SCIEX Citrine™ LC-MS/MS: 6500+ MD

Your *in vitro* diagnostic medical device (MD) mass spectrometer

Introduction

Clinical biochemistry laboratories around the world face many daily challenges, including managing high sample workloads, managing clinician requests for novel tests, and generating and reporting out results in a timely fashion. Irrespective of the methodology employed, high quality and reproducible results are imperative since patient diagnosis and treatment plans are based largely on lab results. For this reason, many clinical laboratories have turned to LC-MS/MS, which is widely regarded as the gold standard for accurate quantification.

Clinical laboratories have historically employed Research-Use-Only (RUO) equipment for mass spectrometry-based testing, however there is a growing demand for medical device (MD) mass spectrometry systems, in part to comply with evolving regulations, and in part due to the increased confidence associated with the stringent manufacturing and post-market requirements for *in vitro* diagnostic (IVD) devices. SCIEX offers a complete portfolio of medical device MS systems, ranging from entry-level to ultra-high performance, to address a variety of users' needs. This article aims to highlight the benefits and advantages of an MD system, and the factors that should be considered when choosing a mass spectrometer for the clinical laboratory.

Reasons to choose mass spectrometry

Immunoassays are a huge part of the wet chemistry analyzer setup within the clinical biochemistry lab, as evidenced by a recent survey of participants at the American Association of Clinical Chemistry conference (Figure 1).

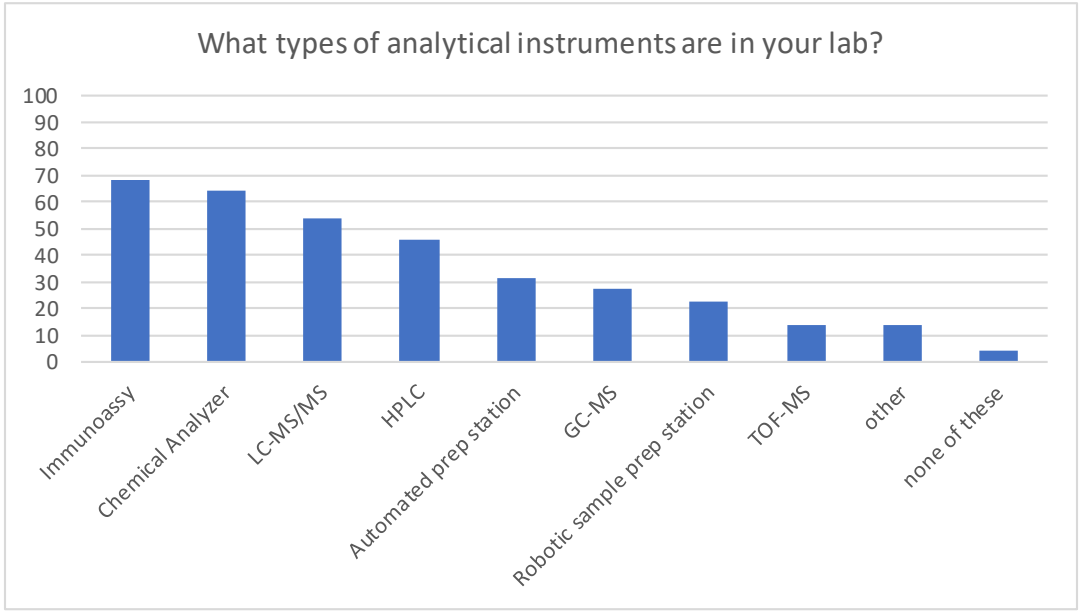

Figure 1. Percentage breakdown of various technologies in a typical clinical biochemistry laboratory

Out of 305 respondents, over 60% continue to employ immunoassays as part of the entire chemistry analytical workflow. There are several reasons for this, one of the clearest being the immunoassays employed are all FDA and CE-IVD cleared, providing a level of confidence for the end user that the tests performed in their lab are strictly tested and regulated. This is of huge importance as compliance within a clinical setting is one, if not, the highest priority.

While immunoassays are still popular for most clinical biochemical tests, concerns arise over their lack of specificity with structurally-similar molecules such as steroids, where cross-reactivity may play a role in false negatives and positives. Assays requiring low levels of detection in the pg/mL range are also not suitable with an antibody-based approach, as the same cross-reactivity issue can result in over-estimation of the compound in question. These shortcomings, combined with the advantages of mass spectrometry, are quickly increasing the adoption of the latter to further improve diagnostic accuracy of routine laboratory tests.

Three of the biggest advantages of MS are the 3 Ss: specificity, selectivity, and sensitivity.

The ability to **specifically** identify and quantify the molecule of interest amongst structurally similar compounds is a huge advantage, and MS with its associated technologies provide ultimate specificity when isolating the compound of interest from its associated matrix. However, that might not be enough with multi-factorial matrices, so selectivity plays a major role alongside specificity.

