# Is Automation the Key to LC-MS/MS Migrating from Research and Reference Labs to Hospitals and Clinics?

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Hospital and clinical labs are applying liquid chromatography/mass spectrometry (LC-MS/MS) technology to a wider range of applications as clinicians see its value in testing for small molecule analytes like opiates, therapeutics, immunosuppressant's, steroids and vitamin D metabolites.

However, the current generation LC-MS/MS technology, geared for use in research and academic laboratories, is poorly suited for large-scale adoption in clinical settings. Only a small percentage of the LC-MS/MS instruments on the market today are in clinical and hospital laboratories because few hospital labs – even large medical centres – can afford on-site LC-MS/MS. Not because of the instrument costs, but because of the operational costs.

Today's LC-MS/MS methods are too manually intensive and reliant on expensive doctoral-level scientists to be cost effective at the hospital or clinical level. A routine task for a scientist in a research lab – reconfiguring an LC-MS/MS system for a new assay, for example – would be challenging for even a highly trained and skilled laboratory technician. With the state of today's technology, any lab that wants to do on-site LC-MS/MS analysis needs a scientist either on staff or otherwise available to ensure proper instrument operation and to interpret results.

Even if a clinical lab could afford its own scientists, or even if technicians could do the work, manually re-configuring instruments for each new test would consume so much time it would likely back up the lab's workflow, which in turn affects patient care. The complexities of today's LC-MS/MS technology leave hospitals and clinics with two choices for meeting their specialty diagnostic needs.

The first is to forgo LC-MS/MS testing altogether in favour of immunoassay methods. Immunoassays can be run cost effectively on automated analysers in hospital labs. However, they are not as precise or efficient as LC-MS/MS especially for small-molecule analytes. They can be thrown off by the presence of metabolites of other drugs with core structures similar to the desired analytes.

The second choice is for hospitals and clinics to outsource LC-MS/MS analysis to reference labs that have adapted LC-MS/MS from research to clinical testing. However, this solution has trade-offs to consider.

Outsourcing spares hospitals and clinics the direct cost of the highly trained staff needed to operate LC-MS/MS instruments, but it is still very expensive – potentially as much as $500,000 per year for a large academic medical centre.

Outsourcing is also slower and less responsive than in-house testing. Clinicians must wait longer for results from reference labs than they would for in-house testing – typically anywhere from two to 10 days.

This limited access to expedient LC-MS/MS results is occurring against a backdrop of rising demand for the type of detailed chemical analysis that LC-MS/MS can supply. The growth rate in the global market for vitamin D testing, for example, was expected to exceed 30% through 2014 [1]. Only LC-MS/MS can provide both vitamin D2 and D3 levels simultaneously in a single assay, a result that may be important for patient care and beyond the capability of immunoassays. There is a similar rise pain management related to the testing for patient compliance [2].

LC-MS/MS analysis could improve pain management by rapidly providing both qualitative and quantitative determinations, but not if hospitals and clinics rely on outsourcing and measure turnaround in days instead of hours. In-house mass spectrometry narrows that time window and improve patient care.

## Incompatible Workflows

Another major contributor to longer turnaround times stems from batch processing, which does not complement the 'random access' workflows more commonly observed in clinical situations.

In a reference lab, batch processing is typically used to maximise efficiency when processing large numbers of samples for the same analyte. In a hospital or clinic, however, the top priority is timely service. Diagnostic labs typically process samples as soon as they arrive from the clinic so patients and clinicians don't have to wait long for results. While batch processing is efficient, it is usually aimed at the determination of a single analyte in a large batch of identical samples; such a situation is less common in a hospital lab where many analytes have to be measured sometimes in different sample types.

Onsite LC-MS/MS could yield results in just a few hours and enable more detailed tests vis-à-vis immunoassays, which are often limited to screening for the presence of a single analyte. Clinicians could, for example, request tests for the concentration of an analyte and related compounds in a patient's system, instead of just for the single analyte's presence, to gain greater insight into their condition. LC-MS/MS is better suited to measure multiple molecules in a single run. Furthermore, the quicker they receive the results, the more able they are to adjust patients' dosages to improve their conditions.

Manual sample processing, workflow bottlenecks, and longer turnaround times restrict the widespread use of LC-MS/MS testing in clinical settings. These limitations can be traced back to a root cause: a lack of fully automated LC-MS/MS solution that is similar to traditional laboratory instruments that are easily operated with little or no human intervention.

A more automated, integrated LC-MS/MS system would offer the possibility of 24/7 LC-MS/MS testing by all of our technicians with basic lab tech skills. While clinical laboratories strive for more automation to improve workflow, there are still issues to address. Often, they lack the in-house IT resources to integrate every step in the process, which means going to vendors or third-party integrators. Even if their efforts are successful, they end up with highly customised solutions that are expensive to maintain and upgrade. For example, instead of system-wide software upgrades, clinical IT staff would have to upgrade each component in the system separately as vendors issued service packs.

