A Deeper Understanding of Genotoxic Impurities

Waters ACQUITY systems with mass detection help to keep ahead of changing regulatory requirements

Technology: Waters ACQUITY QDa, ACQUITY Arc, and ACQUITY PDA Dectector

CHIA TAI TIANQING PHARMACEUTICAL GROUP (CTTQ)

Chia Tai Tianqing Pharmaceutical Group Co., Ltd (CTTQ) is a multinational pharmaceutical company headquartered in People's Republic of China (PRC). The company was founded in 1969 in Lianyungang in Jiangsu Province and has since grown to more than 8000 employees. The company is the leader in liver health in China, is named in the top 20 of the 'Top 100 Pharmaceutical Enterprises in China', and is one of the 10 fastest-growing pharmaceutical manufacturers in PRC, with more than $1.91bn dollars in sales revenue in 2015 (13.2bn RMB).

CTTQ is innovation-driven and focusses on R&D to develop new technologies and patented products. Currently, CTTQ manufactures over 50 prescription medicines in five core therapeutic areas: liver disease, oncology, respiratory diseases, antibiotics, and diabetes. CTTQ sells both active pharmaceutical ingredients (APIs) and finished dosage forms (FDFs) in global markets including Americas, Europe, Asia, and Africa.

The company has two R&D Centers (known as The Institute) which employs more than 820 staff. Alongside these, CTTQ boasts three manufacturing sites and four joint laboratories, plus overseas sites in Spain and the USA. A further 300 staff are employed in QA and QC at the manufacturing facilities. All CTTQ sites are fully cGMP compliant.

More than 8.5% of sales revenue (720m RMB in 2015) is reinvested in R&D each year, with around 180 projects in the product pipeline. State Category I innovative drug projects make up over 30% of the development activity, with generics, APIs, and pharmaceutical ingredients making up the balance. CTTQ's two R&D Centers are based at Lianyungang (the headquarters) and Nanjing. The Lianyungang R&D Center was founded in 1985 and hosts the Analytical department, while the Synthetic Chemists are based in Nanjing.

CTTQ R&D Institute, Lianyungang, China.

WORKING WITH WATERS

CTTQ has enjoyed a working relationship with Waters since 2010 and uses Waters™ Xevo™ QTof, ACQUITY™ QDa™, ACQUITY Arc™, PDA Detector™, and UPLC™ systems. The laboratories at CTTQ have close collaboration with Waters in several areas, turning to them as an educational resource, participating in a variety of academic exchange activities at Waters' hosted events. In these, Waters invites customers across different industries to share experiences and explore best practices to optimize current workflow and improve end results.

Waters ACQUITY systems at the R&D Institute, CTTQ.

A SNAPSHOT OF THE INSTITUTE

Jiang Zhulian is the director of the R&D Institute for CTTQ at Lianyungang. Director Jiang is responsible for all laboratory operations and administration. The core R&D activity in The Institute encompasses antiviral products, anti-tumor products, 5-HT3 antagonists, respiratory medicine, and liver protection products. Between 60 and 80 staff work on analysis, deployed across six different laboratories, one of which is the International Drug Registration laboratory. The R&D team at CTTQ consists of chemists, biologists, pharmacologists, analysts, and medical scientists.

"In the past our work at the Institute (formerly Lianyungang Institute of Analysis) was on generic drugs, but in recent years we also work on innovative drugs, especially small molecule drugs. Since 2016 we have also worked on insulin drugs," outlines Director Jiang Zhulian. Director Jiang explains that The Institute works on many dozens of projects each year, with most recently, generic drug consistency assessment being the main one.

The Institute's R&D Center analyzes all the samples generated in drug development throughout CTTQ. Each project is typically between 20 and 30 different sample sets, resulting in about 40,000 injections.

The Institute at CTTQ (initially at Lianyungang R&D Center) began to use Waters' products in 2010. Having had a good experience with their Xevo QTof, CTTQ turned to Waters again and decided to install an ACQUITY QDa Detector on to their existing Waters ACQUITY UPLC H-Class System to complement the information that they were getting from the Photodiode Array (PDA) Detector.

In the same year, the Synthesis department at Lianyungang acquired a second ACQUITY QDa, a second PDA Detector, and a 2D ACQUITY UPLC System. Having direct access to the ACQUITY QDa meant that results were available immediately, improving efficiency and providing significant cost savings.