Whole blood, serum, plasma, cerebral spinal fluid (CSF), these biological fluids are complex as they contain metabolites that may interfere with analyses. MS provides the level of **selectivity** needed to isolate and quantify the compound of interest, without interference from its surrounding environment. Advanced secondary fragmentation such as QTRAP® Technology further enhances selectivity for challenging matrices such as hair, while maintaining minimal background.

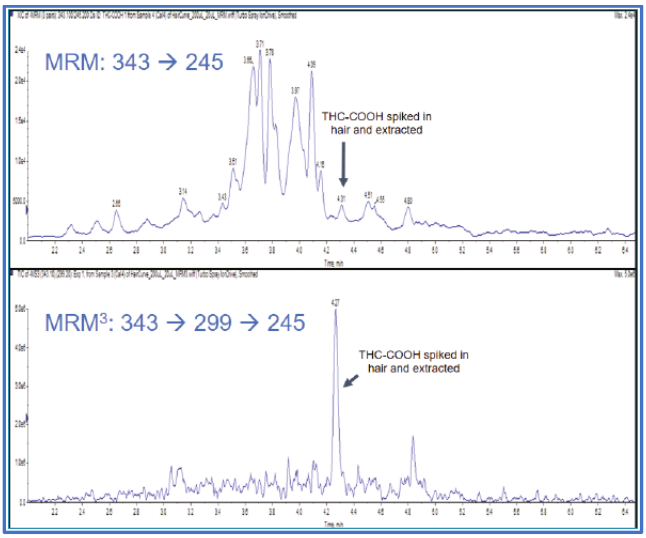

Figure 2. Secondary fragmentation using QTRAP technology illustrates how MS/MS/MS effectively removes unwanted background and isolates the peak of interest

Lastly, **sensitivity** is arguably the biggest advantage when it comes to mass spectrometry. Low level detection and quantification, in the parts-per-trillion range, are often needed for biochemical assays such

as aldosterone when levels are as low as the single digit pg/mL range. The ability to detect trace level compounds in a variety of challenging matrices is one of the hallmarks of mass spectrometry technology.

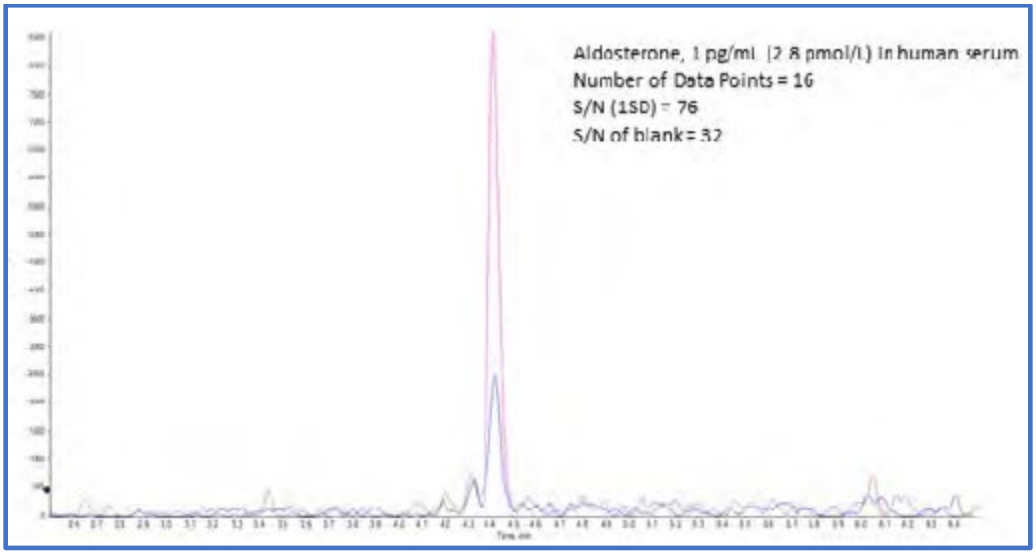

Figure 3. Representative chromatogram for aldosterone at 1pg/mL (2.8pmol/L) in human serum

In addition, mass spectrometers also provide its users the platform needed for their own Lab Developed Tests (LDTs), as the flexibility to be responsive for methodology changes is critical. The option of multiplexing allows for the simultaneous detection and quantification of tens and hundreds of targeted compounds in a single injection. Companion software solutions ease the collection and analysis of vast amounts of data, providing information at the level needed for results reporting.

