Is fully integrated LC-MS/MS the future for the routine clinical lab?

Liquid chromatography-mass spectrometry (LC-MS/MS) is an analytical chemistry technique that combines the physio-chemical separation capabilities of liquid chromatography (via conventional chromatography within a column) with the analytic power of mass spectrometry. It allows the user to properly ascertain the individual mass/charge ratio of analytes present in a chromatographic peak. The high throughput capabilities of this technique will bring value to the clinical lab, where time taken to analyse samples is paramount. Bringing LC-MS/MS testing into the clinical setting has been a slow process, however, the medical device industry is on the verge of a fundamental breakthrough that could help drive the adoption of this technique.

LC-MS/MS is used primarily for the identification and quantification of particular molecules within a substance, and its application in diagnostics is a promising venture due to its potential ability to increase throughputs and streamline the processes needed. As such, patient data can be analysed quickly and accurately in order to provide improved patient care. Broadly speaking, the methodology can be divided into three parts. Initially, sample preparation is undertaken; be it whole blood, plasma, saliva or urine – the sample must be prepared to ensure large proteins and salts that may dirty the instrumentation are removed. Conventionally, this phase has been undertaken manually, which can be time-consuming and prone to human error. As such there is a need for the automation of this step to improve efficiency and reliability before LC-MS/MS is adopted by the clinical laboratory. Once sample preparation is complete, the liquid chromatography and mass spectrometry steps can take place, in which the sample is separated and analysed respectively.

LC-MS/MS and the clinical laboratory

Although adoption of LC-MS/MS in the clinical laboratory has been slow but steady, this technique has demonstrated vast improvements in analytical specificity when compared to conventional immunoassays. Mass spectrometry's strength lies in its ability to be extremely specific to the target analyte, due to the absence of cross reactivity; the likes of which can be common in antibody-based immunoassay (IA) methods. However, the uptake of this technique by clinical labs has not been as rapid as expected, with many choosing to continue using immunoassay-based methods instead.

There are a number of factors causing clinical labs to be cautious about the mainstream use of LC-MS/MS systems. There are numerous LC and MS systems available to choose from, something which in itself can seem overwhelming to a clinical scientist who is not an LC-MS/MS expert. In addition, there is a range of options for calibrators and controls available, along with the internal expertise required to develop and validate methods, and set-up and run the instruments. The final factor to impact the decision is often cost, since investment in such systems is commonly high, especially when taking into account the automated components required to help reduce labour needs for sample preparation. As such, finance options are often limited. When combined, these factors can make immunoassay analysers seem like the simpler option.

The emergence of connected components

Although used in many clinical labs, immunoassay techniques are not always accurate. For example small molecule biomarkers, such as steroid hormones, prove challenging due to the lack of specificity in the binding sites on small molecules, a fact that many clinical scientists are all too aware of. Recent improvements to LC-MS/MS systems have focused on advancing both ease of use and efficacy, essentially to make them a viable alternative to IA methods. Laboratory managers can find ample published documentation that shows just how beneficial LC-MS/MS systems are when used in place of IAs. For instance, a study by Nigel W. Brown and colleagues published in Clinical Chemistry in 2005 demonstrated that LC-MS/MS was far more precise than a microparticle enzyme immunoassay (MEIA), which was 'significantly affected by patient cohort' (Brown, N *et al.* Clinical Chemistry 2005; 51(3): 586-593).

Clinical laboratories are faced with increasing complexities in their daily workflows, and there are pressures to provide detailed analyses of patient samples using streamlined and well-coordinated practices. The need to provide efficient turnaround on samples is also on the increase. There is, therefore, a trend where system manufacturers are looking to provide laboratories with the ability

to advance efficiency through the implementation of compatible technologies, such as the combination of stand-alone elements (automated sample handlers, LC-MS/MS reagent kits, and software), which are supplied together to better manage workflows. These connected component-based systems, by which the different components of the LC-MS/MS system (sample preparation, liquid chromatography, and mass spectrometry) are placed in tandem with each other, is a big step in the right direction to increase productivity and efficiency, while simplifying the number of decisions that the lab needs to make. However, there are still improvements that can be made. The issue lies in the fact that connected components are not the same as a fully-integrated, automated system with dedicated assays and diagnostic kits that are regulatory compliant. The development of properly synergized components can truly simplify the decisions faced by clinical scientists and enable LC-MS/MS to become an integral part of the clinical laboratory.

The needs of the lab

Clinical labs require a high level of automation with a number of its systems, owing to the high turnover rate demanded to meet the needs of patient care. In addition, easy to use technologies that include walk away operations are essential, and considered commonplace to clinical scientists, owing to the multitude of responsibilities placed on laboratory personnel. These busy labs require built-for-purpose, fully integrated analysers that are able to greatly reduce installation, validation, and training times, having the system ready to operate in a matter of weeks, rather than months. Streamlining the procedure without compromising the quality of the analysis via implementation of better integrated systems can be considered an essential next step in the medical devices industry. Furthermore, results obtained from these systems need not be in isolation: standardization between laboratories using the same system will be achievable owing to the inclusion of dedicated test kits that are fully validated and ready for use with the analyser. The ideal next-generation system for the clinical laboratory will encompass every step, including automated sample preparation, handling and LC-MS in one unit. Moreover, it will be labelled as a medical device, have dedicated assay kits, and be produced, serviced, and supported by a single manufacturer. Finally, such a device would ideally be able to connect bi-directionally with the laboratory information system (LIS) and furthermore to the laboratory automation system (LAS).

In the end, technologies that are able to advance the state of play for laboratory sample analysis are required in order to ensure laboratory personnel can be confident in the analyses they are making. Beyond connected components, the introduction of integrated LC-MS/MS systems into the laboratory could lead to a paradigm shift with regards to specificity in small molecule analysis that is expected by clinical scientists. Systems that can lead to better quality of care for patients and improved analysis for physicians will essentially help healthcare systems operate more efficiently.

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