In 2016, the Analysis department added a further ACQUITY QDa, another PDA Detector, and an ACQUITY Arc System. These were added for genotoxicity analysis, to align with the existing HPLC method. At the same time, CTTQ's QC lab located in the Runzhong API factory added an ACQUITY QDa, a PDA Detector, and an ACQUITY UPLC H-Class System to enable method transfer from the R&D lab in Lianyungang's Analysis department into the API manufacturing site.

Also during 2016, the Synthesis department located in Nanjing's R&D Center added their first ACQUITY QDa, PDA Detector, and ACQUITY UPLC H-Class System, to enable them to bring work in-house that was, until that point, sent out for contract analysis.

Now, all the laboratories across the three sites use the ACQUITY QDa Detector with common methods and protocols.

PUTTING THE ACQUITY QDA DETECTOR AND ACQUITY ARC SYSTEM TO WORK

The Institute at Lianyungang was the first site to install Waters' ACQUITY QDa and UPLC PDA detectors, and is also the sole site with an ACQUITY Arc System. The ACQUITY QDa Detector is used by the method development team for the specific needs of detecting genotoxic impurities (GTIs) at very low levels. Previously the laboratory used the QTof for this and find that using the ACQUITY QDa enables them to release the high resolution QTof instrument for more complex work.

Director Jiang explains: *"The lab uses ACQUITY QDa on our existing ACQUITY UPLC H-Class System for method development. We compare the mass data from the ACQUITY QDa with UV data for qualitative and quantitative compounds. Corresponding ACQUITY QDa methods have been developed for different kinds of genotoxic impurities."*

The ACQUITY Arc System provides faster throughput for routine HPLC analysis and for routine rapid liquid phase method development.

> "ACQUITY Arc is a dual-flow system that can be used as an HPLC to reproduce our existing methods, or we can change the flow to perform UHPLC analysis on the same instrument. Compared with HPLC, the ACQUITY Arc can shorten the analysis time, speed up existing methods, improve the efficiency of method development, and facilitate an increase in throughput."
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> JIANG ZHULIAN
> *Director of R&D Institute at CTTQ*

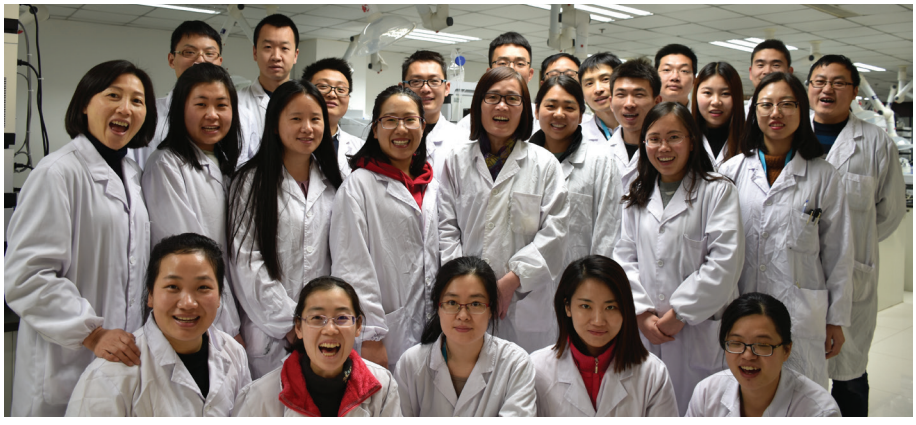
Director Jiang outlines the background to GTI testing, and their use of the ACQUITY QDa: *"Analysis of genotoxic impurities is currently a hot topic in research. Of course, some of our samples require analysis for genotoxic impurities. Conventional UV analysis did not provide us with sufficient sensitivity, therefore The Institute uses both QTof and GC-MS for analysis. GC-MS is operated by our skilled teams, and has a high equipment investment. It needs a large amount of space in the lab and requires professional MS training for those who work with it. While we use both these technologies, we did not want to invest further in more labspace and more staff, so, as we were keen to find a solution to help us detect the GTIs in our samples, we turned to the ACQUITY QDa Mass Detector to solve these problems. The ACQUITY QDa can be integrated directly with existing instrumentation and it is especially suitable for the detection of low-level components or non-UV absorbing compounds."*

"Since installing the ACQUITY QDa Mass Detector, the GTIs can be detected quickly. Since we have been using the ACQUITY QDa, throughput has improved significantly and we have increased confidence in the results that we are generating."

