Simplifying Progress

From CLD to CDMO: A Case Study Demonstrating Successful Cell Line Technology Transfer

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Introduction

Cell line development (CLD) activities require significant expertise and resources. As such, they are often outsourced to industry partners to accelerate time-to-clinic. These collaborations are often extended to include contract manufacturing organizations (CMOs) or contract development manufacturing organizations (CDMOs) who can provide the necessary equipment, consumables, and expertise for upstream manufacturing.

The efforts of the CLD partner do not end at the delivery of a research cell bank (RCB); they must also encompass a confident understanding of scaling to commercial production, navigation of a complex and evolving regulatory landscape, and successful technology transfer to the manufacturing facility. Biopharmaceutical developers will benefit most from a partner offering a comprehensive service with the knowledge and expertise to take their project from early CLD to investigational new drug (IND) application.

In this white paper, we discuss the important considerations for both biopharmaceutical developers and CDMOs during technology transfer and provide evidence from a case study showcasing the successful transfer and scale-up of a cell line from our 4Cell® CHO platform to a global CDMO, FUJIFILM Diosynth Biotechnologies (FDB).

Cell Line Technology Transfer

A variety of factors must be considered to streamline technology transfer from a CLD provider to a CDMO.

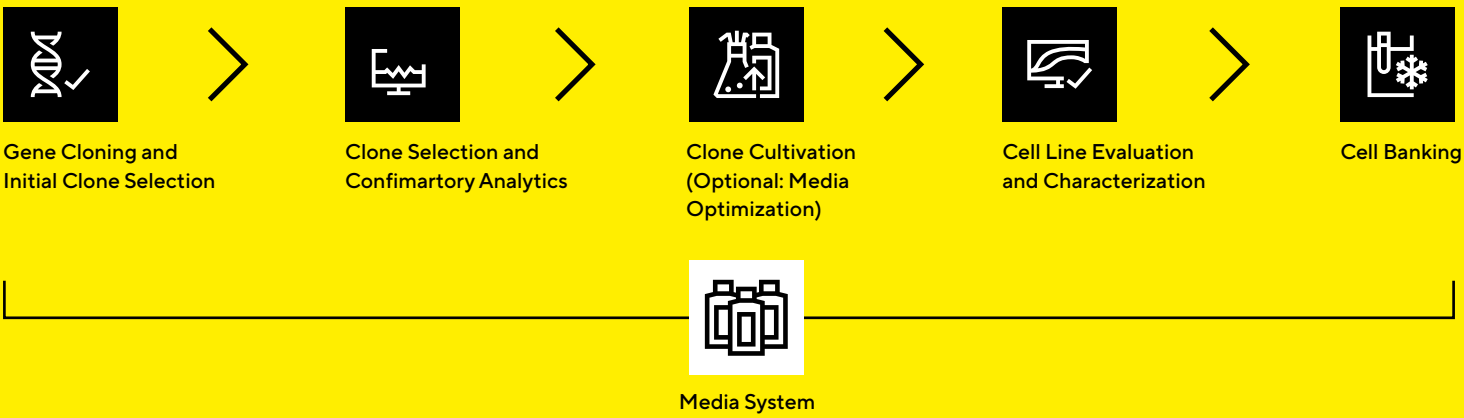
Expertise

A smooth technology transfer should include a full knowledge handover and a complete understanding of the equipment, process, and operational requirements such that the process achieves GMP compliance. The provided cell line must be robust, with repeatable and stable performance across systems.[1] However, the cell line developer should understand how differences between facilities (e.g., equipment, facility setup, and available skills) can impact behavior, scalability, and ultimate performance of host cells, and be able to provide those insights. This relies on clear and direct communication between the CLD service provider and CDMO.

Media

Selecting and optimizing the media formulation and feed strategy is fundamental to a productive bioprocess (Figure 1).[2] Media development can be a time-consuming component of bioprocess development, as the interactions between the cell line, process parameters, and media ultimately dictate the yield and product critical quality attributes (CQAs). A partner offering a comprehensive CLD service will have capabilities across the media pipeline and should be able to deliver the cell line and media strategy as part of the development package. This reduces the need for further optimization in the manufacturing facility.

