Latika Bhonsle-Deeng
Manager Corporate Communication
Rentschler Biopharma SE

Konstantin Petropoulos
VP & Head of Business Development, Marketing & Sales
LEUKOCARE AG

Advanced Formulation Development by Design in the Context of Holistic Drug Production

A strong trend in drug substance (DS) and drug product (DP) biomanufacturing, as is for formulation, is that of increasing therapeutic complexity. These challenges of evolving sophistication take on a new meaning in an ever rapidly changing biopharmaceutical landscape. Solving the complex challenges of tomorrow, calls for innovative mindsets, technological advancement, and proficient and complementary expertise. This need led to the forging of the strategic alliance between biomanufacturing expert Rentschler Biopharma SE and formulation specialist Leukocare AG (*Figure 1*).

Leukocare is a top formulation development specialist in services tailored to client needs. Rentschler Biopharma SE is a leading global contract development and manufacturing organization (CDMO) renowned for its excellent process development and manufacturing of biopharmaceuticals as well as related consulting activities, including project management and regulatory support. Both companies have been collaborating since February 2017, to offer biologics and biosimilar makers a competitive edge through significantly stabilized end products. Leukocare is the specialized technology partner and the exclusive formulation developer for Rentschler Biopharma's biopharmaceutical development and biomanufacturing business. By combining well established scientific know-how and a commitment to high-quality, this strategic alliance leaves no stone unturned for the benefit

Figure 1: Rentschler Biopharma's strategic alliance with Leukocare is tailored to client needs.

of clients and their patients. Till date, the alliance has provided numerous clients with tremendous commercial advantage, by leveraging high-quality formulation developments.

The coming together of world-class capabilities in formulation development and high-quality biomanufacturing is a unique constellation. This alliance leverages technological leadership and long-standing experience, for best-in-class project delivery for all of its clients. Ultimately, the incorporation of early formulation development can further enhance a robust and highly productive manufacturing process. This in turn, strengthens/adds to the overall efficiency of the process and maximizes product potential. The manifold advantages include shorter development timelines, cost savings, extra intellectual property (IP) protection in form of patents, leading to a competitive edge for client products and outstanding services (*Figure 2*).

STRATEGIC ALLIANCES TO STRENGTHEN CAPABILITIES

Rentschler Biopharma has always run a different race. Companies offering complementary services are not seen as competition, rather as an opportunity to evolve through collaboration. Rentschler Biopharma has always aimed to offer its clients the best-available and best-fit solutions possible. Hence, the company seeks out strategic alliances with other organizations that have world-class capabilities and seamlessly integrates their offerings into Rentschler Biopharma's processes. The entire process is coordinated and managed by the CDMO, thus ensuring that all parts of the project are aligned. Both teams work closely together like one unit, embodying close collaboration and full transparency at every step of the project.

The alliance partners continue to conduct their own business interactions and further develop their knowledge and offerings, which in turn creates more value for all stakeholders. With this approach, strategic alliances extend the world-class service portfolio offered by Rentschler Biopharma, while driving further innovation within the company. A glowing example is the successful strategic alliance with Leukocare.

EARLY STAGE FORMULATION MAXIMIZES API POTENTIAL

Rentschler Biopharma is the first and only CDMO to have access to Leukocare's patented SPS® formulation technologies.

