Mission Impossible Made Possible

How Waters brought mass detection to the masses with the ACQUITY QDa® Detector

Jonathan Scott, Product Manager - Mass Spectrometry, Waters Corporation, Wilmslow, UK.

Waters has been bringing innovation to lab environments globally since 1958. Spanning labs focused on healthcare delivery and pharmaceutical development, environmental management, food safety and water quality, Waters has developed a reputation for optimising lab operations and boosting lab performance. Its portfolio of separation and analytical science, laboratory informatics and mass spectrometry offerings is widely recognised as best-in-class. But, for the driven engineers, scientists and PhDs making their careers at Waters, being 'the best' simply is not enough.

Instead, spurred by customer wants, these professionals challenged themselves to the seemingly impossible.

How so?

Bringing mass data to liquid chromatographers was a daunting task. Though the last two decades have seen mass spectrometry move from solely the hallowed halls of premier academic institutions into more routine laboratory environments, mass spectrometry has largely remained a process only for the most highly skilled analytical scientists. Waters, as an organisation, set out to determine if it would be possible to disrupt mass spectrometry by shattering barriers-to-entry by making it available in an instrument that was:

- Easy to use - with minimal specific training required for operation
- Familiar – with user interactions based around PDA operation
- Small enough to fit within or on top of an existing, bench-top liquid chromatography instrument stack

The team at Waters surmised that even though nobody before them had ever even tried, they would somehow make these attributes a reality. No matter how long it took, Waters was determined to bring mass detection to the masses.

The Challenge

The year was 2006. Waters began to hear rumblings from their customers, some of the largest pharmaceutical companies in the world and every other flavour of user, large and small, across industries, that the lack of widespread access to mass-specific data was causing problems, and, ultimately, affecting their bottom lines.

Chromatographers simply did not possess the training or experience necessary to access mass data. This conundrum was causing workflow challenges and limitations within labs. An absence of immediate access to mass data, specifically, a delay in receiving guidance from mass spectrometry experts, either internal or external, limited the level of certainty and confidence labs could align with their results.

Resulting inefficiencies were innumerable. For instance, method development within groups was slow. Quality was compromised. Analyses were conducted across multiple detectors, rather than consolidated into a single method. Lab groups responsible for building methods were forced to perform less specialised mass spectrometry analysis. This was because the labs that should be responsible for more routine work did not have the experience they needed to complete the tasks with confidence. Ultimately, a domino effect of inefficiencies resulted as method developers were then distracted from their primary tasks.

To put these workflow challenges into real-world perspective, consider that minimal exposure to mass-specific data within the liquid chromatography sphere was hypothetically creating:

- Delays in critical pharmaceutical drug development
- Lack of certainty in methods profiling hazardous substances in common, everyday items
- Food quality control inconsistencies

The Process

To combat these problems, internal teams within Waters set out to create a novel product, one that would empower non-expert users through immediate insight into mass data. The goal? To drastically, and quickly, empower a much larger army of scientists than ever before with access to the confidence and selectivity that mass data and detection provides.

Ultimately, this new product, the team hoped, would open the floodgates to new scientists and applications. By driving efficiencies within countless lab environments, the benefits to industry at-large had the possibility to be both exciting and game changing.

"We're always trying to be on the cutting edge of what is possible," said Daniel Kenny, Director of MS development at Waters. "[This] is very, very different in concept. We're not going to try to build the biggest and the best, per se; we're going to build something very targeted, very specific and very focused on a particular need.

"And we're going to make it small and compact and it's probably going to be the smallest…[instrument] that we've ever manufactured. But in some way, that requires and involves a whole new mindset and a whole different set of innovations and inventions to actually make that possible."

Waters was building the first-ever bridge between two previously disparate landmasses: liquid chromatography and mass spectrometry.

Making a Business Case

By 2008, the project and product marketing teams at Waters were presenting to senior leadership about the need for a general-use mass detector. Over several years, the teams determined as a group that a much wider audience than Waters was then servicing had a need to immediately receive and interpret useful, analytical mass data. This would require Waters to take a different approach to mass spectrometry than ever before.

"How do we simplify this to a level to get this to an audience where it just becomes a detector?" said Ed Sprake, Senior Product Manager for high-volume quadrapole MS at Waters. "It's a means to an end, rather than this big complex piece of kit that you have to learn how to use."

Now, all that remained was to transform this idea into reality. This would not be a simple task.

Querying the Field

Before moving 'full steam ahead' and putting aspirations into action, Waters did its due diligence to understand what exactly its customers needed, and to ensure that this was indeed something they would want in their labs. In 2011, the company conducted six external focus groups across the globe, bringing together customers from the pharmaceutical, food and chemical industries for anonymous sessions. The goal was to understand if broad demand aligned with Waters' expectations, and also to identify the highly specific criteria that would spur lab decision-makers to purchase a separations system with embedded mass detection.

