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# CRO Accelerates Laboratory Start-Up for Formulation Development and Analytics

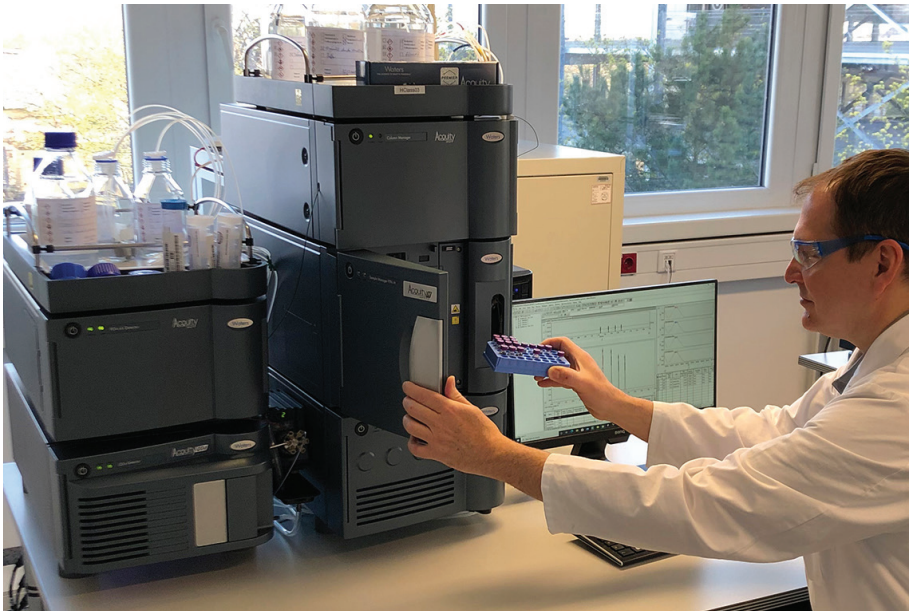
**With the help of Waters instrumentation, software, and support, RaDes was able to quickly launch its new CRO laboratory for analytical method development and the design, evaluation, development, and analysis of formulations**

**Products: Waters™ ACQUITY™ QDa™ Detector, Waters ACQUITY UPLC™ H-Class PLUS System, Waters Empower™ Chromatography Data System (CDS)**

## DEVELOPMENT AT RADES GMBH

RaDes – Rational Design of Formulations – GmbH, based in Hamburg, Germany, was founded in July 2018 by Michael Herbig, Melanie Köllmer, Dirk Evers, and Sascha Gorissen. After working closely together in key functions of pharmaceutical development at Almirall Hermal, the four founders launched this new contract research organization (CRO) to leverage their expertise in the field of semi-solid and liquid dosage forms, including in-depth knowledge of the procedures, guidelines, and decision-making processes in the pharmaceutical industry from concept development to industrialization.

Formulation development at the company emphasizes modern techniques and instruments, structured processes, the predictive power of algorithms, and knowledge of relevant guidelines and regulations. RaDes scientists also have extensive experience in regulatory, clinical, pre-clinical, and IP services for medicinal products and medical devices, as well as for dermatological cosmetics.



*After the RaDes laboratory opened, it quickly became clear that a second ACQUITY UPLC H-Class PLUS System and ACQUITY QDa Detector were needed to meet growing demand.*

## WORKING WITH WATERS

The RaDes co-founders Sascha Gorissen, Head of Laboratory and Project Management, and Dirk Evers, Head of Analytical Development, had worked with Waters for many years prior to the launch of the CRO. When faced with a tight timeline to start this new business from scratch, Waters was one of the first vendors they contacted.

Waters was able to provide RaDes with a complete solution for its new laboratory, including service and applications support, chemistries, software, and instruments. Mr. Gorissen was directly involved in managing the accelerated launch timeline. He describes how Waters helped the new CRO get up and running quickly:

"From our previous experience, we knew Waters instrumentation could meet the high level of performance we needed as a CRO. We also had very good personal relationships with the Waters service engineers. We knew if we had a question or an issue, they would respond very quickly. While an instrument's performance is important, the personal relationships with the service team make a difference."

