Waters™

Advances in High-Throughput ADME-Tox Screening for Drug Discovery

Cyprotex invested in the Waters Xevo TQ-S micro Triple Quad Mass Spectrometer to minimize downtime and maintain high-throughput screening for its ADME-Tox services. The instrument helped Cyprotex to provide its customers with high-quality data for making key decisions on which molecules to move forward into development.

ADME-TOX SERVICES AT CYPROTEX

Cyprotex, an Evotec company, operates from Alderley Park, near Macclesfield in the UK, and Framingham, close to Boston in the USA. The scientific team comprises skilled professionals with extensive expertise with *in vitro* and *in vivo* Absorption, Distribution, Metabolism, Excretion, and Toxicology (ADME-Tox) services. The company's primary clientele work in pharmaceutical research, as well as the chemical, cosmetics, personal care, agrichemical, and tobacco industries. Cyprotex Limited, founded in 1999, became part of Evotec in 2016.

Cyprotex specializes in *in vitro* ADME screening to support discovery projects, regulatory *in vitro* ADME and drug–drug interaction (DDI) studies during preclinical and clinical development, specialist mechanistic *in vitro* human and animal toxicity models, and quantitative structure activity/property relationship modelling expertise. As well as supporting clients directly, Cyprotex has a strong focus on R&D, particularly in the field of *in vitro* toxicology, where the company is helping to develop more clinically relevant models.

Exceptional customer support serves as a cornerstone of the company's business strategy. Cyprotex takes great pride in its ability to swiftly deliver data for most standard screens within 5–10 working days.

Cyprotex, an Evotec company, operates from Alderley Park, near Macclesfield in the UK.

WORKING WITH WATERS

The Cyprotex HT Analytical team has developed an excellent relationship with Waters™ for training and maintenance. This partnership has been forged through consistent collaboration and both companies' shared dedication to customer service. Ms. Hollie Adey, Principal Scientist, HT Analytical, explains:

"Waters engineers are well-versed in our instrument needs, assisting us in fixing any issues that arise. Many HT Analytical team members are keen to learn about maintenance and Waters provides training to ensure we can handle certain tasks. We also have parts on site, so we can fix things ourselves."

Elaborating on the relationship, Ms. Adey continues:

"As many companies at Alderley Park have Waters mass spectrometers on-site, you'll usually find a Waters engineer nearby. If we encounter a problem, we can easily contact them and they'll often assist on the spot. It's convenient to have this support available."

"We focus on adapting to the diverse needs of our clients. A key element, in my view, is our commitment to keeping up to date. We're very much forward-thinking, so we're planning all year round. If capacity reaches a certain point, then we bring in new instrumentation. And it's not just about replacing like for like; it's about future proofing, about what's the next step beyond that. We invest in instrumentation that fits our capacity requirements and gives us something extra, whether it's increased sensitivity or other features that meet our customers' needs as they evolve."

MS. HOLLIE ADEY
Principal Scientist, HT Analytical, at Cyprotex Alderley Park Site.

Ms. Hollie Adey is a Principal Scientist at Cyprotex and co-leads the HT Analytical team at Alderley Park.

Investments in Waters software and instrumentation, most recently the Waters Xevo™ TQ-S micro Triple Quad Mass Spectrometer, have played a key role in Cyprotex's ability to develop its own high-throughput systems to screen potential new drugs more efficiently and more rapidly — increasing the speed of the drug discovery process and reducing costs for its customers.

CHALLENGES OF ADME AND PHARMACOKINETIC SCREENING

The pharmaceutical industry faces significant challenges with rising R&D costs and high failure rates in late-stage clinical trials. In the early 1990s, poor pharmacokinetics contributed to about 40% of late-stage drug failures. However, integrating early ADME assessments into the drug discovery process has made a notable impact, reducing these failure rates to less than 10% by the year 2000.[1] While progress has been made in addressing these issues, today the industry is focused on improving *in vitro* toxicity testing methods to combat rising attrition rates in areas such as toxicology and clinical safety.

Accelerating the path to market for a drug can significantly slash R&D expenses throughout the phases of drug discovery and development. In the mid-1990s, a parallel approach to drug discovery was adopted where optimization of potency, selectivity and ADME-Tox was performed simultaneously.[2]

This method has resulted in improved lead quality by finding a balance of safe, effective compounds with favorable ADME properties, thereby leading to shorter timelines and higher success rates.

Since Cyprotex's founding in 1999, increasing demand for ADME-Tox services has sparked its rapid expansion, and today more than 200 employees work at the Alderley Park location. With a number of scientific organizations in close proximity, Ms. Adey explains that the company's location offers convenient access to Waters support personnel:

"For example, a Waters engineer conducts annual reviews with us, where we discuss breakdowns we've experienced, identify any trends, and explore measures to reduce downtime. These solutions could involve additional training, ensuring availability of spare parts, or optimizing preventive maintenance schedules."

