[PRODUCT SOLUTION]

Waters
THE SCIENCE OF WHAT'S POSSIBLE.™

ACQUITY UPLC H-CLASS METHOD DEVELOPMENT SYSTEM

Increase efficiency. Reduce costs. Improve analytical performance from development to QC.

AUTOMATED, RAPID QBD METHOD DEVELOPMENT IN THE PHARMACEUTICAL ENVIRONMENT

Pharmaceutical organizations recognize that Quality by Design (QbD) is a route to understand and reduce variation in order to consistently produce quality results – and satisfy business needs and regulatory requirements. Guidance from both the U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) identify analytical procedures as key to demonstrating a deep scientific understanding of processes and products.

QbD and chromatography

Since liquid chromatography is the dominant analytical technique used throughout drug development, applying QbD to the method development process can provide a better understanding of the chromatographic parameters that affect the quality of a method. Poorly-designed methods have critical consequences and their cost implications can be significant when batches of pharmaceutical product are at stake.

A well-designed method development study following QbD principles enables you to characterize and define a quality LC method, ensuring robust separations for the lifetime of your product. However, to date, designing such a study has been a slow, manual, and tedious process.

Waters makes QbD-based analytical methods possible

By automating the statistical approach to determining a fully optimized method, and running it on the only fit-for-purpose LC system designed for high-quality, high-throughput results, the Waters® ACQUITY UPLC® H-Class Method Development System makes QbD-based analytical method development a reality. This system's impact is being felt both in the laboratory and the boardroom:

- Minimize LC method development complexities
- Reduce method development timelines from weeks or months to just days
- Ensure top method performance over the lifetime of your product
- Increase regulatory flexibility to maximize productivity and financial benefits

"As QbD thinking evolves further we will see QbD become part of pharma life. The modernization of methods is starting to happen."

SEP SCI. 2010 JAN; 2(1): 8-10.

ACQUITY UPLC H-Class Method Development System.

THE CHALLENGES IN DEVELOPING AN OPTIMIZED METHOD

	WHAT YOU HAVE TRIED			WHAT YOU NEED
	Trial and error, one factor at a time	Traditional method or column scouting	Standalone QbD software approach	ACQUITY UPLC H-Class Method Development System
Experimental design	Manual	Semi-automated	Manual to semi-automated	Automated
Hands-on analyst time	High	Medium	High	Low
Instrument method setup	Manual	Manual to automated	Manual	Automated
Knowledge space	Low	Medium	High	High
Knowledge of variable interactions	None	None	High	High
Robustness	None	None	High	High
Risk of failure	High	Medium	Low	Low
Overall method development time	Weeks to months	Days to weeks	Weeks	Days

THE ACQUITY UPLC H-CLASS METHOD DEVELOPMENT SYSTEM

Develop methods with ultra performance. Execute them rapidly. Implement them with ultra confidence. Make QbD-driven chromatographic methods your organization's best asset.

The ACQUITY UPLC H-Class Method Development System helps scientists develop a robust method that is stable for the lifetime of your pharmaceutical product – in dramatically less time.

The system enables you to have a clear understanding of all the factors that affect chromatographic methods. You'll develop high-quality separations that pass validation and transfer procedures the first time, and that perform productively in operation.

Whether you're looking for throughput and quality enhancements in a single analytical study, or for process improvements that maximize analytical resources and address operational efficiency and cost, the Waters system can make a dramatic difference in your development efforts and also yield significant dividends downstream when transferring methods to QC.

Control your method, control your risk

The ACQUITY UPLC H-Class Method Development System leverages Fusion Software, a patented platform developed by our software partner S-Matrix Corporation, a leader in advanced experimental design software, to automate UPLC® method development. The system uses a QbD-aligned, multivariate approach to rapidly develop methods optimized for mean chromatographic performance and robustness. With a statistically rigorous Design of Experiments (DOE) approach, Fusion Software creates experiments, analyzes data, and presents results as visual and numeric method predictions.

This data-rich approach generates a well-defined operating space for the method, with the supporting knowledge space from an appropriate experimental design. Thus the resulting method has been designed to provide the flexibility to make any necessary process changes that are needed to meet business objectives – without regulatory risk in how a method is used downstream.