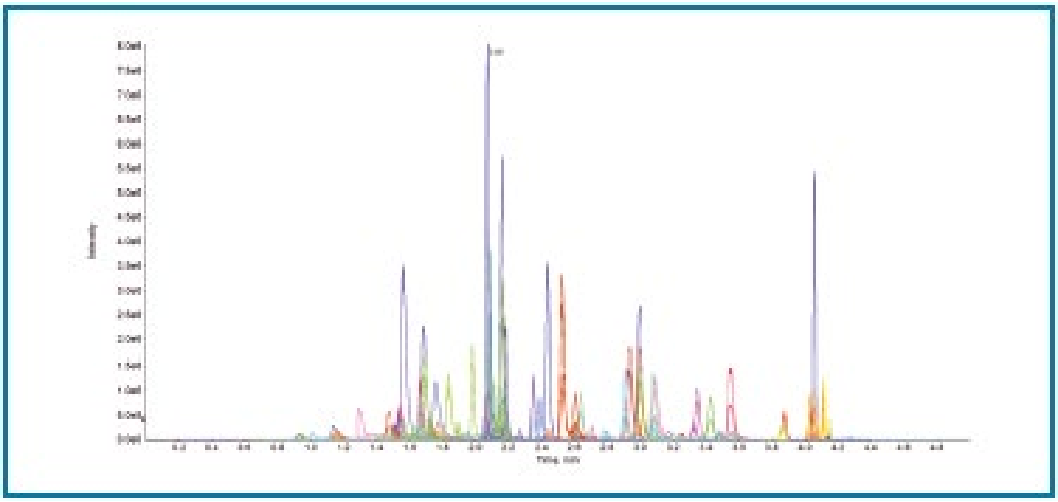

Figure 4. Multiplexing: an example of quantitative analysis for 93 analytes (212 MRMs) in a 5-minute method, with fast positive/negative polarity switching in electrospray ionization (ESI) mode

The benefits of mass spectrometry are clear. The previous sections highlight the clear distinctions of this technology and its advantages. As such, the 6500+ LC/MS-MS system from SCIEX is the most popular mass spectrometer amongst the user base across all market verticals and industries. These instruments are

classified as Research Use Only (RUO), meaning not for diagnostics purposes. In the clinical space, however, different rules and regulations apply because of the diagnostic environment and the nature of the work. Everything from the LC, MS, to the software tools used, need to be CE IVD compliant for the purposes of a diagnostic tool.

Why are Medical Devices important?

The need to ensure quality data generation and good laboratory practices are two of the most critical criteria of a clinical biochemistry laboratory. The reporting out and distribution of confidential patient data is of paramount importance, as well as instrument maintenance and troubleshooting when complications arise, and when repairs are needed. Providing confidence to the user for any situation that may arise, mass spectrometers built as Medical Devices provides trusted hardware and software to meet clinical laboratory needs. Comprehensive application support and service, part of the MD package for clinical customers, ensures confidence for daily operations as well as reliable engineering expertise when the need arises.

Figure 5. Four categories and associated good reasons on why a Medical Device is the system of choice for a clinical biochemistry lab

1. **Patient-safety first**: Not only are Medical Device systems from SCIEX designed and built to ISO 13485 and FDA 21 CFR 820 standards, MD-level software packages unsure the entire system is compliant and auditing capabilities are accessible for risk assessment and mitigation
2. **Designed for clinical users**: tailored service and support packages, online and troubleshooting support, as well as dedicated clinical application experts ensure the end user is in good hands
3. **Minimize risk**: MD instruments only use brand new replacement parts. Along with stringent verification processes, operational quality is maintained at the highest level

4. **Trust Partner:** SCIEX Now telephone support provides quick response for any lab-related questions. Coupled with extensive online courses available in SCIEX University for self-paced learning, SCIEX is the leading provider and trusted partner of medical solutions for mass spectrometry

Government regulations for diagnostic equipment

Technology and instrumentation used for diagnostic purposes are required to adhere to government regulations and its guidelines, to ensure patient safety as well as compliance within the laboratory. Strict operational procedures and requirements are in place to protect the operators from malpractice, as well as maintaining a high level of quality assurance to produce accurate diagnostic results, which directly impacts medical decisions and patient well-being.

In North America, laboratory equipment is split into three categories. Class I poses the lowest risk (control materials and laboratory instruments), Class II has moderate risks (disease monitoring devices or tests that help diagnose a condition), while Class III presents the highest risk (for example cancer screening devices). Unless they have been exempted by FDA, most of the Class II devices are cleared through the 510(k) pathway and is based on demonstrating performance of a new device is substantially equivalent to an FDA-cleared or preamendment device. It is becoming more apparent that mass spectrometers used in a clinical diagnostic setting should be a medical device to protect both the end user and the process that includes patient results generation. This helps ensure customer confidence and compliance through use of diagnostic instruments that meet the stringent FDA Good Manufacturing Practices (GMPs) and Design Control Requirements.

On May 26, 2017, an official paper of the European Commission published a new set of guidelines on newly released European IVD Regulation (IVDR 2017/746). There will be more attention to risk in relation to patient safety in classification of the IVDs, and the Clinical Effectiveness element will bring specific demands in relation to the quality system from manufacturers, especially in relation to Risk Management. Regarding Lab Developed Tests, laboratories will either need to use commercially available IVDs - if available, or to develop, manufacture, and monitor their own laboratory-developed tests in compliance with the requirements of the IVDR. Laboratories which develops these tests must have a quality management system for this specific test, after evaluation and validation. The demands formulated under this Regulation state that laboratories and manufacturers must comply with the regulations by May 2022.