The consensus among all of the groups, as expected, was that lab environments were clamouring for this type of instrument, but that vendors needed to make a mass detector easy to use, 'like the PDA detection' then available. Additionally, users specifically wanted a compact detector that could serve as an integrated part of an LC stack.

An integrated team of Waters product managers, product marketers, subject matter experts, engineers, designers, and more, had its marching orders. 'Project Kestrel', as the instrument we now call ACQUITY QDa Detector was then known, was well underway.

The Collaboration

It all started with a brief for a 'mini MS detector'. Would it be possible to build a compact and intuitive mass detector? What would the compromises be, if so?

From there, hundreds of individuals within Waters were involved in the ideation for and development of the ACQUITY QDa. The team spanned the US, Europe and Asia. What's most interesting is that various teams were working on their own design initiatives concurrently, so staying in incredibly close contact was imperative.

How did they do it?

There were countless cross-functional, face-to-face meetings weekly. Subject matter experts who understood how each component should work, from both a design and manufacturing perspective, were always at the ready. Teams across geographies shared the same computer-aided design (CAD) programs and could check-in on each other's progress through video conferencing.

The entire team was working toward a common goal: to make a game-changing product that would forever alter the lab environment for the better. Through coordinated check-ins and two-way dialogue, ACQUITY QDa became a reality. Given the scope of the project, the timeline from 'thinking to launching' took a full four years. Comparatively, other products usually go to market within 18 months.

Design and Manufacturing

Troubleshooting the Seemingly Inconceivable

After internal subject matter experts and design team leaders made a cursory determination that it was indeed possible to provide a mass detector with a greatly reduced size, without compromising performance, then the collaborative team really got down to business.

In the world of complex scientific instrumentation development, teams typically use the architecture of a previous instrument to form the basis for a new one. Only infrequently does development require a 'start-from-scratch' approach. This was one of those times.

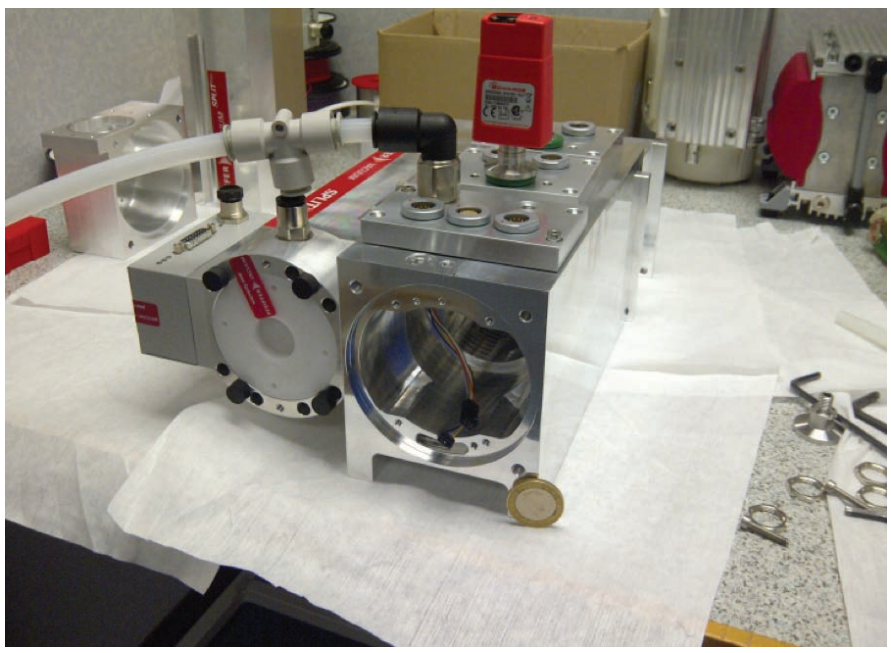
For ACQUITY QDa, the team was only able to repurpose one component from previous generations of instrumentation. Everything else was completely re-designed and re-engineered from a performance point of view. The photomultiplier tube for ion detection was the right size and worked perfectly. The team thought, "Why fix it if it's not broken?"

Beyond this single part, the team was compelled to reimagine everything else.

Research, Research, Research

In 2010, before focus groups even confirmed Waters' belief that its new instrument idea had great promise, the research phase began. For two-and-a-half years, until product development for the ACQUITY QDa launched in earnest in mid-2012, Waters' research group engaged in an ongoing feasibility study. Hand drawings, blueprints, CAD drawings and 3D computer models, plus 3D printed components, were integral to figuring out just what might work.