ACQUITY UPLC H-CLASS METHOD DEVELOPMENT SYSTEM: A FULLY AUTOMATED WORKFLOW

SCREEN

Seamlessly move from screening to method recommendation

To achieve an optimal method, the first phase in development involves rapid screening for the major influencing factors on selectivity: column chemistry, gradient time, buffer/pH, and organic mobile phase.

- With the ACQUITY UPLC H-Class Method Development System, we screen up to six different column chemistries, six different aqueous buffers/pHs, and three different organic mobile phases in one study.
- Waters Method Development Chemistry Kits allow the widest range of column selectivity to be screened, enabling the best possible method to be developed.

During the next phase, Empower Software processes the chromatographic results and imports them into Fusion Software, where models of the screened chromatographic factors are generated based on the critical method performance criteria that you define. Based on your analytical priorities, Fusion searches for and recommends the method that meets all of your performance goals simultaneously.

CLASS-LEADING COMPONENTS COMPRISE THE ACQUITY UPLC H-CLASS METHOD DEVELOPMENT SYSTEM

ACQUITY UPLC H-Class System

- UPLC for analytical quality and throughput
- Stackable, multi-zone Column Manager holds 2, 4, or 6 columns
- Quaternary system for multi-solvent blending, optional internal Solvent Select Valve
- Auto•Blend™ Technology automates mobile phase formulation

Fusion Method Development Software

Empower™ Chromatography Data Software

Waters Method Development and Transfer Chemistry Kits

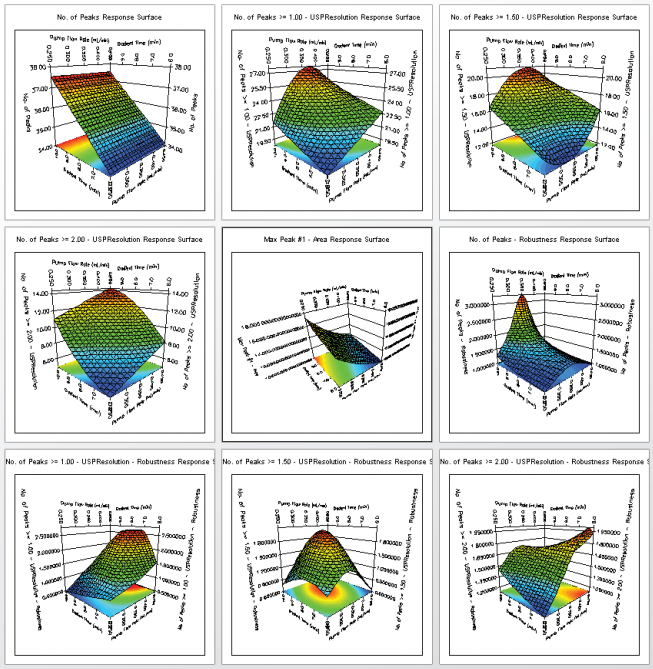
PROCESS, REVIEW, AND RECOMMEND

Visualize a meaningful method by understanding effects of interactive variables

From the data generated by the ACQUITY UPLC H-Class Method Development System, Fusion Software allows you to easily visualize the individual variables and their and interaction effects on key chromatographic responses such as resolution, peak tailing, and retention time. Fusion's Automated Optimizer assists in recommending the best method to advance for further study.

Study Variable Name	Optimizer Answer Level Setting
Gradient Time	10.00
Organic Solvent Type	Methanol
pH	5.543
Column Type	ACQUITY UPLC BEH C8, 2.1 x 100 mm, 1.7 µm

Best conditions from rapid gradient, organic solvent, pH, and column type.



Fusion Software illustrates the interaction of different method variables using intuitive 3D plots.