This gives laboratories enough time to reevaluate their current setup, and plan what instrumentation and technology they wish to implement in the next few years. To ensure compliance for the future, mass spectrometrists must consider the importance of purchasing and validating laboratory equipment with these guidelines in mind.

SCIEX LC-MS/MS solutions for clinical diagnostics

Sciex offers a range of IVD mass spectrometry solutions to meet your laboratory's needs, from entry level to high-end, including the Citrine MS/MS system – our fastest, most sensitive IVD mass spectrometer. But why should you choose to go with a SCIEX IVD mass spec solution for your laboratory? In addition to the regulatory arguments above, are there any practical advantages over a standard RUO mass spec?

Software updates and fixes

To ensure that our customers in the clinical lab have access to all the latest software fixes, anyone that purchases IVD mass spectrometers are eligible to receive every software update and Hot Fix completely free of charge. This means that your laboratory can take advantage of every new software feature, as soon as it becomes available.

Security features

There are several standard security features that differentiate SCIEX's IVD product offerings from other vendors. In contrast with our Research Use Only portfolio, all our IVD LC-MS/MS solutions include standard security features and audit trail functionality – no paid upgrade required. These included safety features help to ensure the integrity of your valuable data, using e-signatures and role-based access privileges to safeguard against unintentional changes.

Software built for the clinical lab

To address the unique needs of the clinical laboratory environment, SCIEX has developed the user-friendly Cliquid MD software for instrument control and data processing. This software is also available as an optional paid upgrade for RUO mass spectrometers but comes standard with all of our IVD mass spec solutions.

