Waters
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The Method Detectives: Building a New Business Model with Analytical Procedure (Method) Lifecycle Management

Using a toolbox of Waters LC systems, chemistries, and software, an innovative pharmaceutical services provider solves customers' challenges with method development and validation

Technology: ACQUITY UPLC System, ACQUITY UPC², ACQUITY QDa Detector, Empower Chromatography Data Software

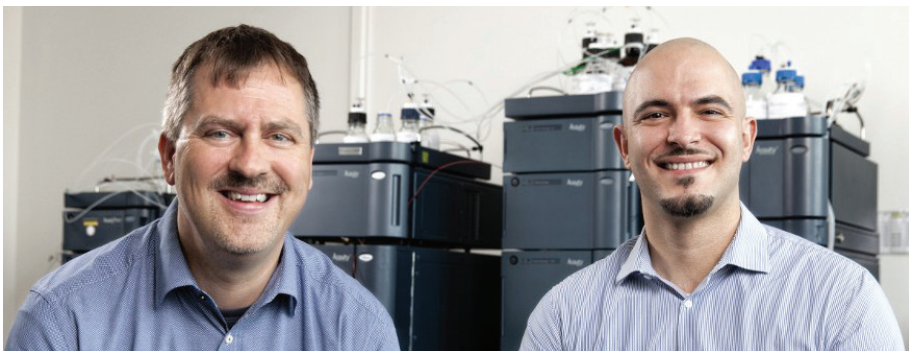
PHARMACEUTICAL METHOD DEVELOPMENT AT CHROMICENT

Chromicent GmbH is a pharmaceutical service provider offering services in all stages of the analytical method lifecycle. Founded in 2013, the company specializes in the development of analytical methods using an analytical quality-by-design (AQbD) approach under the umbrella of the new Analytical Procedure Lifecycle Management, (also known as Method Lifecycle Management or MLCM) initiative that is gaining traction in the industry. In addition, method validation, analytical instrument qualification (AIQ), laboratory efficiency improvement, and Good Manufacturing Practice (GMP) compliance services are available from Chromicent.

Located in Berlin-Adlershof, Germany, Chromicent's 550 m² laboratory and training facilities comprise laboratories for pharmaceutical technology, biological analysis, ion chromatography, high- and ultra-performance liquid chromatography (HPLC and UPLC™), mass spectrometry, and wet chemistry. Additional services include forced degradation studies support, impurity profiling, cleaning validation, extractables and leachables studies, stability studies, consulting, training, and GMP auditing.

The Chromicent team consists of 15 professionals who strive to offer customers a highly innovative, forward-looking, and future-proof approach for pharmaceutical method development.

MLCM combines activities of analytical method development, improvement, qualification, validation, transfer, and maintenance related to GMP production. As part of its approach, Chromicent uses AQbD as an early risk assessment to clearly identify method parameters that have an impact on analytical performance, as well as risks associated with variability such as sample preparation, instrument configuration, and environmental conditions.



Dr. Alexander H. Schmidt and Mijo Stanic, Chromicent founders and joint CEOs.

WORKING WITH WATERS

The connection between Chromicent and Waters extends beyond the typical vendor-customer transactional relationship. It's a valuable partnership where both companies work to advance lifecycle management in method development.

At the heart of the association is Chromicent's choice of Waters chromatography systems and its belief that they offer them the best accuracy, reliability, and flexibility in the industry. By combining Waters' expertise in analytical instrumentation and software with Chromicent's leadership in analytical method development and validation, the two companies have worked together on conference presentations, equipment, and customer training and applications projects – with plans to expand this collaboration further as interest in method lifecycle management grows.

Dr. Alexander H. Schmidt, co-founder and joint CEO of Chromicent.