As part of this process, the team created various 'Frankenstein's Monsters', ad hoc physical prototypes consisting of various existing parts.



Early ACQUITY QDa Detector prototype

"During the feasibility stage, we'd use existing mass spectrometers and make some kind of Frankenstein-monster," said Jonathan Pugh, Principal Consulting Analytical Scientist at Waters. "We'd take half of one and marry it with another half, just making test rigs, really, to look at individual elements with whatever we've got available."

From this 'messy' start, they worked to refine the ACQUITY QDa, iteration by iteration.

"Some risks, some problems cropped up that we never forecasted for," said Ian Trivett, Principal Mechanical Design Engineer at Waters. "We never realised they were going to be there, and so we had to adapt and resolve those on the fly. It's the consequence of stepping out of your comfort zone in the design of the instrumentations that you're quite familiar with to something that's new."

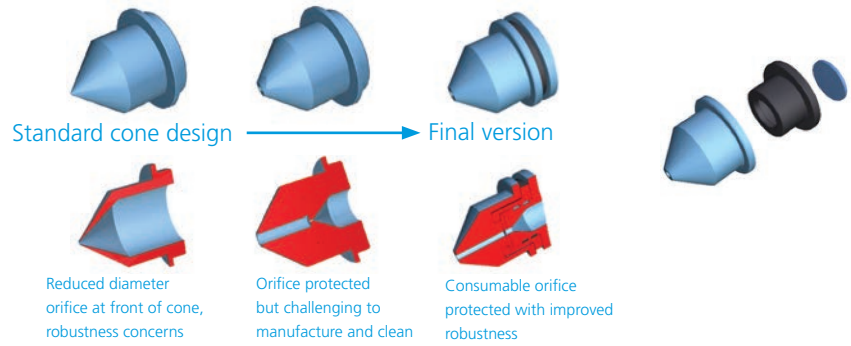
Accessibility and 'Geekery'

The team conquered several technical challenges in the quest to develop the ACQUITY QDa as the most accessible mass detector that are worth noting, specifically:

- Reverse cone geometry with reduced orifice diameter: this was a requirement that the team had to achieve due to miniaturisation needs, but it ultimately led to two major user benefits. Reduced maintenance through improved robustness and a consumable orifice.
- A single-piece electrospray probe: this technical achievement ensures that users can fit or replace a probe just as they would plumb LC tubing.
- An internal calibrant: users can rely on this to automatically calibrate the instrument at the push of the on button without any mouse clicks, guaranteeing data accuracy.
- Pre-optimised source geometry and parameters allowing analysis without sample-specific adjustment.

Waters' tackling of these challenges has led to three new, related patent filings.

Reverse cone geometry evolution...

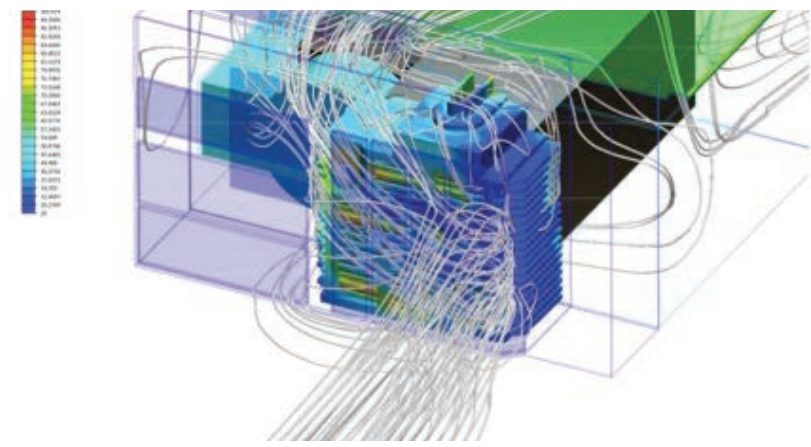


Evolution of reverse cone geometry

"Each area had its own iteration, where it was designed, reviewed, changed, designed, reviewed and changed," said Marcus Dawber, Mechanical Design Team Leader at Waters.

Feeling is Believing

Given all of the challenges that the team confronted, 3D design and simulation technology was critical to the ideation process. While design ideas were initially sketched and then transmitted into 2D CAD, the Waters team converted their initial ideas into solid geometry as soon as possible. The team found that seeing components in 3D, or physically holding them sooner rather than later, greatly aided their process. They relied on rapid prototyping techniques, conducted computational fluid dynamics (CFD) analysis and utilised the 3D printer that the team had on-site to evaluate components' real-world viability in near real-time.