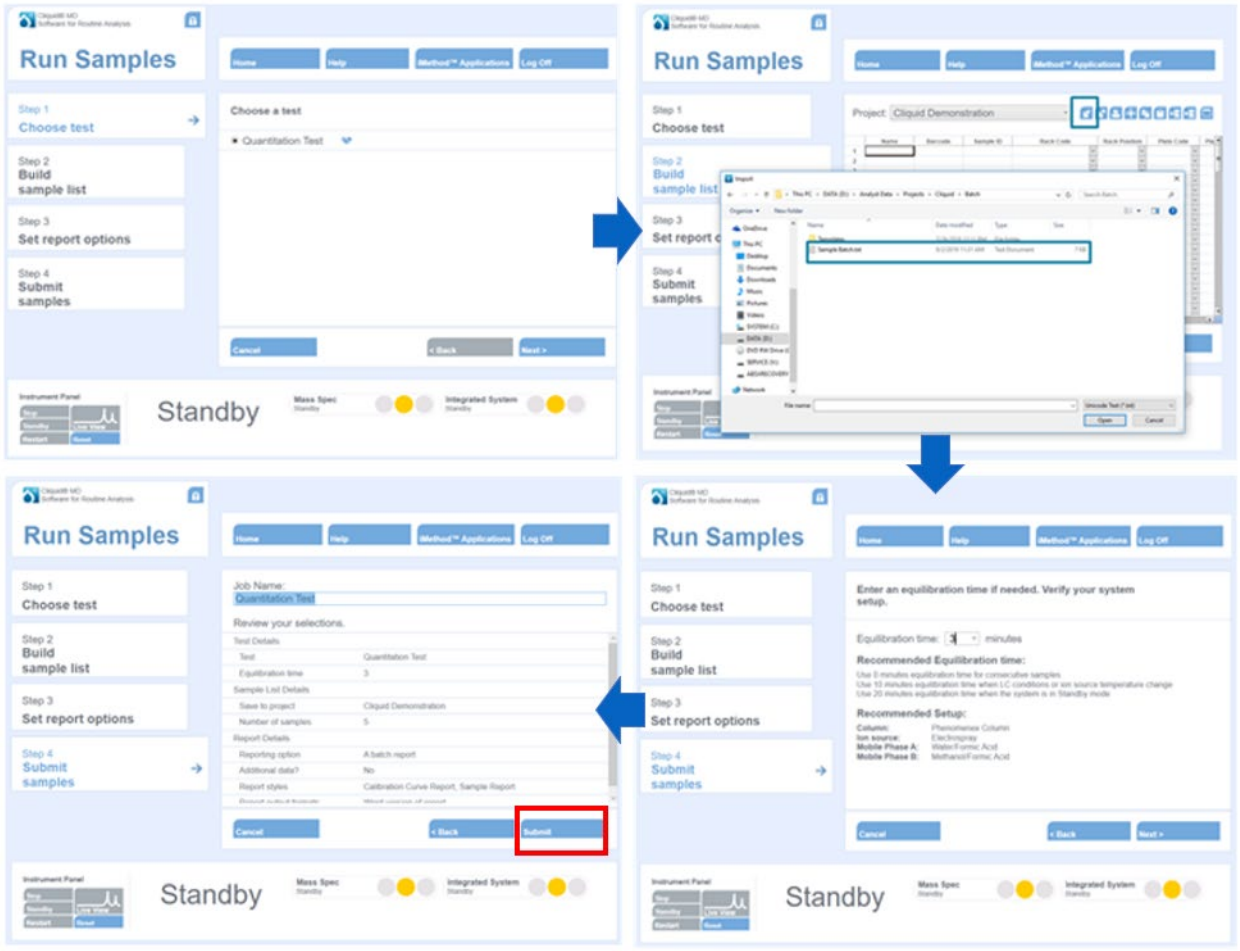

Figure 6: The guided 4-step workflow in the Cliquid software makes mass spectrometry simple: select a test, import or create a worklist, select a report, and press start.

What are the advantages of the Cliquid software?

The Cliquid MD software user interface is built with an intuitive point-and-click interface and four-step workflow, making routine mass spectrometry analysis simple and straightforward. The customizable, step-by-step workflow reduces training needs, and makes LC-MS/MS accessible to novice users.

Only the Cliquid MD software enables fully automated data processing. Submit your samples and walk away – your processed results and report will be waiting when you return. There are also processing options: Analyst MD software used for chromatogram acquisition is a single click away, in case there is a need to review the raw data and implement any adjustments. Data acquisition and reporting: made simple by Cliquid.

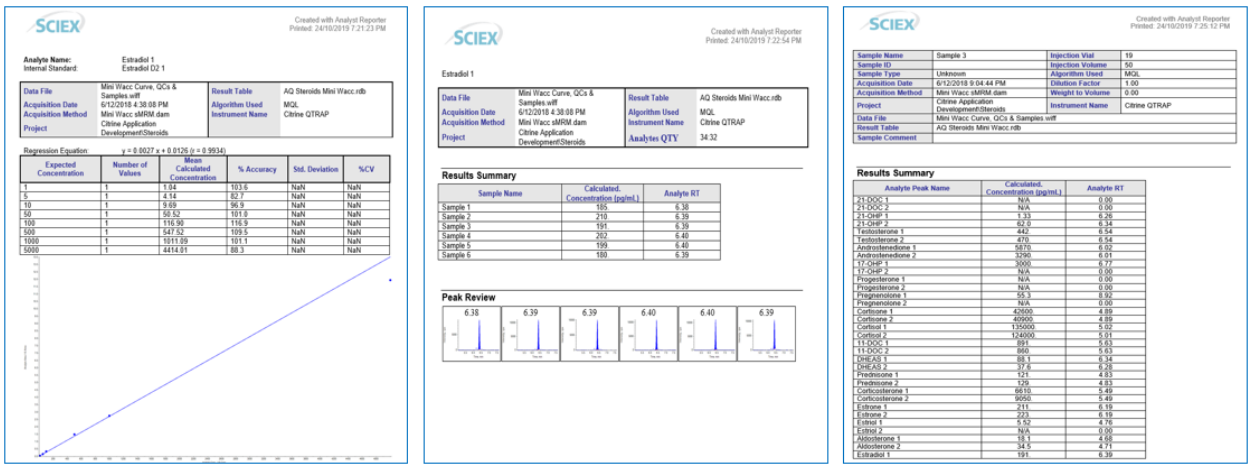

Figure 7: Examples of calibration curve and standards, chromatographic view of each injection, and sample summary report: choose how to report and export your results to Word, Excel, PDF or other text-based documents.

Numerous reporting options are available depending on the preferred layout from the operator. Whether it is single injection data-rich analysis, or batch summery reports, the end user has many choices by which the results are presented and reported out. The availability of bi-directional LIMS connectivity with Cliquid software allows for tailor-made reports and layouts that best fits their structure and needs. This intuitive software suite places the power of data analysis in the hands of the user.