Dr. Alexander H. Schmidt and Mijo Stanic, Chromicent founders and joint CEOs, explain their company's innovative approach: *"We developed the company around the APLM and AQbD philosophy. The result is more than a method – it is a quality tool. Using AQbD yields robust methods that will meet future requirements and developments. Our methods will not only tell you what design space an application will work in, but also where it will not."*

Working closely with Waters, Chromicent is leading the way in demonstrating how the benefits of Method Lifecycle Management are changing the future of pharmaceutical method development.

METHOD LIFECYCLE MANAGEMENT IN REGULATORY GUIDELINES

In modern process management, the lifecycle focuses not only on quality but also on the total costs of the process from investment to operation to retirement. The pharmaceutical industry has begun to apply this concept to the lifecycle of an analytical method – consisting of design, development, validation (including instrumental qualification, continuous method performance verification, and method transfer), and finally retirement of the method.

Chromicent's core competencies lie in development and validation of chromatographic methods. The company focuses on MLCM because Chromicent's founders strongly believe this approach provides an opportunity to use the knowledge gained from the application of scientific and quality risk management to provide continuous improvement and assurance of data quality for its customers.

Regulatory bodies also have increased their focus on lifecycle management for analytical methods. Improvement of analytical methods based on performance is quickly becoming a compliance expectation.

Both the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), as well as the United States Pharmacopeial (USP) Forum are developing new guidelines that include lifecycle management of analytical methods.

The implementation of the ICH guidelines Q8 to Q11 within the pharmaceutical industry is intended to modernize the current approach for development and manufacturing of pharmaceuticals to a more scientific and risk-based approach. A new proposed ICH guideline Q12 will provide guidance to facilitate the management of post-approval changes in a more predictable and efficient manner across the product lifecycle.

Adoption of this new ICH guideline will promote innovation and continual improvement, as well as strengthen quality assurance and the reliable supply of a product. In addition, further new ICH guidelines and a new general chapter of the USP are in the works to provide specific guidance about the analytical procedure lifecycle management approach.

Chromicent's founders strongly believe analytical procedure lifecycle management and AQbD are essential to meet today's pharmaceutical regulatory guidelines – not just those proposed for the future. The company's method development and validation services are designed to comply with the ICH Q8 guideline and to meet all necessary requirements for marketing approval.

"ICH Q8 was implemented in 2005, opening the door for lifecycle management in pharmaceutical method development. But the industry was hesitant to adopt it. The most difficult thing was that lifecycle management is not a checklist. Instead, it refers to an implemented philosophy. The authorities are writing the ICH Q12 to clarify the use of lifecycle management. But it's logical to use ICH Q8 right now and reap the benefits of this approach."

DR. ALEXANDER H. SCHMIDT
Co-founder and joint CEO, Chromicent

Waters ACQUITY™ UPLC instruments in Chromicent's laboratory.

Chromicent's leadership team believes incorporating AQbD offers huge advantages for their customers. With methods developed via AQbD, the impact of possible variables over a method's lifetime has already been considered, so the need for revalidation is minimized. The result is a systematic approach that includes defining the method's goal, assessing risk assessment, developing a design space, implementing a control strategy, and continually working on improvements to increase method robustness and knowledge.

The novelty and opportunity in this approach for the pharmaceutical industry is that working within the design space of a specific method is seen as an adjustment, and not a post-approval change. Dr. Schmidt and Mr. Stanic believe this idea is a paradigm shift for pharmaceutical product development and manufacturing.

Dr. Schmidt explains: *"The pharmaceutical industry learned to use the regulations like a checklist. The vision of the AQbD concept was too complicated at first, so everyone put it under the table. But the documentation in an AQbD product is so clear that everyone understands it and it gets approved faster. Plus, if you need to make a change in your method, the regulatory bodies consider it to be an adjustment – not a change that requires resubmission for approval."*

Because there is a greater understanding of methods developed with AQbD, Chromicent has shown the number of failures and transfer issues that occur over the lifecycle of the method are often reduced. The company contends its clients can achieve a **50% cost saving** compared to standard quality control methods because AQbD results in robust analysis techniques with minimal associated quality control costs and significantly shortened analysis run times. For commercial processes, the high quality of the data provided by AQbD methods may also allow for more timely data release, reduced regulatory risk, and lower costs.