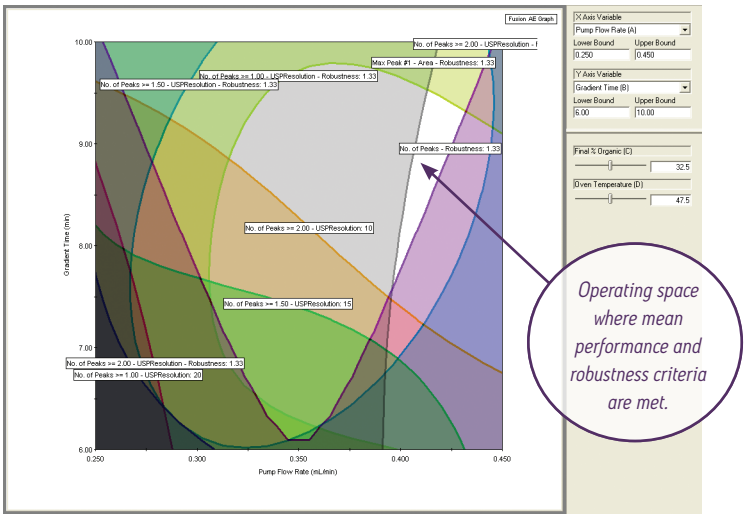
INTERPRET AND OPTIMIZE

Convert knowledge of interactions into method performance and robustness

The Fusion overlay graph provides a color-coded display of the QbD Design Space that enables you to visually interpret where the method meets the mean performance goals and robustness criteria. The predicted optimal method is easily discerned.

Study Variable Name	Optimizer Answer Level Setting
Pump Flow Rate	0.427
Gradient Time	8.85
Final % Organic	29.66
Oven Temperature	46.3

Final method conditions.

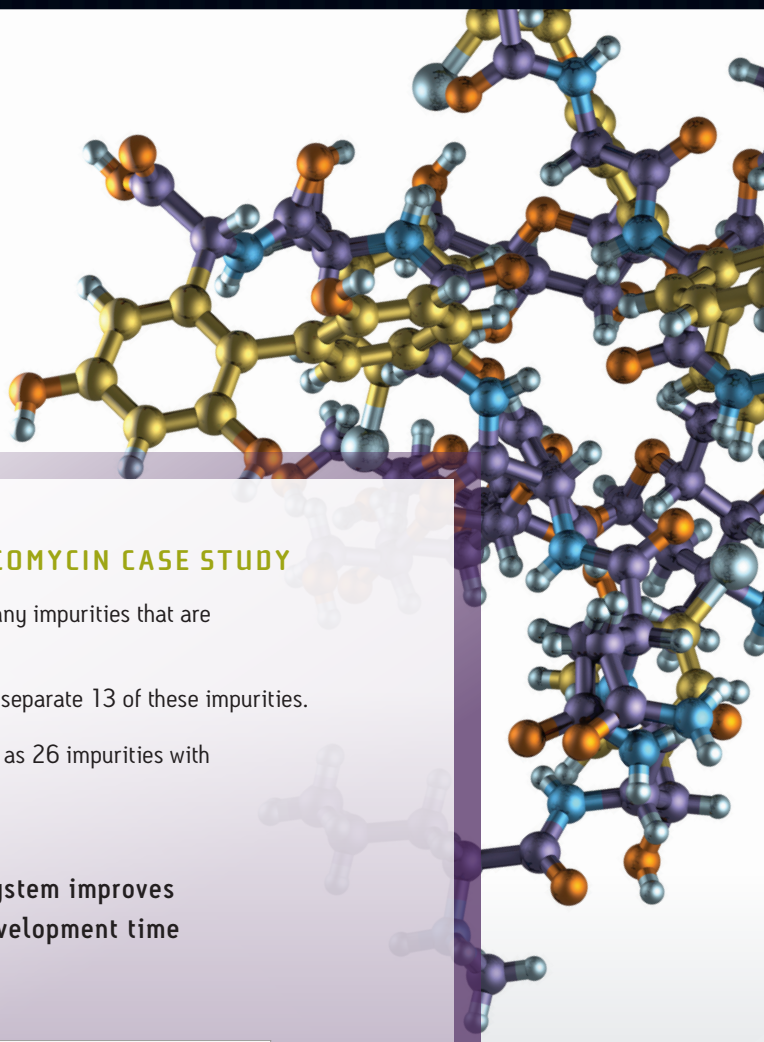


The Fusion overlay graphs allows for visualization of the defined method performance criteria. The white area of the overlay graph indicates where both the mean performance goals and robustness criteria are met – the predicted operating space. The Automated Optimizer predicts the optimized method within the operating space.