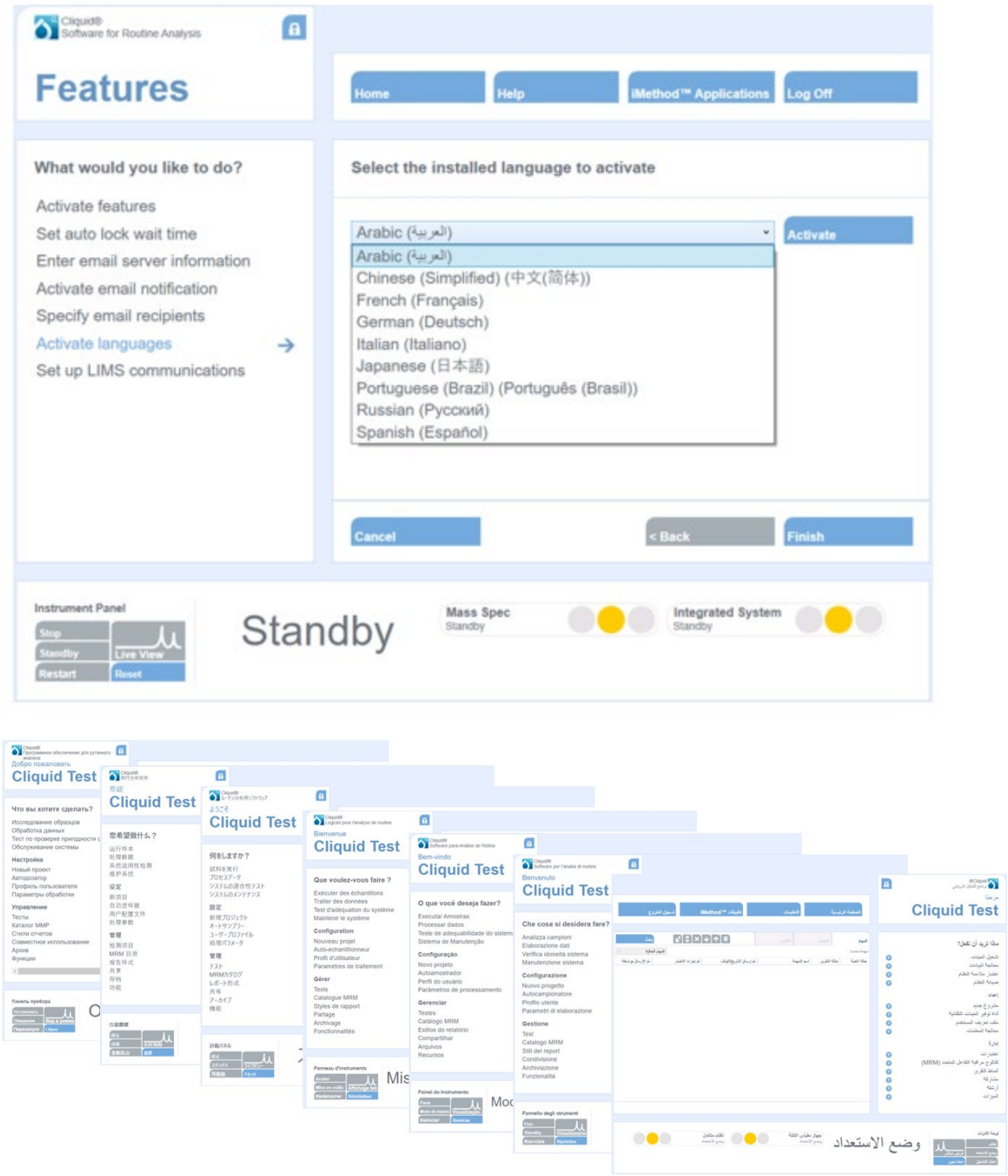

Figure 8: Select from a variety of available languages to display the user interface in the language of your choice.

The multi-lingual interface in Cliquid MD 3.4 allows users to carry out their work in the language of their choosing – select from English, French, Italian, German, Spanish, Portuguese, Russian, Simplified Chinese, Japanese, or Arabic. The customization of different language packs provides ultimate flexibility for the entire laboratory, as multiple cultures make up the modern workplace, and user-friendly user interfaces enables familiar operator experiences while minimizing errors.

Bi-directional LIS compatibility

A critical component of the clinical laboratory workflow is seamless communications with the Laboratory Information System (LIS). Only our Cliquid MD software – standard with all SCIEX IVD mass spectrometers – enables bi-directional communication with your LIS or middleware, allowing the direct import of worklists from the LIS into the software, and one-click release of your results back to the LIS. Interfacing with your LIS has never been simpler.

