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Standardization of LC-MS/MS in Clinical Laboratory

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The technique of liquid chromatography with tandem mass spectrometry (LC-MS/MS) undertakes the indispensable role in clinical laboratory because of its unparalleled advantages of specificity, sensitivity, and multiple analytes measurement in highly complex biofluids over other techniques such as immunoassays. In the past two decades, with the continuous improvement in performance, LC-MS/MS has obtained considerable development in clinical laboratory. Currently its application area expanded to endocrinology, screening for inborn errors of metabolism, therapeutic drug monitoring/toxicology confirmation, vitamin analysis, and more recently, the peptide and protein quantitation [1].

However, the application of LC-MS/MS does not necessarily produce accurate results. The limitation of this technique must be recognized. One of the major barriers hampering the successful implementing of LC-MS/MS in clinical laboratory is the method standardization or harmonization. As we know that LC-MS/MS assays are typically home-brewed or laboratory developed tests (LDTs), significant between-laboratory imprecision and inaccuracy may occur if these methods lack of standardization [2]. Errors may be introduced from inappropriately following of guidance for method validation, improperly use of standard materials, mistake of preparation of calibrators and quality controls, inappropriately choice of the alternative matrices, or lack of adequate quality assurance [3].

There is no doubt that inter-laboratory agreement could be improved through standardization of LC-MS/MS analysis. Then how to perform the standardization in clinical laboratory? First of all, it is crucial to follow a practicable guideline of LC-MS/MS in clinical diagnosis environment. Before a new LC-MS/MS method introduce into patient care, it should undergo rigorous and systematic validation to provide confirmation that performance requirements are met and to make sure it will produce accurate, reliable, and reproducible results with respect to the nature of the testing and the environment of regulation. Those key elements for method validation should be included in the guidance: matrix effect, selectivity/interference, linearity, accuracy and sensitivity, precision, stability, reference interval and method comparability. Collaborative efforts have been made from Food and Drug Administration (FDA), European Medicines Agency (EMA) to publish the guidelines on bioanalytical method validation [4,5]. Clinical and Laboratory Standards Institute (CLSI) has also published guidelines specifically modeled toward validating assays for clinical laboratory use [6]. However, till now there is not an accepted standard protocol for validating an LC-MS/MS method for clinical use. The use of traceable standard reference materials or commercial kits is essential to the improvement of inter-laboratory performance. Laboratory-developed LC-MS/MS methods generally use their own procedures, instrumentation, reagents, and calibrators. This is the main cause leading to poor agreement between laboratories. Standard reference materials are particularly important for clinical analysis because they are prepared under stringent procedures and verified by strict homogeneity testing and value assignment. Commercial kits are fully validated by manufacture and rigorously reviewed by regulatory administration such as FDA before launched in market. These kits generally include procedures, columns, calibrators, quality controls, and therefore eliminate the efforts to laborious method development and validation in clinical laboratories. It was demonstrated that the between laboratory agreement improved significantly for LC-MS/MS assays by using a common standard or a cleared kit [7,8]. However, for many LC-MS/MS methods new to clinical use, standard reference materials or commercial kits are not always readily available. Proficiency testing (PT) or external quality assessment (EQA) is one of the standardization measurement help to make LC-MS/MS assays more comparable with other laboratories by using similar methods for a specific test. Generally it is mandatory for a clinical laboratory to participate PT/EQA programs. However most of these programs still base on peer-group mean value to estimate the closeness of the results. The successful outcome of qualification in PT/EQA may only prove your test results being precisely wrong. Accuracy based or trueness verification PT/EQA with target value assigned by reference measurement procedure is more desirable. In the worst circumstances, there is no availability for any of above mentioned standard reference materials, commercial kits or PT/EQA programs for LC-MS/MS analysis, a commutable comparison with patient samples between clinical laboratories should be helpful.

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