The company works together with customers to develop tailor-made, individual solutions with services such as:

- Consultation, concept development, and evaluation
- Formulation development
- Analytical method development and chemical stabilization
- Performance-testing *(in-vitro/ex vivo)*
- Process development
- CMC regulatory assistance and post-approval support

"We decided to build our own company based on what we do well and what we like to do, which is formulation development. Our goal is to pursue a 'rational design' approach to develop formulations and analytical methods in a targeted and robust manner, thus providing solutions that reduce risks and costs for our clients. Formulation development depends on the customer's focus, so we have a lot of different active pharmaceutical ingredients (API) to handle. There's no routine analysis, and it requires a very broad area of expertise."

SASCHA GORISSEN
*RaDes Co-Founder & Head of Laboratory and Project Management*

With the aid of Waters instrumentation, software, and support services, RaDes was able to launch the new CRO in just a few months, as well as expand the laboratory as demand for its services grew.

## FORMULATION DEVELOPMENT

Semi-solid formulations are often complex and their critical quality attributes are generally less well understood compared to typical solid dosage forms. Therefore, such formulations are usually still developed empirically, i.e., by testing known approaches until an acceptable way is found. This tactic makes it more challenging to develop formulations systematically, robustly, and economically.

In contrast to this "quality by trial and error" approach, the RaDes founders wanted to pursue a rational design based on a systematic understanding of the formulations in terms of chemical and physical stability, skin penetration and cosmetic properties. They believe that this quality by design (QbD) approach leads to a robust, marketable product that can be modified in a targeted manner if required. It also minimizes risk for customers from a technical, regulatory, and economic perspective. Mr. Gorissen explains:

"This knowledge allows us to provide our customers with a systematic, target-oriented procedure through which erroneous paths and subsequent changes can be minimized. In this way we can obtain answers as to why something works or not, so that specific modifications can be identified. It also provides the basis for innovations and enables us to solve even the toughest challenges in formulation design and analytics. We are convinced that such a systematic understanding of formulations means considerable economic saving potential in the medium and long term, as troubleshooting at a later stage can be avoided or carried out much more specifically."

In relation to the total development costs of a medicinal product, the exploratory development of a formulation is generally inexpensive. However, with the selection of a final prototype, a strategically and economically significant decision is made. The sum of future expenses with regards to investment, operating and production costs, as well as the expenditure for release testing and regulatory support for various prototypes, can differ by several million euros.

The RaDes team evaluates such future-projected aspects of prototypes and creates risk-based scenarios that allow customers to develop optimized and sustainable solutions. Mr. Gorissen describes how this approach can work with the RaDes clientele:

"Prototype development is only the beginning of the life cycle of a formulation. Right from the start, we consider the impact on future potentials, risks, and costs. For example, one of our first customers came to us with some completed formulations, and the principles of these formulations worked well. However, they wanted to know which formulation performed the best, so they could choose the right one to focus on for development. We conducted the performance testing and provided the data that showed the customer which formulation showed the most potential, as well as another formulation that could be a backup."

## BUILDING A NEW LABORATORY

The opportunity to build a new CRO from the ground up enabled the RaDes founders to invest in the most advanced instrumentation and software that would facilitate the company's approach to formulation development. Mr. Gorissen describes those early days:

"We had to build the laboratory from scratch. That included installation of labs, offices and IT infrastructure as well as buying and installing equipment. We needed everything. It takes a lot of money to fully equip a new laboratory, particularly before you have customers. And we did that in less than three months. It happened quite fast."