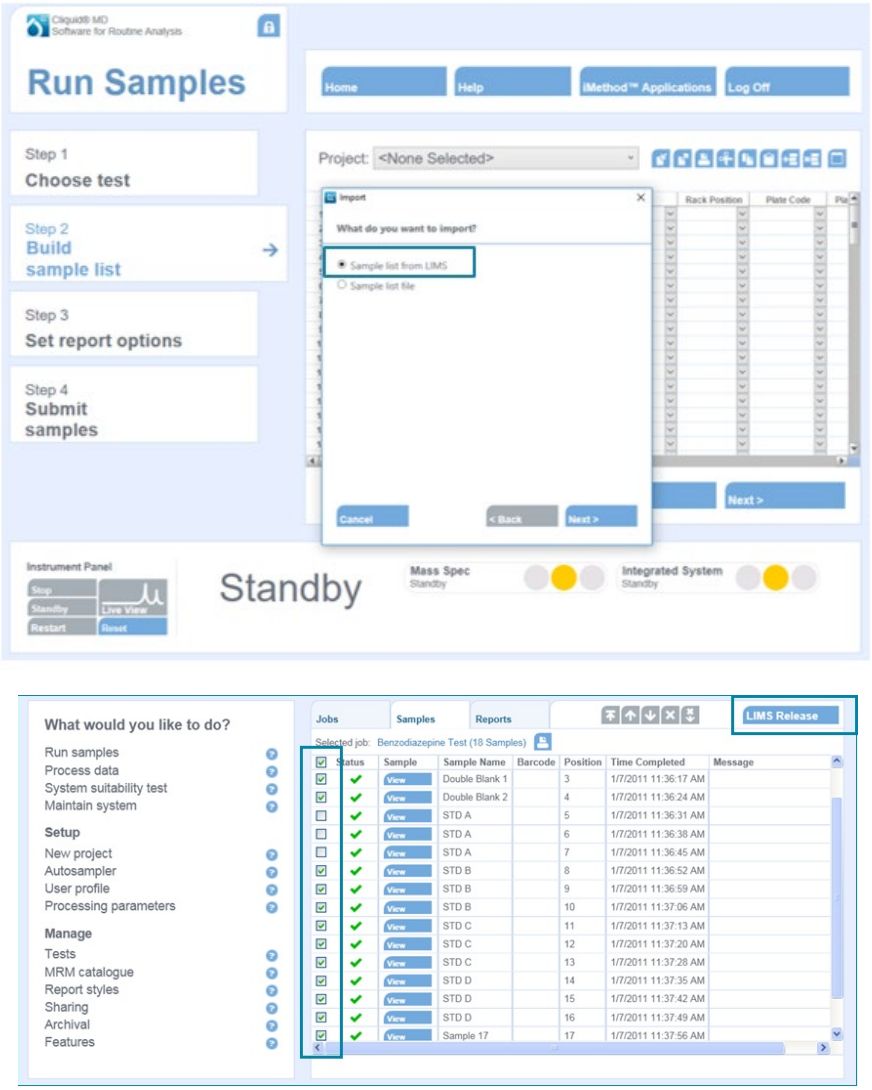

Figure 9: Selecting and releasing your samples to the Laboratory Information System has never been simpler.

Dedicated Clinical Support and Service

SCIEX University offers a series of Success MD training programs, specifically designed for users of our IVD mass spectrometers. These programs offer a blend of self-paced online courses and instructor-led and

hands-on training, provided by a qualified Service Professional onsite. The learning path is personalized to your instrument, workflow, and experience level.

Any unscheduled instrument downtime in the clinical lab can lead to delays in reporting out critical results, and potential costs associated with sample send-outs. To get you back up and running as quickly as possible, our Clinical Service plans offer **dedicated telephone call back** from a qualified Service Engineer and guaranteed **2 business day onsite response** for remedial repairs of the LC-MS/MS system. Repairs to IVD mass spectrometers use only brand new SCIEX parts, to maintain the highest level of system performance. Our trained Service Engineers run through a comprehensive checklist of system performance tests after every service call, to ensure that you are getting the most out of your instrument.

