS based protein and peptide assays. We applaud the FDA's willingness to enter into a public dialogue with the health care community on this important issue.

Foremost, it is important to recognize that protein and peptide assays measured by mass spectrometry differ widely in the number of targets measured, the choice of intact protein or surrogate peptide markers, the type of quantitation, and post-analytical data processing. AACC suggests that the FDA take this diversity into consideration before drafting guidance or attempting to regulate these assays.

The majority of laboratory errors occur during the pre-analytical phase of testing, which therefore is an important area to assess during the validation process. Many considerations are shared by current protein and peptide clinical assays as well as emerging LC-MS assays. Unique features for protein and peptide based LC-MS assays include, but should not be limited to, proteinase selection, digestion conditions, protein or peptide capture antibody selection, and

protein/peptide purification and enrichment process selection. Data processing components such as the calibration scheme, peak integration method, and data reporting should be considered.

It is critical that the assay measurement system be designed to ensure that processing conditions affecting analytical performance are tightly controlled within the method as established by the assay developer or clinical laboratory. Validation should establish the procedure controls of these variables, separately or in aggregate as appropriate, within the context of the overall assay performance assessment and specifications. These variables should be considered within the existing framework of guidelines for assay validation rather than as an exhaustive, mandated list that may not adequately match all MS-based workflows for protein characterization.

LC-MS has demonstrated superb consistency across different labs, different instrument models and different assays. While appropriate harmonization is important, it is important to recognize that many current FDA-approved assays have well-documented variability in their harmonization. We believe that any FDA guidance should be consistent across all analytical platforms.

While recognizing that some LC-MS specific considerations should be evaluated, we believe that the validation requirements for LC-MS assays for proteins and peptides should be similar to those for current IVD instruments/methods, and it is important that regulatory guidelines not place an undue additional burden on this technology relative to other established analytical principles in light of the potential analytical advantages of LC-MS.

In summary, we applaud the FDA for working with the community on this important issue of LC-MS based protein and peptide assays. AACC agrees that established validation is critical to ensuring the quality of testing results. Fortunately, many regulations and guidelines, such CLSI 62-A, are already in place to assist with validating LC-MS assays. AACC suggests that the FDA consider these existing guidelines before taking any action in this area. Thank you for the opportunity to participate in today's session.