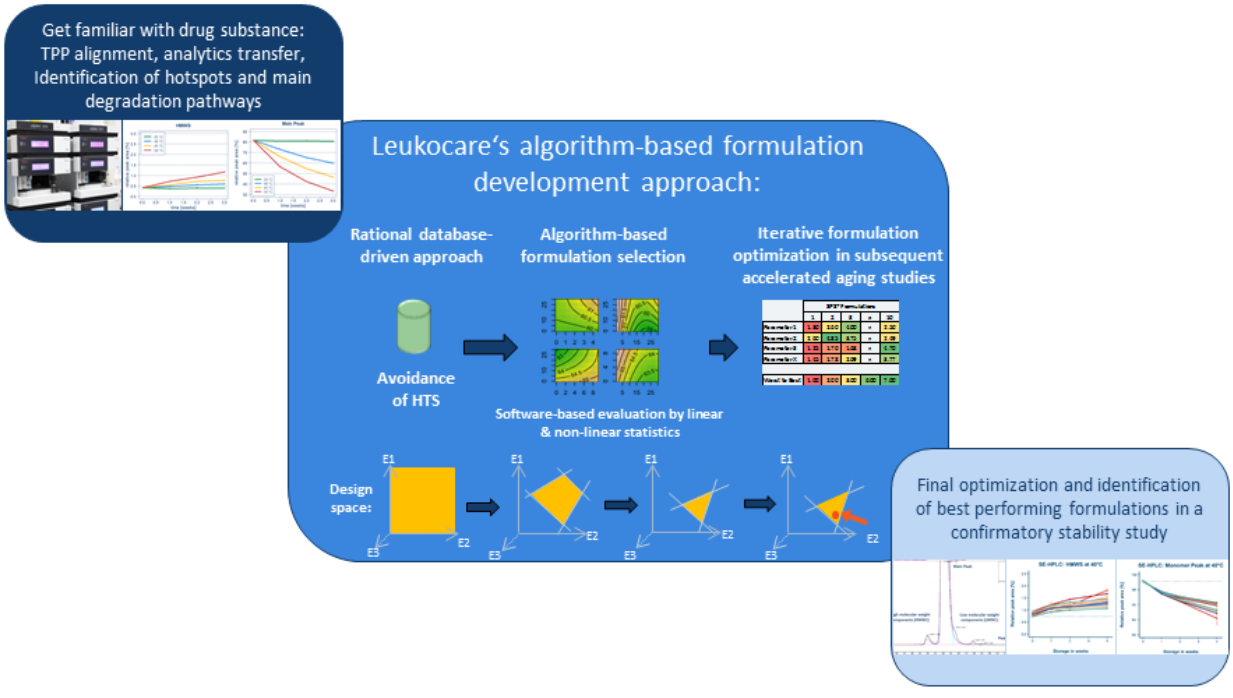

Figure 2: The Leukocare workflow for optimized formulation development.