SCIEX University and customer experience

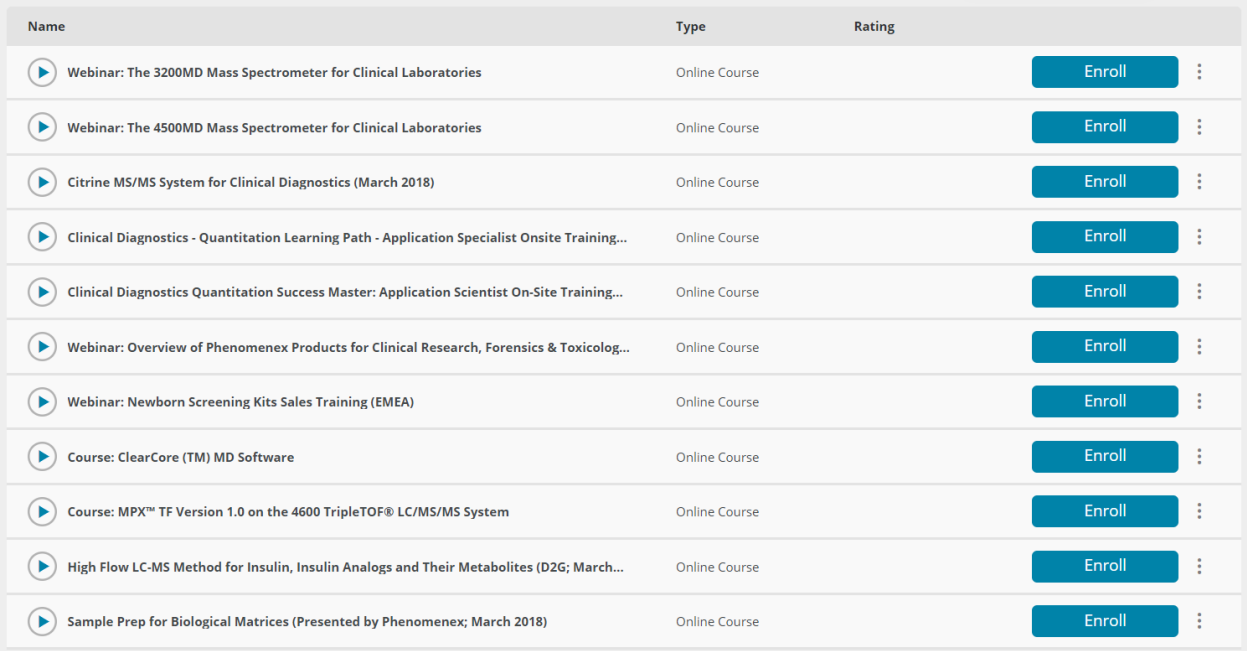

Figure 10. Plethora of online SCIEX University courses geared towards clinical customers are available online for self-paced learning and education

From beginners through to mass spectrometry experts, training is an integral part of working life. This is why SCIEX has built a comprehensive online course curriculum at the disposal of our users. Available online 24 hours a day, and tailored to your specific needs, SCIEX University MD courses are specifically designed with the clinical customer in mind, ensuring every aspect of the diagnostic workflow is covered. This is proving to be an invaluable source of information, as well as one of the biggest benefits of choosing an IVD mass spectrometer product.

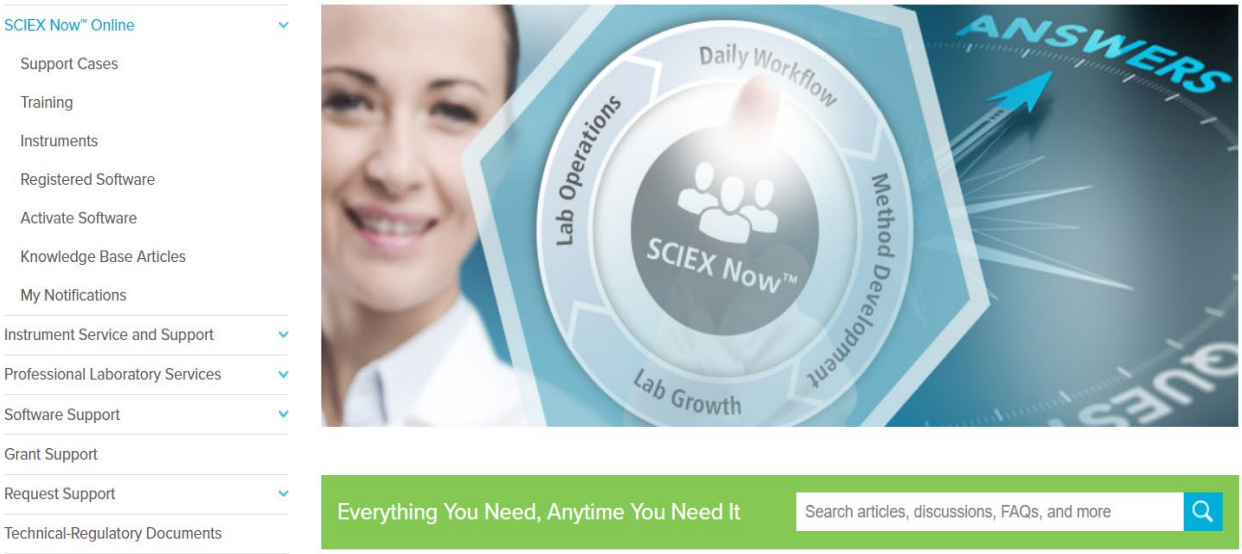

Figure 11. SCIEX Now telephone and online support provides safety and peace of mind

In the busy clinical biochemistry laboratory, time is a resource critical to the operational needs of the entire workplace. When a question needs to be answered, help is available from SCIEX through the SCIEX Now portal, an online and telephone support network where customers can get their specific questions answered quickly and clearly. This ensures that problems are resolved quickly and effectively, a point not lost on mass spectrometrists that require minimal downtime and maximum uptime.

Summary

SCIEX offers a range of latest technologies in mass spectrometry that are the ideal tools for quantifying biological compounds in complex matrices. This has become the gold standard for detecting and measuring a range of biochemical analytes in clinical biochemistry. When choosing such technologies for your clinical needs, there are many reasons for electing an IVD mass spectrometer built to MD standards, as both software and hardware are strictly maintained to the highest standards for diagnostic purposes. Recognizing that post-sales support is just as important, SCIEX University and SCIEX Now are also integral parts of the clinical diagnostic workflow, providing tailored support for every clinical customer and every clinical need.

The choice is clear, the Citrine LC-MS/MS mass spectrometer is the instrument of choice when considering a diagnostic tool in the clinical biochemistry lab.

SCIEX Diagnostics

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