Yet the benefits are not just for pharmaceutical companies. The lifecycle management approach has significant advantages for the regulatory agencies as well.

Dr. Schmidt explains: *"The authorities are often overwhelmed with small changes. Using AQbD, the frequency of requests for minor changes would be reduced. They would be able to focus on more significant changes or more important topics. This would benefit the pharmaceutical industry, the authorities, and the consumer."*

ANALYTICAL PROCEDURE LIFECYCLE MANAGEMENT

Method development at Chromicent takes a product's lifecycle into consideration – from the idea, development, transfer, marketing approval, market launch, and sale, to its discontinuation. Rather than looking at one factor at a time, which typically involves the optimization of one factor while the others remain constant, AQbD introduces multivariate analysis. This approach allows an overall understanding of method performance based on the multidimensional combination and interaction of these factors to be obtained, and it leads to the definition of the optimum design space.

A greater understanding of the method variables leads to more robust and reliable methods, thereby increasing their fitness for purpose throughout their lifecycle.

"AQbD identifies the analytical target profile, which is specific and part of the marketing application. Then you have your method which you have developed, validated, and used. If there are changes after approval, you can do the changes within your quality assurance system in AQbD without needing to inform the authorities. That is a very important part for the companies and for the authorities, because the authorities receive so many variations, they are always busy with little insignificant changes. It's more efficient for everyone."

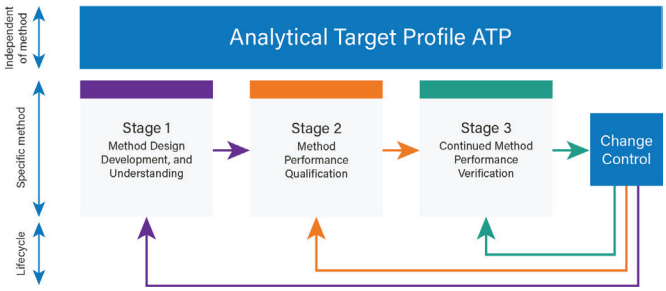
DR. ALEXANDER H. SCHMIDT
Co-founder and joint CEO, Chromicent

TROUBLESHOOTING METHODS

Chromicent's services focus on three main areas:

- Stage 1: Method development in an AQbD framework in compliance with ICH Q8
- Stage 2: Method robustness and validation studies in compliance with ICH Q2 as well as method transfers
- Stage 3: Continuous improvements of methods while in routine use and troubleshooting of existing methods.

Soon after the company's launch, the founders discovered an untapped need in its customer base.



Dr. Schmidt describes this realization: *"We thought the first stage would be the primary business for us. Now we realize it's the third stage, where the customer already has a product on the market and a method with a problem. Usually these problems are an unacceptable variation in product consistency, but they don't know where the problem is. So, we start with stage three – the troubleshooting. In most cases, we are the last chance to save the product."*

Waters instrumentation and software is particularly advantageous for Chromicent in troubleshooting methods because it is highly robust, dependable, and reproducible, even for the most demanding separations. Chromicent begins the troubleshooting process by performing a robustness test which often results in developing a new method.

The company's innovative development strategy follows AQbD principles and can be divided into five steps:

1. Definition of method goals
2. Risk assessment
3. Design of experiments with screening and optimization steps
4. Design space that includes model building, working point selection, and verification as method validation
5. Method control strategy based on the knowledge gained about the developed method.

"Established methods are often ineffective, slow or lack robustness so that out of specification results accumulate. We can show approximately 50% of failure is because the method is not robust. Using AQbD, you can often achieve significant method robustness gains with a very small change. But you must know what the problem is, and what to change."