CONFIRM OPERATING SPACE

Confirmation: The results speak for themselves

Since the optimized method proposed by Fusion is based on models of experimental data collected within the statistically-sampled design space, it is expected that the predicted method compares favorably with the actual final chromatographic result.

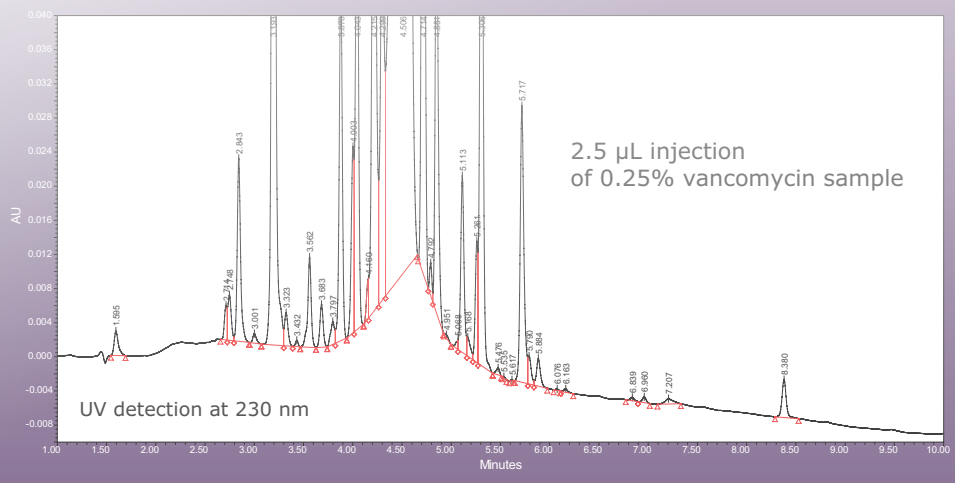


QbD METHOD DEVELOPMENT IN ACTION: VANCOMYCIN CASE STUDY

Vancomycin is a large molecule (MW 1485.71) that contains many impurities that are difficult – if not impossible – to separate chromatographically.

- Traditional HPLC gradient methods have shown the ability to separate 13 of these impurities.
- UPLC methods have demonstrated the separation of as many as 26 impurities with manually-developed methods.

The ACQUITY UPLC H-Class Method Development System improves the separation to 39 impurities – and decreases development time from weeks to less than two days.



Response variable	Predicted response	Experimental response
Number of Peaks	36.9 Peaks	39 Peaks
Number of Peaks ≥1.0 Rs	26.1 Peaks	27 Peaks
Number of Peaks ≥1.5 Rs	19.3 Peaks	18 Peaks
Number of Peaks ≥2.0 Rs	13.3 Peaks	12 Peaks

A vancomycin sample was run to confirm the predicted optimal method conditions.

"Quality by Design is a big theme, and presents industry with a $20- to $30-billion opportunity to optimize technical development... The industry will need to have more cross functional processes, linking 'technical development', which often is still in R&D, and production which is in operations. Removing the wall between them will be a key value driver."

MCKINSEY'S ULF SCHRADER ON TOYOTA AND QUALITY LESSONS FOR PHARMA. PHARMAQBD.COM. 2010 JUN 8.

Efficiencies and productivity that extend into production

With the development of robust methods that start with the ACQUITY UPLC H-Class Method Development System, you have a strong base for your commercial operations. Whether the method will be transferred to an ACQUITY UPLC System at a business partner's facility or a PATROL UPLC® System on the manufacturing floor, you will deliver new efficiencies and process understanding across your organization.

By utilizing a Quality by Design approach at the outset of you method's lifetime, your organization has the potential to benefit from regulatory flexibility should you need to adjust the method within the defined operating space – thus minimizing the need for additional equivalence studies and additional regulatory submissions.