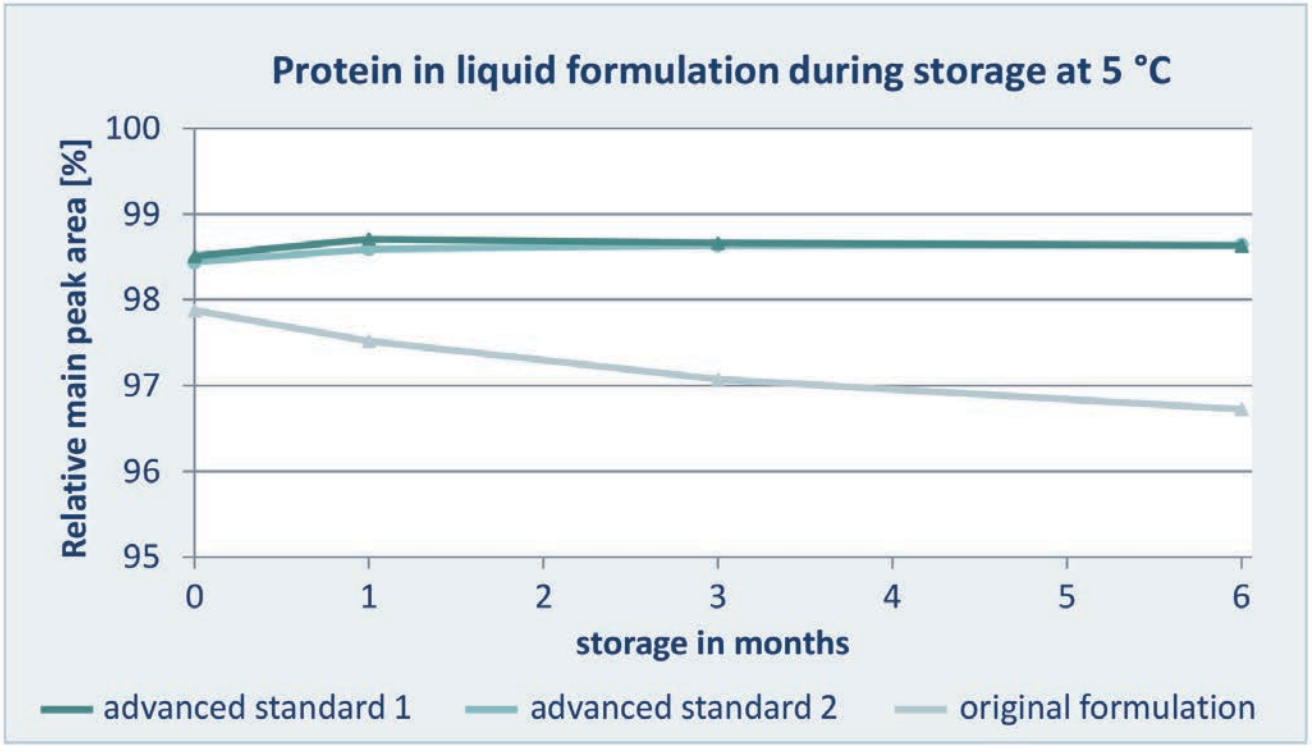

Figure 3: Aggregation Propensity demonstrated by the measurement of monomer fraction by SE-HPLC (Size-Exclusion High Performance Liquid Chromatography) of best performing formulations generated by Leukocare (Leukocare formulation 1 / 2) and client formulation (original formulation).

The contribution of early stage formulation development, to successful therapeutic commercialization is often underestimated. Formulation issues are known to often cause significant delays during clinical development and towards commercialization eventually leading to project failure. Thus, a clearly mapped out formulation strategy at the early stage of the product development is vital to project success. The deployment of a tailored and potentially commercially viable formulation early in the process offers many significant gains. It enables (i) reduced time to market, (ii) higher probability of success as well as (iii) added advantages due to IP that further add to a product's competitive edge.

Leukocare and Rentschler Biopharma's strategic alliance partnership for formulation development, combines bioinformatics and an algorithm- and database-driven approach for drug product stabilization. This tactic helps to explore a broader design space as compared to conventional approaches, so that it strongly increases the probability of success, avoiding high-throughput-screening, thus saving precious drug substance material. Moreover, it improves the stability and quality of biologics such as antibodies at all concentrations and vaccines, including live viral vectors, in liquid and dry formulation. Furthermore, it protects proteins in biologically functionalized medical devices.

Firstly, Leukocare's technologies prevent molecule degradation and potentially improve storage at room temperature (or even higher temperatures) by increasing thermal stability of protein therapeutics. Secondly, many biopharmaceuticals have to be lyophilized for stability reasons, today. The transfer of lyophilized to liquid formulations (i) facilitates the reduction of manufacturing costs, (ii) adds convenience in administration and (iii) avoids any loss of therapeutic efficacy and activity during the lyophilization process.

CLIENT-FOCUSED SOLUTIONS FOR THE WIN

Since the last three years, the alliance has worked on diverse projects. This diversity stems from the type of molecule, the specific needs of every client and the overall project expectations. Every molecule, every project and every client are unique. Key to the success of the Rentschler Biopharma/Leukocare alliance has been the implementation of tailored approaches, that have been customized for every project.

This leads to optimal solutions for clients. While the optimal solution for one client could mean delivering a fast track formulation within a fixed timeframe for an early clinical stage project, it could also translate into best-in-class formulations including IP protection with market advantages for another client. A third client might need problem-solving on existing formulation towards a better solution. Thus, four project case studies are presented here, which will shed light on these very diverse aspects.