DR. ALEXANDER H. SCHMIDT
Co-founder and joint CEO, Chromicent

The idea of changing an approved analytical method often makes the company's first-time customers nervous, until the Chromicent team walks them through how the AQbD approach can easily solve the issue, and how AQbD provides greater regulatory flexibility because results that fall within the well-defined design space are not considered to be changes in the method.

"The first thing a new customer says is, 'We cannot change anything.' But we go back and show them how they can. I explain the regulations and Mijo shows them what needs to be changed. One of our customers was under threat of having to remove their products from the market. They thought they had a production problem. We showed them it was the method, and the product was perfect. It's a misguided idea that you must live with a bad method. The documentation related to a quality by design product is so clear that everyone understands, and it gets approved."

DR. ALEXANDER H. SCHMIDT
Co-founder and joint CEO, Chromicent

Another part of Chromicent's method development and validation process is method transfer.

"Sometimes method transfer problems arise because the customer doesn't have appropriate knowledge of the method they receive. So the process of method transfer is very important. In most cases, we do it in person. We'll go to the receiving lab and conduct training on their system. And then it works."

MIJO STANIC
Co-founder and joint CEO, Chromicent

Dr. Schmidt believes much of the industry's misunderstanding of MLCM is based in fear – fear of delays in approval and getting their products to market. But this first exposure to AQbD highlights the approach's numerous benefits, including improved method understanding, better data quality, reduced OOS, easier method transfer, increased flexibility for post-approval changes.

"Quality-by-design based method development results in increased method robustness. Thereby a decreased effort is needed for method performance verification, and post-approval changes as well as minimized risk of method related out-of-specification results. This strongly contributes to reduced costs of the method during its lifecycle."

DR. ALEXANDER H. SCHMIDT
Co-founder and joint CEO, Chromicent

But perhaps more than anything, Chromicent's AQbD approach for method development and validation can potentially protect its customers' reputations by preventing problems in the first place.

Dr. Schmidt describes this change in a customer's mindset: *"If they have to troubleshoot a method at Chromicent, next time they are more likely to come back and say, 'Make it right from stage one.' That's better than waiting for someone to find out you have a problem."*

FUTURE STEPS

MLCM and AQbD are set to change the way the pharmaceutical industry brings products to market as global regulatory bodies continue to develop new guidelines that specifically address lifecycle management of analytical methods.

Mr. Mijo Stanic, co-founder and joint CEO of Chromicent.

Waters and Chromicent are proactively educating their customers about the benefits of Method Lifecycle Management and AQbD – particularly how these approaches can be used under the current guidelines to develop methods that are robust, user-oriented, designed for routine analysis, easily transferable to any laboratory, and time- and cost-efficient.

The adoption of Waters ACQUITY UPLC and ACQUITY QDa™ technology has contributed to Chromicent's business success with this objective, by providing more information faster and earlier in the method development process. The company also relies on Waters Empower™ Chromatography Data Software to handle the data and ensure data integrity, which is critical to MLCM. Data trending is the backbone of Chromicent's approach by enabling timely identification and actions, controlling variability and risk, and serving as the basis for continuous improvement during the product lifecycle.

Waters instruments in situ in Chromicent's laboratory.

Waters Empower Chromatography Data Software enables analytical laboratories such as Chromicent to understand how sources of variability impact method performance. This data trending contributes to reducing risk, lowering costs, and improving regulatory compliance.

In addition to these benefits, Chromicent believes the paradigm shift of MLCM moves the focus of pharmaceutical method development from regulatory compliance back to the scientific advances that are the catalysts for advancing the field of modern medicine.

Dr. Schmidt explains: *"For me, the most important part of MLCM is that this approach brings science and compliance together. Compliance is how everything comes together when it's sent to the authorities. But if you're only focused on compliance, you can't develop anything new. The most important thing is science. That's where the real innovation is."*

"This area is really exploding. And our years of experience and scientific innovation positions both Waters and Chromicent to lead the way in improving the development and validation of pharmaceutical analytical methods. It's a win-win situation."

MIJO STANIC
Co-founder and joint CEO, Chromicent

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