Annual Report 2021

EVOLVING

HSE·AG

“HERE IS GRANDEUR IN THIS VIEW OF LIFE, WITH ITS SEVERAL POWERS, HAVING BEEN ORIGINALLY BREATHED INTO A FEW FORMS OR INTO ONE; AND THAT, WHILST THIS PLANET HAS GONE CYCLING ON ACCORDING TO THE FIXED LAW OF GRAVITY, FROM SO SIMPLE A BEGINNING ENDLESS FORMS MOST BEAUTIFUL AND MOST WONDERFUL HAVE BEEN, AND ARE BEING, EVOLVED.”

On the origin of species, Charles Darwin

(Source www.darwinproject.ac.uk)

Contents

Forword 7

Vision – Mission – Promises 11

Clever integration of vital pre-analytics 13

Benchtop analysis scaled down to the size of a handheld case – and made ready for the field 15

Rapid development of economically optimal consumables 19

Rapid, cost-efficient automation of a start-up technology 23

Facts & Figures 26

Thank you 30

hseag.com

Dear Clients and Partners
Dear Employees
Dear Shareholders
Dear Stakeholders

We are pleased to present the annual report for the 5th and by far the most successful business year of HSE·AG to date. Once again, we acquired both large companies and start-ups as new clients in the life sciences and in human diagnostics, and business with existing clients was also developed further.

This repeated success emphasizes the outstanding positioning of HSE·AG. The company's understanding of the sum of all interactions between the components of systems for sample processing and analysis of nucleic acids, proteins and cells is one of a kind. Clients want HSE·AG to design complete systems and also individual system components to automate manual workflows, including plastic consumables.

Start-ups get advice and expertise from HSE·AG to advance their innovative technologies from an early stage of development to series production. Among other things, HSE·AG supports companies in stabilizing acquired technologies that are still immature and in making them marketable. With HSE·AG taking on the testing of new technologies and the development of next-generation products, companies can reduce their risks while relieving their internal development departments.

Pioneering projects

As in the previous year, 2021 was dominated by the Corona pandemic. The life sciences were able to demonstrate their enormous innovation dynamics. Efficient molecular diagnostics and the rapid development of mRNA vaccines have saved millions of lives, and most people have been able to live relatively normal lives with comparatively few limitations despite the pandemic.

Over the course of centuries, pandemics have repeatedly led to global catastrophes. The Black Death, in the middle of the 14th century, wiped out nearly 40% of the world's population. In our recent history, Spanish flu claimed many more lives than World War 1 which came before it, and the AIDS pandemic has also claimed more than 35 million lives since 1980. It is only a matter of time before the next epidemic or pandemic comes. Therefore, further development and expansion of diagnostics and treatment of infections is crucial. HSE·AG works on the diagnostic platforms and technologies of the future with leading manufacturers worldwide.

Sample quality is a crucial starting point for any diagnostic application. Biological samples are usually very heterogeneous and are made up of a large number of different components. However, in most cases, just one specific molecule is analyzed. Since heterogeneity often prevents simple analysis of this molecule, elaborate upstream sample preparation processes must be performed. These make the systems complicated and expensive. In addition, most analyses require special labeling procedures to identify the target molecule.

In collaboration with the start-up Lino Biotech, HSE·AG is developing a novel system that also works with heterogeneous biological samples and does not require labeling. It is based on the so-called focal molography. Laser light is coupled onto a chip by means of a grating. The scattered light encounters mologrames that can be prepared to specifically bind the molecule of interest. The binding results in diffraction, which can then be measured.

HSE·AG was also active in 2021 in another field that is central to humanity: food security. Most of us have grown up with the concept of peace, health and food security. At the same time, famines have been a recurring threat in centuries gone by. Even in the 20th century, more than 50 million people died of hunger. Advancing global warming could exacerbate the situation again. It is already having a measurable impact on crop yields in a variety of regions in the world.