## Partial Automation, Partial Results

Clinical diagnostic labs without in-house LC-MS/MS capabilities are under pressure from their own clinicians to develop them. The comparatively few hospitals and clinics that have invested in LC-MS/MS instruments are under pressure from administrators and insurers to reduce cost and improve quality. Automation can address these needs, but the current state of automation continues to be an obstacle.

Instrument vendors are lagging to address the right solution for the clinical labs need which is an integrated component as a part of a complete system that minimises human intervention. Instead, each instrument vendor is automating their part of the LC-MS/MS process, leaving the customer to piece together an end-to-end solution usually for a particular analyte or related group of analytes.

In most cases today, 'automation' means adding mechanical sample handling capabilities to an existing LC-MS/MS instrument to replace manual processes.

The combination of mass spectrometer and automated handling system is an obvious improvement. This partial automation falls well short of meeting clinical laboratories' needs. It creates islands of automation that must be bridged with manual processes, which introduces the potential for error that automation is supposed to reduce.

Partial automation also does not give clinicians easier access to a wide menu of tests, because those still require substantial input from scientists. For example, when clinicians want to switch from one assay to another, issues like calibration standards, HPLC columns, solvents and buffers, and sample-specific handling procedures arise. They are beyond the scope of most technicians' knowledge, which means more intervention from the scientist. As a result this can undercut the return on investment from a more fully automated and integrated system.

## A Full Clinical Automation Model

To achieve the desired balance of high quality, greater flexibility and reasonable cost, clinical laboratories need full automation that moves the sample through the full battery of sample-handling processes in preparation for LC-MS/MS analysis. Based on today's technology, a clinical diagnostic laboratory that wanted an end-to-end automated system capable of a broad menu of tests would have to integrate the major systems, and do so for every assay. That is a serious barrier to adoption.

Since currently no one vendor supplies all the various components, multi-vendor solutions mean higher overhead costs in managing relationships with different vendors: purchasing maintenance contracts and training, administrating software licenses, etc. When multi-vendor systems don't deliver accurate results, the complexity of tracing the root cause is multiplied by the number of vendors.

Most hospitals and clinics usually have limited IT resources and are wary of systems with high IT overhead for just that reason. Integrating and maintaining complex systems like mass detectors and mass spectrometers is not how they want to deploy their IT resources. If LC-MS/MS is going to work for them, it has to be a push-button proposition. A technician should be able to load a sample as soon as it arrives at the lab, push the button, come back in an hour and get the results. Anything less than that creates variability that they are not geared to manage.

To make an LC-MS/MS system practical for hospitals and clinics, it would have to encompass all the various HPLC components including pumps, columns, solvents, buffers, mass spectrometer calibrants, sample calibrators, internal and calibration standards, sample handling robotics including centrifuges and cool storage, waste disposal systems, etc. in an integrated unit. They would have to be connected by a robotic system for moving samples from one process to another. Its software should integrate easily with medical laboratory information systems to eliminate manually keying test results into patient records. Furthermore, the system and all reagents must have regulatory approval as a medical device.

Until technology providers can deliver a system like this, LC-MS/MS will exist at the periphery of medical diagnostics instead of in the mainstream where it belongs. Clinicians will hear about its enormous analytical effectiveness, but not embrace it fully because they know that it comes with complex and semi-automated workflows that do not fit into the typical clinical laboratory or the flow of patient care. The automation and integration that will transform LC-MS/MS into an integral and cost-effective part of medical diagnostics are technically feasible, as demonstrated by the partial automation on the market today. All that remains is for technology providers and regulators to step up and meet the demand.

Bori Shushan, PhD, is the founder of Clinical Mass Spec Consultants, where he advises industry and institutions in the use of LC-MS/MS with specific emphasis on clinical applications. He is a consultant for Thermo Fisher Scientific.

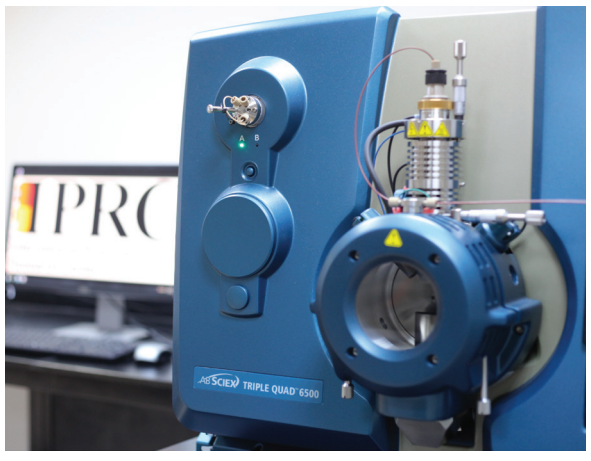
## References

*1. "Global Vitamin D Testing Market 2010–2014," TechNavio, January 2012.*

*2. "New advances in pain management screening and confirmation," MLO Online, last accessed August, 1, 2013.*

## Triple Quad LC/MS/MS Systems Enable New Levels of Sensitivity for Clinical Trials of Inhaled Drugs

**AB Sciex** have announced that the International Pharmaceutical Research Center (IPRC) in Jordan is investing in two AB Sciex Triple Quad™ 6500 LC/MS/MS Systems in order to offer new capabilities for bioanalysis studies of Phase I clinical trial compounds. The sensitivity of the 6500 Systems will enable the IPRC to detect drug compounds or metabolites in human samples down to femtogram levels for the first time, as well as increasing significantly the IPRC's daily sample throughput.