CASE 1

The first project aimed to optimize an existing formulation for a clinical stage therapeutic protein. The key deliverable to the client in this project, was the exchange of one specific excipient in the formulation while retaining product stability. In an

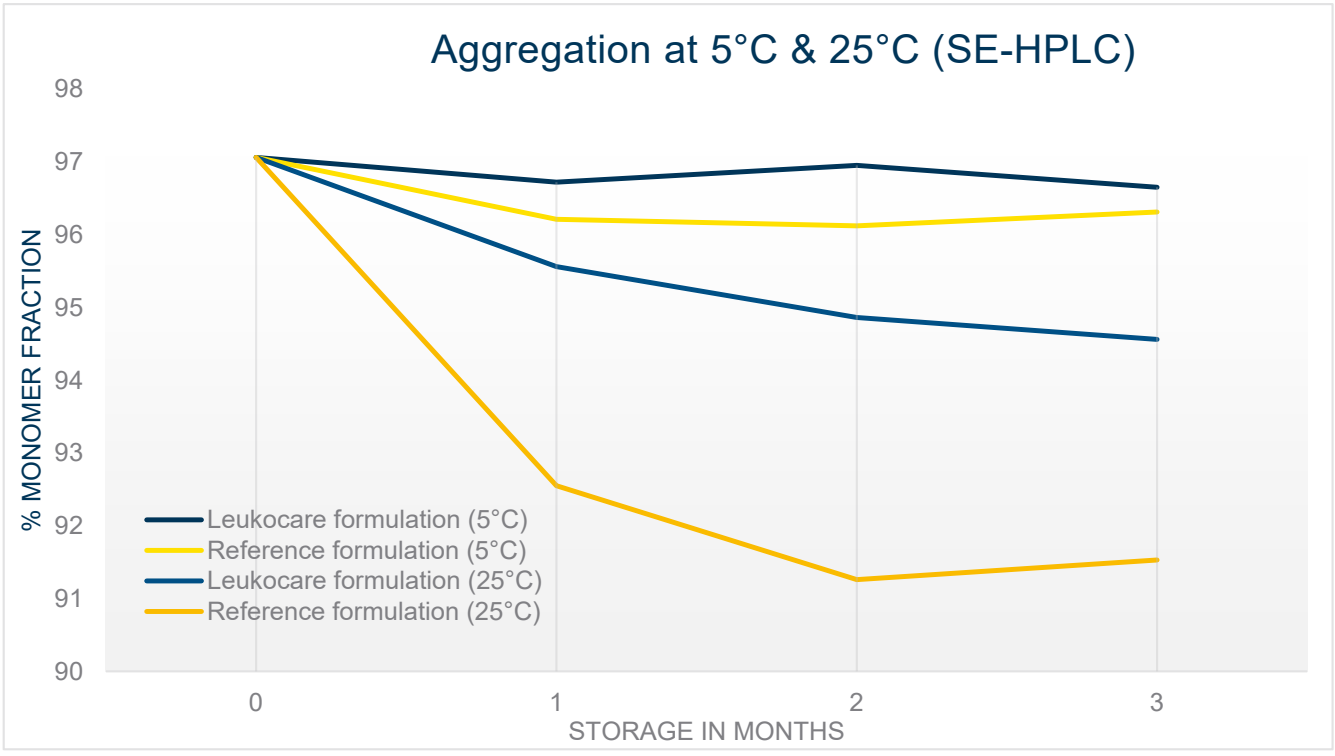

Figure 4: Aggregation Propensity demonstrated by the measurement of monomer fraction by SE-HPLC (Size-Exclusion High Performance Liquid Chromatography) of best performing formulations generated by Leukocare (Leukocare formulation 1 / 2) and client formulation (original formulation).

ideal scenario, the exchange of the excipient would contribute to further improving stability. This challenge was mastered by an in-depth data analysis, resulting in a better understanding of the weak structural spots and the degradation of the specific protein. This information was used to identify tailored formulation variants. These tailored variants were developed keeping in mind both, (i) client requirements, that is the exchange of the unwanted excipient, as well as (ii) further improvement of the stability of the protein stability. Ultimately, the protein's stability was significantly improved in comparison to the original formulation as demonstrated by the measurement of aggregation propensity (*Figure 3*).