*Waters provided RaDes with a complete solution for its new laboratory, enabling the CRO to get up and running quickly.*

One of the RaDes team's first instrumentation purchases was the ACQUITY UPLC H-Class PLUS System equipped with the eλ-PDA (UV/Vis), and the ACQUITY QDa Detector. The purpose of this investment was to enable RaDes researchers to speed up method development and the rapid analysis of larger quantities of stability and *In-vitro* release test (IVRT) samples. The mass detection capabilities of the ACQUITY QDa Detector allows for poorly UV-active compounds to be detected with high sensitivity. It's possible to easily identify co-elutions and monitor changes in elution order. As a result, RaDes scientists could reduce the risk of unexpected co-elutions or components and confirm trace components with the analytical confidence of mass detection. Mr. Gorissen explains:

"From the analytical point of view, we knew what we needed in the laboratory as standard equipment. We had a lot of experience with Waters, and we knew their instrumentation was vital for our work in formulation development. Also, as a CRO, uptime is vital. If an instrument isn't working, we're not working. We knew if we had any issues, Waters would be there to help."

The ACQUITY QDa Detector was designed to work in harmony with chromatography systems and pre-optimized without the sample-specific or user adjustments typical of traditional mass spectrometers. As a result, RaDes analytical scientists can consistently generate the highest quality mass spectral data, without the need for any specialist training. This is particularly advantageous for the needs of a CRO.

"The ease of use is the biggest benefit of the ACQUITY QDa Detector. The installation was performed by service technicians from Waters, and it integrates easily with the ACQUITY UPLC H-Class PLUS System and Empower Software. Our laboratory technicians don't need specialized experience with complex MS technology to use the QDa. That's very convenient."

SASCHA GORISSEN
*RaDes Co-Founder & Head of Laboratory and Project Management*

After the laboratory opened, however, RaDes found the company needed to quickly scale up to meet demand as new customers signed on. Mr. Gorissen explains:

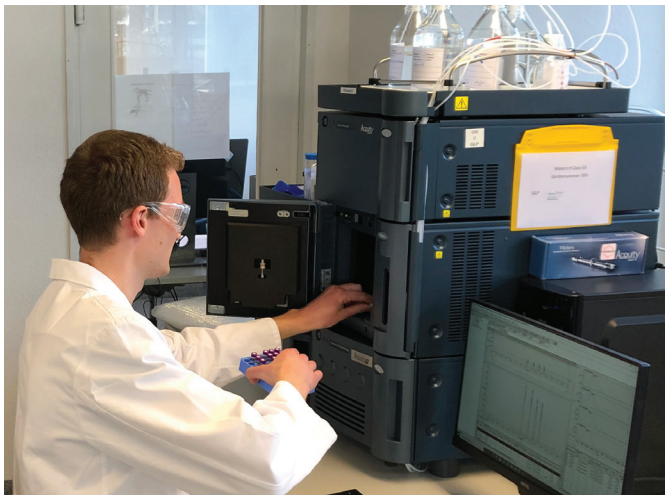
"We needed to increase our capacity to ensure we could meet the timelines for new customers, as well as existing customers. But we knew we also needed to invest in more instrumentation before we could pursue new customers. We started with one UPLC and two classical HPLCs. We quickly realized that we needed a second ACQUITY UPLC H-Class PLUS System and ACQUITY QDa Detector as demand for our services grew."

The need to expand has continued for the company, as many RaDes customers return to the CRO for future projects. As a result, the company installed a third ACQUITY QDa Detector in early 2021. Mr. Gorissen describes the purpose behind this purchase:

"Adding another ACQUITY QDa Detector provided us with additional mass detection capabilities and greater flexibility, particularly if a customer needs information quickly. Flexibility is a selling point for our company. It helps us attract customers, and 90–95% of our customers come back with other projects later. Since we opened, our company has continued to grow and add new customers. So, we need to continually add resources, and increase our capacity as well."

## ADVANCEMENTS IN LIQUID AND SEMI-SOLID FORMULATIONS

RaDes specializes in analytical method development and validation for semi-solid products that are difficult to analyze (e.g., problematic extraction, low doses, low UV activity), and for structural elucidation of complex degradation pathways. In liquid and semi-solid formulations, active ingredients are often dissolved and can react in a variety of ways, which often requires stabilization. Similarly, the unfavorable drug to matrix ratio and quantitative extraction from the matrix can present challenges.