With its own extensive array of scientific equipment, Cyprotex's HT Analytical team is solely responsible for the maintenance and operation of its analytical instrumentation.

"We optimize thousands of compounds per month, and data acquiring time per batch can be anything from a few hours to overnight runs, giving us the capability to run several different batches within this time. A typical start to the day for the HT Analytical team involves assessing the instruments and running system suitability checks to make sure the instruments are performing to the expected level, if not this information can aid troubleshooting and maintenance can be performed promptly. Assay data troubleshooting also aids diagnosis of any instrument issues."

MS. HOLLIE ADEY
Principal Scientist, HT Analytical, at Cyprotex Alderley Park Site.

Next, half of the HT Analytical team focuses on setting up jobs for optimizations with new compounds, while the other half ensures the instruments are ready for the upcoming night's assays. Cyprotex supports its employees with flexible working schedules, with coverage typically spanning from 7:00 AM to 6:00 PM to provide support to the assay teams throughout the day. Ms. Adey continues:

"Our processes are designed to support early drug development, but we also offer DDI testing which is usually performed later in the development process. Clients will supply us with very limited information regarding the compound/s, often just the molecular weight. We perform generic assays across the ADME-TOX field but we also offer client specific variables/assays dependent on our clients' needs."

WATERS INSTRUMENTATION

Effective management of resources is essential for Cyprotex's operations. In 2017, the company invested in three Xevo TQ-S micro Triple Quad Mass Spectrometers to increase capacity. Since then, they've added another four Xevo TQ-S micro to their lineup of high-throughput instrumentation. Cyprotex has found the small footprint of the instrument in combination with the consistent low levels of quantitation with a wide dynamic range provides the robust performance the company needs, even with the most complex sample matrices. Ms. Adey explains the advantages the instruments provide:

"Our setup is very generic, with every instrument configured identically for consistency and efficiency. Whether assays run on one or three instruments, the results remain the same. This uniformity is crucial for ensuring consistency across our operations. Also, as sensitivity requirements from our clients increase, the capabilities of the Xevo TQ-S micro enable us to provide the best solutions for our clients."

The Xevo TQ-S micro can reproduce high-quality analytical performance injection after injection, even with highly complex sample matrices. Reliable instrument operation maximizes laboratory efficiency, delivering outstanding sensitivity for such a compact instrument. In addition, the Xevo TQ-S micro also possesses other software functionality, which is put to full use by the HT Analytical team. QuanOptimize automates and optimizes method development for large compound sets, while IntelliStart™ undertakes automated system checks to ensure optimal performance.

"We require a high level of robustness, ensuring reliability even during long runs with extended injection times. When optimization is necessary, we have tools like Waters QuanOptimize at our disposal. Additionally, we utilize IntelliStart for infusion processes to further enhance efficiency and accuracy."

MS. HOLLIE ADEY
Principal Scientist, HT Analytical, at Cyprotex Alderley Park Site.

When navigating the transition from older instruments to newer models like the Xevo TQ-S micro, companies like Cyprotex must consider ease of integration and data migration. Ms. Adey points out that the ability to seamlessly transition from older Waters instrumentation to new Xevo TQ-S micro stood out as a key benefit during this transition period.

"Software compatibility is a crucial consideration. When we're purchasing new analytical equipment, we prioritize its compatibility with our in-house LIMS system. If it's for capacity reasons, we might not have much time to install and fully establish within our processes. We need something that can be quickly set up and is ready to use. Space is another factor; we need to consider the instrument's footprint. Additionally, data size is important since we need to ensure audit traceability. We have clients over several years, who during this time request minimal changes for data comparison. All changes go through rigorous validation testing to demonstrate consistency while also showing the client the benefit of this change – for example, lower levels of sensitivity. Clients can analyze the same compound over several incidences and expect consistent results every time."

The StepWave™ ion guide in the Xevo TQ-S micro is designed to cope with the challenges in the modern laboratory that are produced by high-sample throughput and difficult matrices. Neutrals and gas load are passively removed for enhanced transmission with the ions actively transferred into the mass analyzer, improving sensitivity and robustness.

"Surprisingly, we don't clean the StepWave that often, which speaks to the robustness of the instruments. It's not a task we need to perform frequently."

MS. HOLLIE ADEY
Principal Scientist, HT Analytical, at Cyprotex Alderley Park Site.