CASE 2

The formulation development during the second project pertained to a designer molecule that was in preparation to enter clinical studies. The client requested for a formulation that would push the envelope and go beyond industry standards and allow for long term liquid storage at 2-8°C for the therapeutic. Furthermore, it was important to control both the number and the amount of excipients, in order to manage formulation complexity and cost of goods in mind. At the same time, the novel formulation should potentially create new IP, adding further commercial value to the therapeutic. Leukocare's database and algorithm-based formulation approach were implemented in this project, to sequentially improve formulation candidates, leading to high stability. This ultimately resulted in the best-suitable liquid storage formulation for the candidate molecule. Key to the success of this project was Leukocare's in-depth expertise in stabilizing effects, related to a multitude of excipients, relevant for the stabilization of biologics such as amino acids and a combination of the same. The implementation of formulation development know-how in downstream processing of this molecule resulted in increased product yield as well. This elegantly reflects the strength of this alliance and the immense benefits of the close collaboration for our clients (*Figure 4*).

CASE 3

The formulation for a monoclonal antibody based on 'industry standard formulations', whilst delivering superior stability, was the focus of the third project. While applying the database supported and algorithm-based formulation approach, the development focus was essentially on standard excipients and combinations thereof. The project's success can be attributed to Leukocare's deep expertise in the optimal application of Design of Experiments (DoE), even in a limited formulation development design space. Software-based readouts by linear and non-linear statistics enabled the most predictive selection of highly stable formulations to choose from for the molecule candidate (*Figure 5*).

CASE 4

The fourth project brought with it yet another challenge. A liquid formulation with standard requirements - stable at 2-8°C for intravenous (IV) injection, drug product concentration 50 mg/ml) for a monoclonal antibody was to be delivered. At the