*RaDes scientists have extensive experience in analytical method development for medicinal products and medical devices.*

The RaDes team addresses these challenges with the group's extensive experience in chemical stabilization (reduction of oxidation, hydrolysis or isomerization), as well as the interaction of active ingredients and excipients with packaging materials. The company also provides customers with risk assessments of secondary degradation phenomena, such as reactions of or with degradation products of active ingredients and excipients. These often follow non-linear, complex kinetics and are not predictable from the routine assessment of short-term stability data.

In addition to developing formulations, RaDes believes strongly in investing in a better scientific-technical understanding of the basic principles of liquid & semi-solid formulations.[1,2]

For polysorbates as stabilizers in biopharmaceutical formulations, Dirk Evers from RaDes recently co-published two papers with Boehringer Ingelheim GmbH & Co KG (Biberach, Germany). The first one is focused on the identification and quantification of the complex mixture of subspecies in polysorbate 20.[3]

The second paper deals with the label-free quantification of fatty acids as potential degradation products of polysorbates. Here, for the first time in this context, an isolator column was used to remove trace levels of fatty acid from eluents to improve sensitivity.[4] Polysorbates are widely used as non-ionic surfactant in biopharmaceutical formulations. Recently, stability issues in polysorbate containing formulations were observed leading to the formation and appearance of sub-visible and visible particles.

RaDes and Boehringer Ingelheim developed a method for the selective marker-based quantification of adequate polysorbate 20 components of interest without the need to apply derivatization or complex detection techniques. Using the ACQUITY QDa Detector coupled to the ACQUITY UPLC H-Class PLUS System, the method was shown to be beneficial in determining selected polysorbate 20 species during formulation development of biopharmaceuticals, as well as during stability testing and troubleshooting.

RaDes and Boehringer Ingelheim successfully demonstrated that the analytical procedure could reliably quantify several polysorbate components at its 100% level, and even at lower concentrations that occur in the case of polysorbate degradation.

As a result, the method is very well suited to determine selected polysorbate 20 species in several stress studies during formulation development of biopharmaceuticals to monitor degradation processes. Mr. Gorissen describes the role of Waters instrumentation in this research:

"The ACQUITY QDa Detector is perfect for this type of analysis. The excipient analysis is normally done by a different type of detector, but we could demonstrate that the ACQUITY UPLC H-Class PLUS System in combination with the ACQUITY QDa Detector had much better sensitivity and selectivity together. Our customers are getting much more information than they ever had before. It's extremely useful for product development."

SASCHA GORISSEN
*RaDes Co-Founder & Head of Laboratory and Project Management*

## NEXT STEPS

Building on its initial success, the RaDes team is looking towards the future. The next major goal on the CRO's list is to finalize its quality assurance system and set up Good Laboratory Practice (GLP) compliance for its customers. The company has already hired a new head of quality assurance, who is tasked with establishing quality standards for study conduct, data collection, and results reporting.

"We started to implement this quality management system and promote our ability to perform performance tests under GLP. We're seeing a high demand from some customers, and they are very interested to see an established quality management system. Quality is always important, even at early stages."

SASCHA GORISSEN
*RaDes Co-Founder & Head of Laboratory and Project Management*

This addition will confirm the quality and integrity of the RaDes studies to support research or marketing permits for products regulated by government agencies. But perhaps more importantly, the RaDes founders believe this commitment to continuous improvement, as well as the team's perseverance and the determination to solve even difficult problems, are important success factors for the company. Mr. Gorissen describes the CRO's higher goals:

"From many years of experience in the development of dermatological medicines, we know that good products make an important contribution to patients' quality of life. We are motivated and dedicated to contributing to the development of medicines that help to improve patients' health and alleviate suffering."

## References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