Figure 1: *Typical Cell Line Development Considers the Media System Throughout the Process*

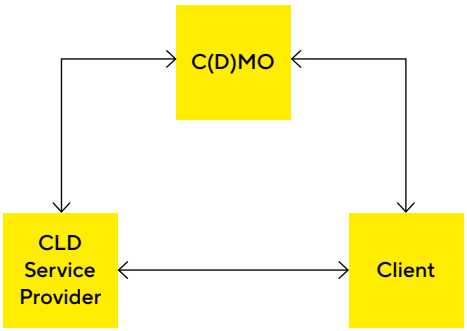


Collaboration Management

As alluded to above, strong lines of communication are essential for coordinating complex CLD and manufacturing projects. Coordinating with multiple project managers from CLD providers and CDMOs can create logistical challenges for biopharmaceutical developers. Preferably, the chosen partners will work directly together to develop and manufacture the cell line, creating a single point of contact for the biopharmaceutical company and streamlining the collaboration (Figure 2). This would lessen the necessary involvement of the biopharmaceutical company (the client), lightening the administrative workload.

As part of this ongoing collaboration, CLD providers should deliver early-stage material to CDMOs to support the performance of parallel activities, such as setting up the downstream process, to accelerate the entire process development timeline.

Figure 2: *Strong Lines of Communication Are Required to Ensure Streamlined Collaboration*



Product Quality

Cell line developers should be able to provide evidence of high product yields and products with the necessary CQAs. However, performance must be maintained once the process is transferred to the manufacturing facility and scaled to the desired volume. This requires robust, reliable cell lines and suitable methods to demonstrate quality throughout development and manufacturing.

Regulations

Biopharmaceutical developers will want reassurance that their cell line and upstream production process satisfy regulatory requirements. The biopharmaceutical regulatory landscape is constantly evolving to keep pace with scientific and technological advances. Specialist knowledge is necessary to keep up with local and global requirements for quality and safety during the development of the cell line and through to commercial manufacturing.

Scale-Up

The CLD provider should be able to deliver a robust and scalable cell line and demonstrate successful scale-up to 200 L with their cell line and media. The CDMO should ideally need minimal optimizations as culture performance should be reliable during expansion from shake flasks to larger scale bioreactors, retaining CQAs. Such considerations will save significant time and costs.

Sartorius Provides a Comprehensive CLD Solution

Sartorius 4Cell® CHO Platform service package brings together CLD, fully-optimized 4Cell® SmartCHO cell culture media, protein characterization, cell banking, and biosafety testing (Figure 3). The 4Cell® SmartCHO cell culture media was designed specifically for our CHO platform. This ensures that each clone is provided with the ideal culture conditions to maximize performance.

As a result, our clones are provided production-ready, and do not require scalability studies or media optimization, accelerating process development.

As well as providing an accessible, scalable, and robust system, Sartorius has a team of Client Managers who act as a single point of contact throughout the CLD process and during the transfer to the CDMO of the client's choice.

In the following sections, we provide data demonstrating the efficient technology transfer of our high-performing cell line to a CDMO, providing everything required to establish a clinical or commercial process.

Figure 3: *Sartorius 4Cell® CHO Platform*

Services

DNA to Cell Banks

Predictable performance and accelerated drug development with our integrated CHO platform

Cell Line Development

RCB and Basic Analysis
- Stable, ready to scale clones
- From DNA to RCB in 9 weeks
- Predictable protein titers: up to 10 g/L

Protein Characterization

Advanced Molecule Analysis
- Product quality assessments
- Assay development expertise
- Full assay lifecycle management

Cell Banking

Frozen MCB Vials
- GMP master & working cell banks
- 500 vials @ 12 million cells/vial
- Qualified Person for cell bank release

Biosafety Testing

GMP-qualified MCB | WCB
- Validated GMP release assays
- Sterility, mycoplasma, and virus testing
- Genetic characterization

Media

4Cell® SmartCHO Media

Customer Case Study – Fully Optimized Technology Transfer

We developed a cell line using our 4Cell® CHO Platform and 4Cell® SmartCHO media and transferred the process to our CDMO partner, FUJIFILM Diosynth Biotechnologies (FDB). They verified our findings in their own Ambr® 250 system before performing seed train expansion in shake flasks and bioreactors to populate a production bioreactor. FDB then compared growth performance, metabolites, culture parameters, and CQAs in their facility to the data generated at Sartorius' platform to test the reproducibility of the results.