Cyprotex works to create flexible, resilient lab workspaces that can adapt to new scientific research requirements as they come along. As such, the company also invested in the Waters Xevo TQ Absolute Triple Quad Mass Spectrometer and the Waters ACQUITY™ Premier UPLC™ System for projects involving challenging compounds that require even higher levels of sensitivity and have specific chemical characteristics that require an inert LC system. Ms. Adey explains:

"We have experience in-house with several different compound chemistries including PROTACs, peptides and lipids. This is where we offer the Xevo TQ Absolute – an upgraded instrument from the Xevo TQ-S micro – and the ACQUITY Premier UPLC system, offering an inert system with increased sensitivity, especially in negative ion mode. A dedicated method development instrument means we can offer our clients a non-standard approach to fit the specific compound requirements."

The HT Analytical team uses seven Xevo TQ-S micro across its high-throughput instrument lineup.

INCREASED CAPACITY

Acquiring new equipment and upgrading infrastructure can be costly for companies like Cyprotex – not only the initial purchase of instruments but also ongoing maintenance, calibration, and operational expenses.

Scaling up also may disrupt existing workflows, leading to inefficiencies or bottlenecks. As a result, Cyprotex always looks ahead to what it needs to meet the future needs of their customers.

"We are constantly planning and keeping an eye on Waters to learn about their next new instrument. For us, it's often an upgrade of requirements. For instance, a particular assay may require higher sensitivity. In such cases, we would transition to different instrumentation to fulfil client needs — this could be lower levels of detection or high-throughput of samples."

MS. HOLLIE ADEY
Principal Scientist, HT Analytical, at Cyprotex Alderley Park Site.

Additionally, Cyprotex continuously monitors capacity to determine the need for new instrumentation. Currently, its instruments are running at up to 80% capacity. Ms. Adey describes the importance of the company's relationship with Waters when managing laboratory resources:

"When our instruments consistently operate above 80%, downtime becomes a significant concern. Especially for high-throughput operations, having multiple instruments is essential. We initially implemented the Xevo TQ-S micro after the Xevo TQ-MS was no longer being manufactured. Due to the crossover with software and similar hardware, this was easy to establish within the HT processes. We only needed some updates to our in house LIMS system and additional training to become fully functional within the laboratory."

ENVIRONMENTAL IMPACT

Wherever possible Cyprotex considers the environmental impact of its operations, including re-using packaging and recycling cardboard, paper, tin, wood, ink cartridges and toners. Within its offices and laboratories, the company works to reduce its energy consumption.

Cyprotex also expects all suppliers and partners to work towards and uphold similar ethical and moral standards, so the compact design and energy efficiency of the Xevo TQ-S micro was a benefit, especially in conjunction with the recent Accountability, Consistency and Transparency (ACT) label awarded to the instrument by My Green Lab.

"Evotec, our parent company, focuses on sustainability for the company and our clients. This includes a sustainability pledge by donating trees, reducing plastic usage by replacing them with more environmentally friendly materials, and reducing electrical use. From what I've discussed with Waters, it's been on their mind for quite a few years too."

MS. HOLLIE ADEY
Principal Scientist, HT Analytical, at Cyprotex Alderley Park Site.

Cyprotex invested in the Waters Xevo TQ Absolute for projects requiring higher levels of sensitivity.

NEXT STEPS

Currently, Cyprotex is planning for its future instrumentation needs, which could include a further investment in the Waters Xevo TQ Absolute Triple Quad Mass Spectrometer.

"The Xevo TQ Absolute offers improved negative ion sensitivity, which addresses some customer needs. As the demand for method development and high-throughput capabilities rises, it becomes essential to have dedicated instruments tailored for handling specialized compounds. We've observed distinct trends in various compound types, including PROTACs, smaller compounds, peptides, and lipids, highlighting the diversity beyond our standard small molecular weight generic methods. Understanding client needs and accommodating different capacities is crucial."

MS. HOLLIE ADEY
Principal Scientist, HT Analytical, at Cyprotex Alderley Park Site.

In 2024, plans for Cyprotex also include a collaboration with Waters and Trajan on rapid chromatography services. This initiative involves upgrading to the PAL 3 dual-head CTC system, currently being tested alongside one of Cyprotex's Xevo TQ-S micro instrument. Ms. Adey elaborates:

"Currently, we're running gradients at approximately 1.2 minutes per injection, but our goal is to bring this down to around 50 seconds per injection with the rapid chromatography system. Implementing changes requires thorough justification, especially when it involves client-facing aspects like data delivery. We need to assure our clients that while we're aiming to provide faster results, the quality will remain consistently high. We prefer the PAL instruments due to their robustness and compatibility with our setup."

References

1. Kola I and Landis J (2004) Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 3; 711-715.
2. Manly CJ et al., (2001) The impact of informatics and computational chemistry on synthesis and screening. Drug Discov Today 6(21); 1101-1110.

Waters™

Waters Corporation
34 Maple Street
Milford, MA 01757 U.S.A.
T: 1 508 478 2000
F: 1 508 872 1990
waters.com