"These two 6500 Systems will make a significant different to our capabilities as well as to our productivity," said Dr Isam Salem, Vice President, Operations, IPRC. "We will be able to provide Phase I clinical trials for inhaled drugs and hormones for the first time, thanks to the extreme sensitivity of the 6500 Triple Quads. They will enable us to determine with confidence whether or not inhaled drugs are absorbed into the general circulation, even at the femtogram level.

"It's critical that we have absolute confidence in the quality and robustness of our data when submitting clinical trials results to the regulatory bodies," added Dr Salem. "We have always depended on AB Sciex hardware and software systems. We have a long and collaborative relationship with the company, based on its excellent support and high quality instruments, which have never once let us down."

The 6500 System with Ion Drive™ Technology increases the quantity of ions produced while enhancing the way ions are transmitted and detected, increasing the limits of quantitation.

"Our customers depend on the reliability and performance of our instruments and software to obtain the answers they need to critical scientific questions," said Khalid Ghaffar, Manager Sales HGM MENAm AB Sciex. "In turn, our local support teams strive to maintain collaborative relationships with our customers through delivering comprehensive and high quality technical support services."

**For More Info, email:** 33772pr@reply-direct.com

## Prosolia's PaperSpray® Technology Now Available as a Factory Option to Mass Spectrometers

Labs performing clinical research and forensic toxicology of dried sample spots can now purchase Thermo Scientific mass spectrometry (MS) systems equipped from the factory with PaperSpray technology, designed to virtually eliminate sample preparation for screening and quantitation of drugs in biological fluid samples.

**Thermo Fisher Scientific** has entered into a value added reseller agreement with Prosolia, Inc to permit Thermo Fisher to sell the Prosolia Velox 360™ device with Thermo Scientific MS systems, providing a single point of contact for purchasing, installation and service.

The Velox 360 device is an automated sample handling and ionisation source for mass spectrometry featuring PaperSpray technology. PaperSpray technology combines paper substrates with electrospray ionisation, designed to simplify sample preparation and speed up mass spectrometry analysis of biological fluids.

The Velox 360 device can be coupled to The Thermo Scientific Q Exactive Series MS family as well as the company's triple quadrupole and ion trap instruments.

**For More Info, email:** 34189pr@reply-direct.com

## Collaboration to Advance Forensic Testing Announced

**Sciex** have announced a research collaboration with Labor Berlin, the largest clinical laboratory in Germany, for the development of a hybrid Quadrupole Time-of-Flight (TOF) MS/MS reference library of relevant forensic chemical compounds. The library will cover thousands of chemical substances, allowing users of Sciex TripleTOF® 6600 mass spectrometers for forensic testing to more effectively and efficiently develop and validate new analytical methods for forensic compound screening. The reference library generated by this collaboration will ultimately allow forensic scientists to identify and analyse unknown substances or toxins, including pharmacological agents or forensic drugs in samples more easily, accurately and with more confidence.

The generation of the hybrid Quadrupole TOF library of chemical substances used in conjunction with mass spectrometry techniques is particularly important for applications in forensic toxicology. Forensic samples may contain unknown substances that a person may have ingested up to several weeks prior to the sample being taken. Therefore, forensic testing requires a precise, sensitive and robust approach to sample analysis.

Labor Berlin will provide the pharmacological input to the collaboration and Sciex, a global leader in life science analytical technologies, will assemble the hybrid Quadrupole TOF library using its expertise and highly robust and reliable instrumentation.

"These library databases offer benefits to forensic testing scientists to enable them to detect the latest emerging novel psychoactive substances, and their metabolites, to enhance their forensic discovery screening workflows," said Vincent Paez, Sr. Director, Food, Environmental and Forensics Testing at Sciex. A key feature of the library database is the inclusion of spectra collected in authenticated samples, providing relevant metabolite spectral information which is difficult to discover by other means.

"We chose to collaborate with Sciex because it is a manufacturer of superior analytical products, and the collaboration with Labor Berlin will make it possible to generate methods for almost any substance," said Dr Torsten Binscheck-Domaß, Head of the Clinical and Forensic Toxicology Department at Labor Berlin. "The hybrid Quadrupole TOF library is the first part of the collaboration, and we are in discussions about other larger projects that will be possible with Sciex in the future."

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