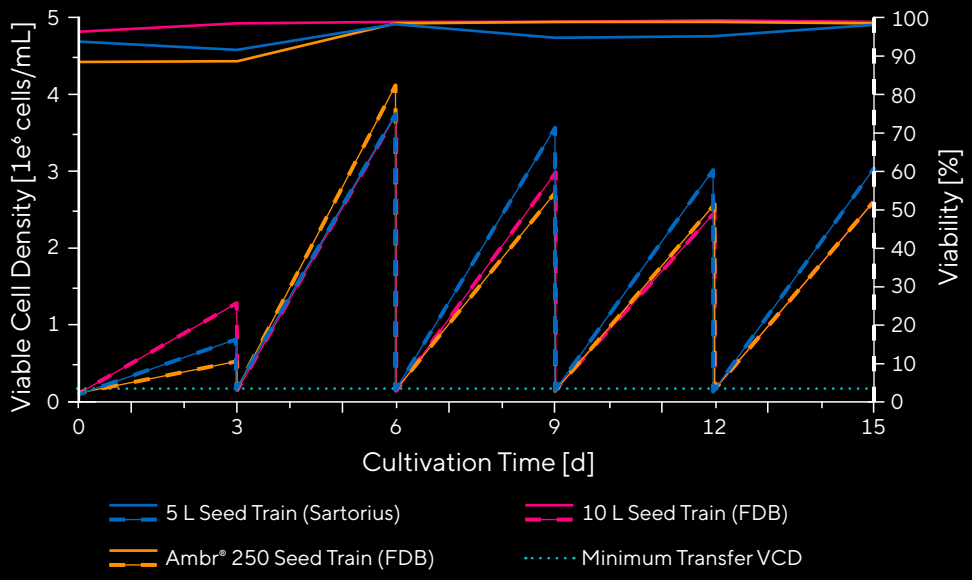
Growth Performance

Seed Train Expansion

Shake flask expansion (N-3) of the cells using the provided media generated sufficient cells to populate a 25 L rocking motion bioreactor (N-2). The viable cell density (VCD) was comparable to our in-house expansion data (5 L Seed Train) and the scaled-down Ambr® 250 bioreactor. Figure 4 shows that the cell line's behavior in the FDB's facility did not deviate significantly from its behavior in our platform or in scale-down models, indicating its scalability and robustness.

The cells were then used to seed rocking motion (N-2) and stirred-tank (N-1) bioreactors, generating a sufficient volume to inoculate the production bioreactor.

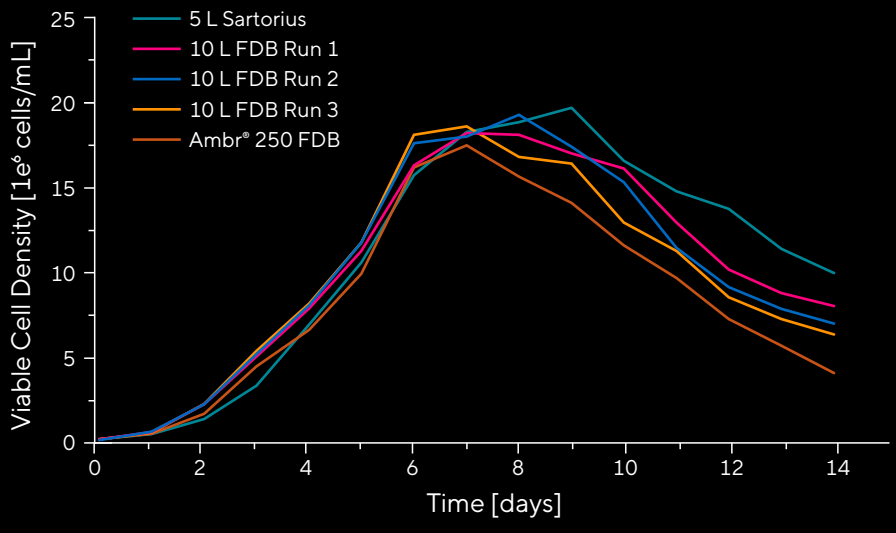
Figure 4: *Viable Cell Density (VCD) and Viability Are Consistent Between Facilities During Shake Flask Expansion (N = 3)*



Production Bioreactor

The cell line was cultivated in three 10 L production bioreactors with differing feeding strategies using 4Cell® SmartCHO media. The findings were compared to FDB Ambr® 250 data and Sartorius bioreactor data at 5 L scale. VCD was comparable between bioreactors, scales, and facilities, indicating high reproducibility, irrespective of the production system (Figure 5). The next steps should be to confirm this scalability up to 200 L.