More immediately, the benefit of deploying well-characterized, robust methods results in fewer validation and transfer failures, which translates into reduced compliance risk and costs.

A FULL SUITE OF ANALYTICAL TECHNOLOGIES TO SUPPORT DEVELOPMENT AND MANUFACTURING

Extending from your method development efforts, UPLC Technologies and Empower allow you to understand more about your application, make better decisions, and increase the probability of developing a quality pharmaceutical product that will consistently perform as intended.

What's more, these innovations form the platform of a laboratory model that is much more user-friendly, capital-efficient, and easily integrated with existing instrument workflows – all critical in an era of doing more with less.

ACQUITY UPLC System

The market's first UltraPerformance LC® System that revolutionized pharmaceutical laboratories around the world for LC and LC/MS applications. Along with ACQUITY UPLC H-Class, solvent usage can be reduced by more than 80% and a 15-fold time savings when compared to conventional HPLC. On average, one ACQUITY UPLC System displaces three HPLC instruments and is the preferred LC system of all major pharmaceutical companies today.

ACQUITY UPLC H-Class System

With the ACQUITY UPLC H-Class, you can continue running existing HPLC methods on a forward-looking LC platform that allows you to confidently and seamlessly transition to UPLC separations, when you're ready. The familiar design of its Quaternary Solvent Manager and Sample Manager, with flow-through needle design, gives you all the flexibility and usability of your current HPLC while still achieving the highly efficient separations that only UPLC can provide.

PATROL UPLC System

The only system available that delivers real-time UPLC speed, sensitivity, specificity, and accuracy to the manufacturing floor with a rugged and simplified operator interface appropriate for the environment. For an entirely new, more efficient approach to automated, direct inprocess online and atline analysis.

ACQUITY UPLC Column Solutions

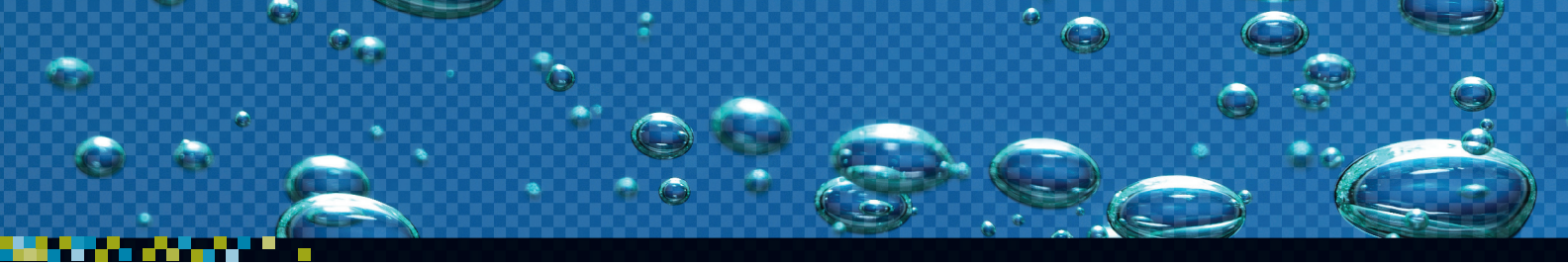
Waters offers a vast array of columns with a wide range of selectivity, including the new Charged Surface Hybrid (CSH™) Technology columns. With additional tools such as Waters Method Transfer and Method Validation Chemistry Kits, seamless transfer from an HPLC to a UPLC, or vice versa, is ensured. Add an easy-to-use, stepwise calculator tool to optimize your conditions, and turn once tedious and time-consuming processes into a productive workflow with timely, consistent results.

Empower 2 Method Validation Manager (MVM)

Empower Software is the industry-leading chromatography data system for advanced data acquisition, management, processing, reporting, and distribution. MVM allows you to perform chromatographic method validation from protocol planning through final reporting in one application, easily satisfying compliance requirements while cutting method validation time and costs as much as 80% by eliminating manual steps.

Empower Driven Services

Innovative services from Waters that optimize laboratory resources and budgets through continuous improvement and lifecycle asset management by integrating Empower Software-driven instrument services and business analytics.



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