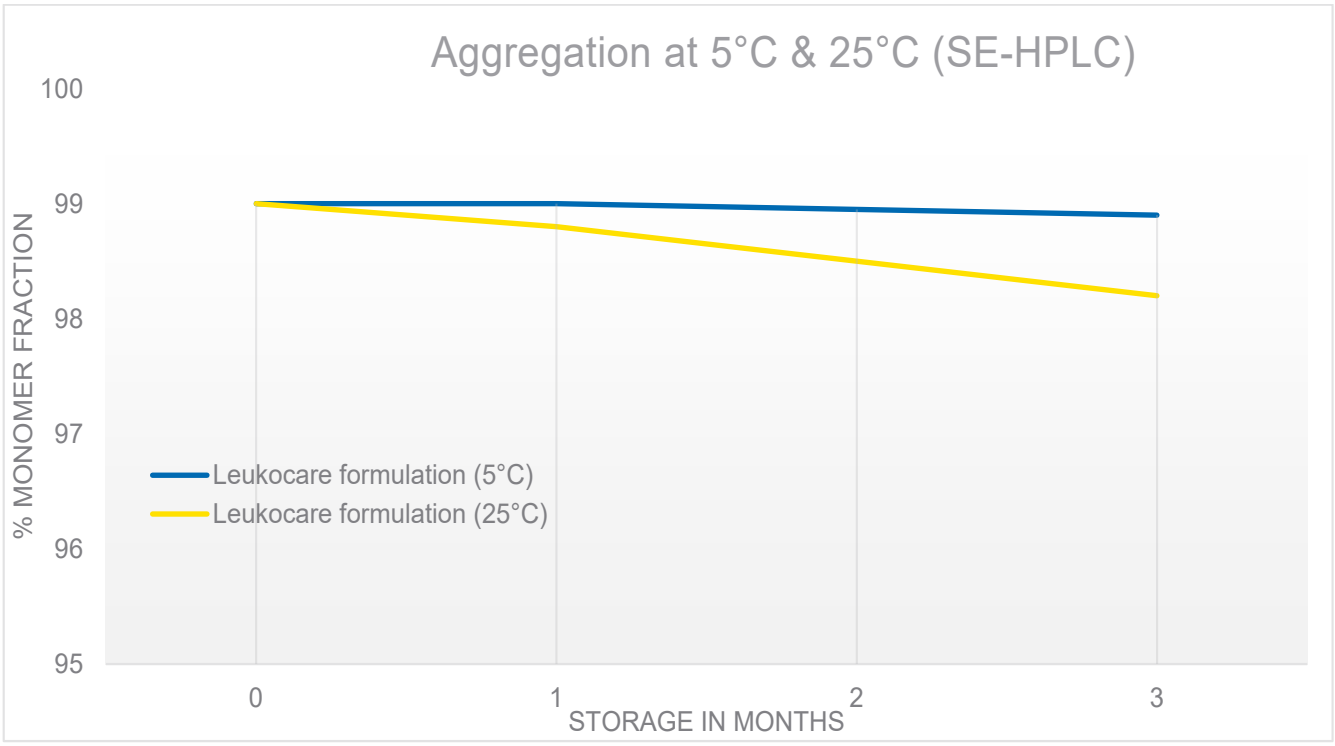

Figure 5: Short-term stability study at 5°C & 25°C showing improvement of stability (here: measured by SE-HPLC of best performing formulation generated by Leukocare ('Leukocare formulation') as compared to reference formulation ('Reference formulation').

same time, the formulation had to allow room for further development of a high-concentration formulation to enable subcutaneous (SC) injection at a later stage of the project. Hence, a combination of excipients, having the potential to generate higher concentrations of the monoclonal antibody formulation for SC application was considered and implemented from the very start of the project. Similar to the previous project, the biostatistical preparation and analysis of application of in-depth biostatistics for optimal DoE generated data stood the experts in good stead.

Additionally, Leukocare's vast expertise in high concentration formulations was vital for this project's success. A large number of highly stable formulations were created by the client. Moreover, the formulation continued to display comparable stability, even after the producing cell line clone was changed. At the same time, bridging studies - low (50 mg/ml) versus high (150 mg/ml) concentrated formulation - confirmed the very low aggregation propensity and low viscosity (< 7 mPa·s), potentially allowing even higher concentrations of the formulation. This clearly emphasizes the technological competence and know-how in simplifying clients' complex challenges.

LEVERAGING TECHNOLOGICAL LEADERSHIP FOR CLIENTS AND PATIENTS

Since 2017, the Leukocare/Rentschler Biopharma alliance has consistently aimed at exceeding client expectations with the goal of offering best-fit solutions while bringing essential therapeutics to market more easily and faster. This is attributable to the expert teams from both organizations, that work together like one unit. This seamless collaboration is fueled by continuous communication and transparency to the client. Scientific expertise, an innovative mindset, the ability to think outside the box - all of these attributes contribute immensely to this successful alliance. At the core is the strong commitment to driving the translation of medical research into outstanding treatments - for clients and their patients all over the globe. **CP**

DR. LATIKA BHONSLE-DEENG studied Biomedical Sciences at the University of Delhi, India. During her PhD thesis at the Max-Planck-Institute of Neurobiology, Munich, she investigated the autoimmune disease multiple sclerosis. She then consulted international companies, focusing on strategic projects in corporate finance and healthcare. She is an expert in scientific communication, having worked as a freelance journalist, specializing in European life sciences. Since 1st November 2019, Dr. Bhonsle-Deeng has been Manager Corporate Communication at Rentschler Biopharma SE.

DR. KONSTANTIN PETROPOULOS is VP & Head of Business Development, Marketing & Sales at LEUKOCARE with more than 10 years of experience in the biotech & pharma industry. Prior to joining LEUKOCARE, Konstantin held different positions with increasing responsibility at Bayer AG & MorphoSys AG. He holds a PhD in Molecular Biology from the Ludwig-Maximilians-University Munich and an MBA from the FOM University of Applied Sciences.