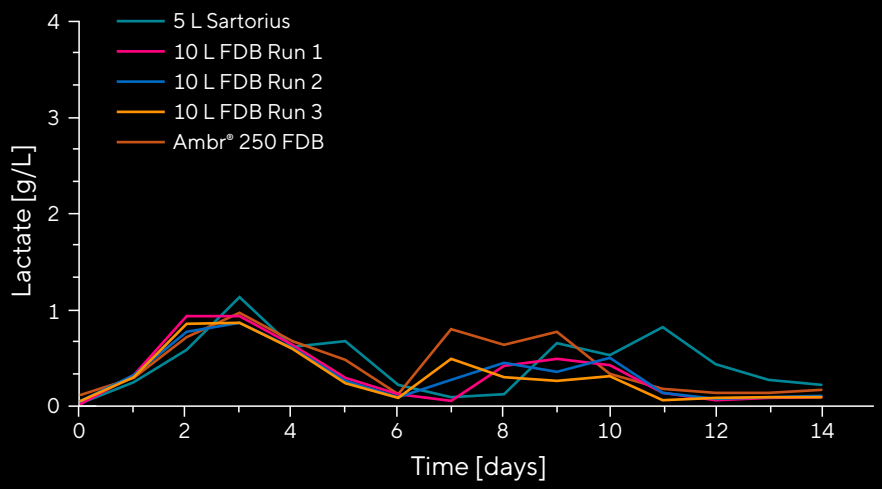
Figure 5: *Viable Cell Density (VCD) in Production Bioreactors is Consistent Between Systems and Facilities*



Metabolites

The balance of nutrients in the culture is essential to performance. High lactate levels can negatively impact cell performance and product CQAs. Lactate peaks around day 2, consistent with its production and accumulation during the exponential growth phase (Figure 6). Levels were well-controlled throughout the experiments, with comparable trends between the different bioreactors, scales, and production systems (Figure 6). Glucose, glutamine, glutamate, ammonium, and osmolality profiles were comparable between bioreactors (data not shown).

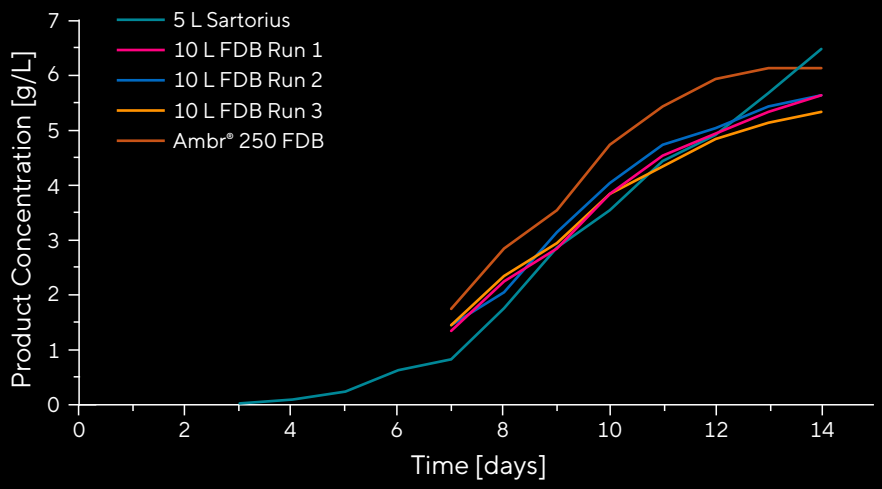
Figure 6: *Lactate Levels in Cultures Are Comparable Between Sartorius and the FDB*



Product Titer

Titers were measured during the cultivation and at the end of the process (Figure 7). Titer profiles were comparable between bioreactors at the end of the process.