Computational Fluid Dynamics Analysis

Electronics Design

Miniaturising electronics components so that mass detection could be integrated into the liquid chromatography stack also proved difficult. Here, the team relied upon field-programmable gate array (FPGA) chips and the digital circuit functions that reside within them. Another approach allowed the Waters team to use electronic PCBs to conduct mechanical as well as electrical functions. This concept is important because making parts multifunctional, given limited space to work with, became a key philosophy of the project.

With reduced power requirements, the instrument can run effectively at 464W, meaning it does not generate substantial heat and is environmentally responsible. In contrast to legacy instruments, this is up to an 85% reduction in power consumption. Additionally, the nominal voltage range of the ACQUITY QDa is 100 - 240 V, allowing operation across multiple geographies without expensive adaption to laboratory infrastructure.

In the end, the team was able to create a 'jigsaw' design approach, where all of the various mechanical and electrical components fit together in a manner that led the overall instrument to be smaller while still reliable. This meant the relevant circuitry on the single control card was deliberately positioned to allow direct connection to the instrument componentry, minimising any wasted space.

Beta Testing

Roughly twenty labs across the globe were able to take advantage of ACQUITY QDa in beta. This real-world exposure to the instrument provided invaluable feedback to the project team. The team reacted to customers' experiences with ACQUITY QDa during the testing phase to improve it for wider distribution.

The Results

Industry and academia have adopted the ACQUITY QDa at a rapid rate making it Waters' fastest selling MS product in history.

"The main reason behind the success of the ACQUITY QDa is the fact that we understood what the barriers were for people to adopt this sort of technology," said Kenny. "We recognised those barriers and we've done our best to remove them."

"The ACQUITY QDa Detector has been specifically designed for chromatographers. It is as easy to use as an optical detector and does not necessitate specific training or expertise. The detector is well adapted to speed up the method development process through efficient peak tracking and minimises the risk of coelution."

Davy Guillarme, Senior Lecturer, School of Pharmaceutical Sciences at University of Geneva, University of Lausanne.

Dan Kenny, Director of MS Development at Waters Corporation

The ACQUITY QDa® Detector with the ACQUITY UPLC® I-Class System

"If you design something completely from scratch, you've got an open book so you can really optimise everything fully," said Richard Moulds, Consultant Electronics Engineer at Waters.

Waters' customers have quickly benefited from access to the ACQUITY QDa. For example:

- Chromatographers with no MS experience are now leveraging mass-specific data and eliminating the prior delays waiting for results from core MS labs.
- Push-button simplicity has removed the obstacle of introducing mass-specific data to chromatography labs.
- The small footprint and low noise levels ensure that it enhances a lab's capabilities without causing any disruptions.

As a consequence, many labs now implementing the ACQUITY QDa Detector, including those in heavily regulated environments, are realising important workflow changes leading to significant return on investment.

The Future

The Waters team has been energised by the accomplishment of building, and truly succeeding at, an endeavour that others in the company's competitive space deemed too difficult to pursue. So now, Waters will look to determine how it may apply knowledge gleaned from the ACQUITY QDa development to improve the ease of use and user experience on future instruments.

New Tribrid Mass Spectrometer with Improved Sensitivity Redefines the Limits of Protein and Small Molecule Quantitation and Characterisation

As the newest addition to the pioneering line of **Thermo Scientific** Orbitrap Tribrid mass spectrometers, the Thermo Scientific Orbitrap Fusion Lumos Tribrid Mass Spectrometer is designed to expand performance in advanced proteomics, biopharma and metabolomics applications, including quantitation using isobaric tags, low level PTM analysis, data independent acquisition (DIA), and top down proteomics. The new instrument features enhanced sensitivity resulting in improved analyte detection, characterisation and quantitation, enabling scientists to perform more comprehensive sample analyses faster and with better accuracy than ever before.

To achieve proteome-wide coverage, the Orbitrap Fusion Lumos MS combines the versatility of a Tribrid system with the selectivity of Orbitrap technology, and the sensitivity and speed rivalling that of a triple quadrupole instrument. The new features include: brightest ion source - up to 5x improvement in limits of quantitation for peptides and small molecules; Segmented quadrupole mass filter powered by Advanced Quadrupole Technology – increase in selectivity of the analysis by improving isolation resolution, ion transmission and peak shape; Advanced Vacuum Technology – enhancement in detection limits by improving transmission of ions to the Orbitrap mass analyser; High-Definition Electron-Transfer Dissociation (ETD HD) – improvements in dynamic range and detection limits by performing ETD reaction on a larger precursor ion population, enabling greater sequence coverage in less time; ADAPT Technology – adjusts key parameters 'on-the-fly' without prior knowledge of sample amount, enabling maximum protein identifications from samples of unknown concentration in a single run and saving the user time and sample.