JIANG ZHULIAN
Director of R&D Institute at CTTQ

"ACQUITY QDa meets our testing requirements for method development and for impurity analysis, especially for the compounds that are not detected using our conventional UV detection. (These were analyzed by CAD detector previously, which doesn't works well for nitro compounds and less well for analysis of sulfonate compounds). The ACQUITY QDa works well – it performs its mass detection function efficiently. I would recommend the ACQUITY QDa for any similar laboratory that needs this functionality combined with UV detectors, as it provides the lab with a complete testing program."

CTTQ reports that analysis time has been cut by two-thirds, resulting in significantly improved productivity. Furthermore, as well as the time and cost savings provided by doing the work in-house, there are further cost savings in solvent usage. The lab uses the ACQUITY QDa overnight to run analysis of genotoxic impurities, and continues to use the QTof for other non-routine projects.



The R&D team at CTTQ, Lianyungang, China.

GENOTOXIC IMPURITIES

Genotoxic Impurities (GTIs) are impurities in pharmaceutical products that have the potential to react with DNA and induce genetic mutation, which may consequently lead to cancer. Pharmaceutical companies are therefore under increased scrutiny by the regulatory authorities to control these unusually toxic impurities at low levels to ensure quality of the drug product and patient safety.

It is therefore essential to have a reliable and highly sensitive method for the UV level detection of mutagenic impurities in both drug substances and drug product assays.

Waters ACQUITY systems at the R&D Institute, CTTQ.

ACQUITY QDA DETECTOR AS A RESEARCH TOOL

Director Jiang explains that the ACQUITY QDa is also used by CTTQ Institute as a research tool: *"As well as analysis of genotoxic impurities, we also use the ACQUITY QDa for detection of unknown compounds. It reduces our risk of accidental co-elution of analytes, while the mass detection helps to identify trace components."* The mass detector also helps CTTQ to improve the quality and efficiency of each analysis, and eliminates the need to run additional tests or introduce other techniques (saving further time).

There are additional user benefits that met CTTQ's wish to make the most of its existing labspace: *"The ACQUITY QDa can be placed directly on the top of existing instrumentation in the lab, taking up less bench space and floor space. The detection of low content of components and impurities plays a significant role, especially in the detection of genotoxic impurities, greatly improving our work efficiency."*

Energy consumption is lower than traditional large mass spectrometers too, and the ACQUITY QDa can be powered down when not in use, saving further energy costs. In addition, because the ACQUITY QDa does not require excessive maintenance it is possible to maximize system uptime. The ACQUITY QDa is already used around-the-clock, running 24 hours in the labs.

Having decided to install an ACQUITY QDa in The Institute, CTTQ summarizes its key advantages as being easy to learn and use, even for those chromatographers who have limited experience of mass spectrometry.

"The ACQUITY QDa is extremely easy to operate – it is very similar to conventional UV detectors and can be controlled using existing Empower™ Software without any need for additional or specialized mass spec knowledge. Both hardware and software are easy to use. To get up and running on the ACQUITY QDa needs only very basic training. This makes the ACQUITY QDa very easy to adopt in all our laboratories."

LOOKING AHEAD

Director Jiang outlines how CTTQ is evolving in its use of the MS detector: *"We have been using an ACQUITY QDa now for more than two years. It is compatible with our routine chromatography equipment and because it is pre-optimized, is suitable for most sample analysis, providing better data and insight as well as confidence in experimental results."*

"Our analysts can achieve consistent, high quality mass spectrometry data in routine assays without the need for any special training or expertise. This eliminates the need to outsource the analytics to CROs, and this saves our analysts time – they do not have to wait for the results. Because of this, the ACQUITY QDa will be widely used in our future analysis. It saves us time and money."

JIANG ZHULIAN
Director of R&D Institute at CTTQ

Director Jiang summarizes: *"As a pharmaceutical research Institute, the ACQUITY QDa is well suited to our needs. It offers intuitive operation making it easy for the user. It provides us with more information on the sample than we could achieve without it. It integrates seamlessly with our existing LC methods. The ACQUITY QDa increases the efficiency of our lab and it gives us increased confidence in the results that we produce."*

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