Figure 7: *Product Titer is Comparable Across Systems, Scales, and Facilities*

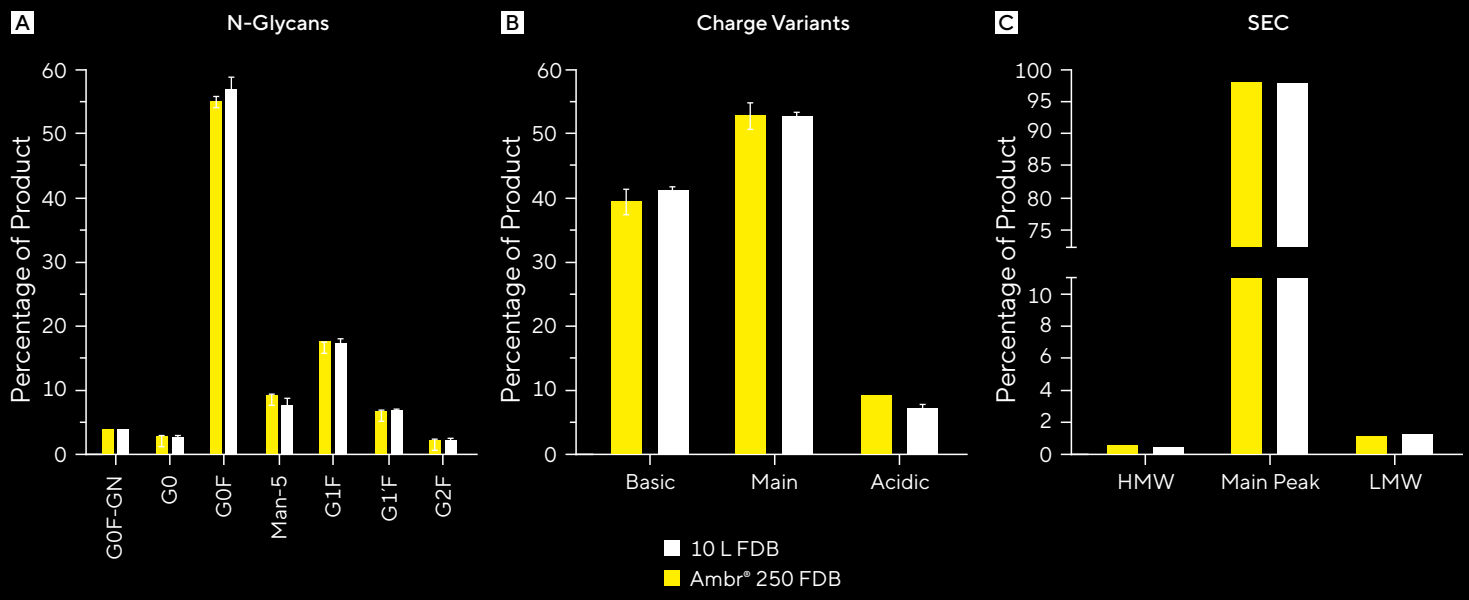


Maintenance of Critical Quality Attributes (CQAs)

A variety of methods were used to demonstrate that product quality was maintained between bioreactor processes. Figure 8 shows the presence of N-glycans, charge variants, high molecular weight species (HMWS), and low molecular weight species (LMWS), which are largely maintained between the Ambr® 250 culture and the FDB bioreactor.

Charge variants are of particular importance as they possess a broad range of underlying causative mechanisms. As such, it is important that they are maintained in the desired CQA target range during scale-up to avoid undesired effects on product stability, heterogeneity, and possibly efficacy.[3,4]

Figure 8: *Product Quality Attributes Are Successfully Maintained Following FDB Scale Up*



Note. **(A)** N-glycans, **(B)** Charge variants, **(C)** HMWS and LMWS by SEC. Material from Sartorius' 5 L bioreactor was not analyzed.

Conclusion

Small changes to cell culture processes can have significant impacts on yield and product quality. Therefore, it is important that cell lines are robust and that the transition from cell line development to manufacturing is performed carefully. However, coordinating with multiple stakeholders can make technology transfer and scale-up challenging.

The data presented here show that our optimized cell line is high performing, irrespective of the culture system used. This robust performance is supported by our highly productive 4Cell® SmartCHO media, which is designed as an all-in-one solution across processes and various CHO clones. These key factors eliminate the need for the CDMO to perform time-consuming and costly optimization runs.

This case study, in collaboration with FUJIFILM Diosynth Biotechnologies (FDB), shows how Sartorius can collaborate with a CDMO of the biopharmaceutical company's choice and support fast and efficient technology transfer. The cultures performed as expected from the outset, and CQAs were comparable between facilities, highlighting the robustness and reproducibility of our CHO platform. The seamless transition from the Ambr® 250 to 5 – 10 L bioreactors confirms the scalability of the platform from CLD to FDB.

Such a one-stop solution reduces the logistical and administrative efforts of engaging with multiple stakeholders, streamlining development and manufacturing processes. Drug developers can be confident that when they partner with Sartorius, they can successfully transfer a high-performing cell line and media to CDMOs such as FDB.

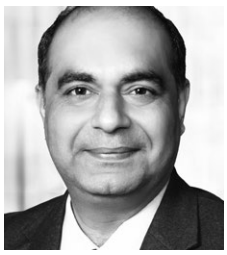
Author Bio

Lukas Klein
MSc, Scientist Bioprocessing, Sartorius

Lukas Klein has been working at Sartorius since 2016. At the beginning of his career at Sartorius, he supported customer cell line development projects in the laboratory as a technical assistant. In 2017, Lukas started his new role as an Associate Scientist in the Product Development department, where he supported the execution of internal and customer development projects in the field of media and bioprocess development.

Since 2022, he has been developing his expertise in fed-batch and perfusion CHO cultivations across scales, from Ambr® 15 and 250 to rocking motion and benchtop systems, and is also responsible for project planning and execution of the experiments.

He earned his M.Sc. in Biomedical Sciences from the University of Applied Sciences Albstadt-Sigmaringen, Germany.



Divay Bagga
Product Manager CHO Platform, Sartorius

Divay joined Sartorius in 2021 as Field Marketing Manager within Cell Line, Media, and Testing Solution where he successfully implemented the tactical marketing plan in APAC.

Trained as a microbiologist, Divay has a unique 24-year background in business development, tactical marketing, cell line development business collaborations, and strategic planning with a mission to provide his biopharmaceutical clients with a reliable solution for large molecules at an early discovery phase. Very curious, he is passionate about science, technology, and human experiences.

Dirk Mueller
PhD, Manager of Media and Process Development, Sartorius

Dirk Müller heads a product development team within Cell Line, Media, and Testing Solutions at Sartorius. In this function, he supports the development of media formulations for mammalian cell lines and early-stage cell culture processes with a knack for intensified process formats.

Before joining Sartorius, Dirk worked at Insilico Biotechnology in several positions, including team lead for the optimization of mammalian and microbial bioprocesses using predictive computational cell models.

Dirk obtained his PhD in Biochemical Engineering from Stuttgart University and conducted post-doctoral research in Computational Systems Biology at ETH Zurich.

Catherine Krikelis
Product Manager, Cell Line,
Media and Testing Solutions, Sartorius

Catherine is the global product manager for protein production media at Sartorius. She has been with Sartorius since 2021 and believes that media and feed strategies have been one of the main drivers of yield, titer, and cell density improvements over the last 15 years, especially for CHO cultures.

She holds a degree in biology from the University of Poitiers, France, and professional diplomas from the Chartered Institute of Marketing and the Pragmatic Institute. Catherine is a customer-focused product manager, passionate about helping pharmaceutical companies succeed in drug development.

Katy McLaughlin
PhD, Scientific Content Writer,
Sartorius

Katy is part of the Marketing Communications team at Sartorius, where she supports the creation of a variety of written pieces, from published articles to web content.

Before joining Sartorius in 2021, Katy was employed as a Post-Doctoral Research Associate at the University of Edinburgh, where she also completed her doctoral studies. Here, she carried out research in genetics and cellular biology and began taking on writing projects, eventually entering into a career as a freelance writer for various biotech companies and agencies.

Romina Gandenberger von Moisy
MSc, Manager of Product Specialists
Cell Line Development and Testing

Romina Gandenberger von Moisy has led a team of technical experts for cell line development & testing services within Sartorius since 2021. She joined Sartorius in 2017 and started her career as a Scientist for cell line development.

Before taking up her current position, Romina worked as an Application Specialist. In this role, she provided technical support to customers and ensured that the project scope fulfilled their requirements.

Romina holds an MSc in Biomedical Sciences from the University of Applied Sciences Albstadt-Sigmaringen, Germany.

Claas Wodarczyk
PhD, Manager of Client Management,
Sartorius

Claas heads a team of client managers carrying out cell line development, cell banking, and testing projects for customers.

Before joining Sartorius in 2021, Claas worked as team lead and project manager for technology and cell line development at Rentschler Biotechnology. He also worked as a lab head for USP development and GMP transfer (CMO) and product manager for veterinary diagnostics at Boehringer Ingelheim.

Claas studied Biochemistry at the University of Hannover, earned his PhD in the field of molecular and cell biology at GBF (HZI) Braunschweig, and conducted a post-doctoral research project on kidney diseases at DiBit Milano.

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