In addition to land area, water and fertilizers, seeds are a critical component of food production. Pollen fertility must be ensured to provide efficient pollination in seed production. HSE·AG has developed the world's first portable impedance-based flow cytometer with Amphasys. With this, even non-experts can assess the fertility of pollen in the field and, thus, the optimal time for harvesting the pollen.

Focus on the client

Our clients and employees are equally fascinated by both the complexity of life and the technologies that can be used to explore this complexity. However, it is not primarily technical challenges that stand in the way of project success in the life sciences. The most important success factors are, in fact, the project team and the teamwork.

The project managers – typically one at the client's site and one at HSE·AG – play a crucial role. They are not only responsible for creation and implementation of the project plan and the goals agreed in it. Their biggest challenge is internal and external communication. This starts with agreeing on terms such as prototype, continues with reaching a consensus on the development process and ends with the question of whether the project should be driven forward as an agile project, via a waterfall model or a mixed form.

"HOWEVER, IT IS NOT PRIMARILY TECHNICAL CHALLENGES THAT STAND IN THE WAY OF PROJECT SUCCESS IN THE LIFE SCIENCES. THE MOST IMPORTANT SUCCESS FACTORS ARE, IN FACT, THE PROJECT TEAM AND THE TEAMWORK."

A particular challenge in system development projects is the very high level of complexity that is always present. The interactions of the components from the working conditions in the laboratory, to the biological/medical applications, the chemistry, the consumables, the device elements, the software, the hardware and the electronics must be understood and mastered. Therefore, unpredictable events occur continuously in these projects, and decisions have to be made regarding them. A communication plan that involves all stakeholders, from the client to the specialists in the various disciplines, is therefore essential. And, of course, efficient V-model-based design controlling with requirements engineering and traceability is also needed.

Typically, in system development projects, the requirements for the product to be developed also change over time. For this reason, efficient change control is absolutely essential. HSE·AG's project managers, engineers and scientists are proficient in these approaches, implement projects accordingly and advise clients on both technical and market-related decision-making. This gives our clients maximum transparency and allows them to make the best decisions at all times.

Looking ahead

2021 was characterized globally by restrictions due to the corona pandemic. However, the rapid availability of vaccines has significantly reduced the risk of the pandemic. Nevertheless, as a result of this easing, the volume of tests carried out for our clients did not decline to the extent expected, but remained roughly at the previous year's level.

Currently, diagnostics companies are trying to expand the testing portfolio of their platforms. The goal is to maintain the high sales from the pandemic. To this end, tests such as those for tuberculosis, which were neglected during the pandemic, are being ramped up again. Nevertheless, overcapacity is likely to remain, triggering cut-throat competition.

HSE·AG therefore expects companies in this field to continue to drive their innovations while continuing to increase cost flexibility and outsource their activities. As a specialized and focused service provider, HSE·AG can benefit from this trend. Corresponding inquiries from leading life sciences companies confirm this assessment.

A second defining trend concerns the reorganization of global supply chains. Supply chain problems have arisen worldwide, triggered by the pandemic, highlighting the issue of global dependencies. A deglobalization trend can currently be observed enabling companies to act more independently at a regional level. This will lead among other things to a preference for local providers. HSE·AG should benefit from this. Although HSE·AG's clients are globally active companies, their development focus is predominantly in Europe.

With a clear focus on simplifying and automating laboratory workflows for nucleic acids, proteins and cells, HSE·AG believes it is excellently positioned to continue to operate successfully in a changing world order.

Hans Noser
Chairman of the Board

Michael Collasius, Ph.D.
Chief Executive Officer

“In HSE•AG, we have found an expert partner for the development of a complex microfluidic interface and its integration into our modular cell analysis platform.”

Dr. Marco Di Berardino, CTO,
Co-founder & Executive Partner,
Amphasys AG

VISION

We help our clients achieve their next scientific breakthrough.

MISSION

By combining our application and engineering expertise, we aim to develop superior tools that enable our clients to understand the key principles of life. In doing so, we implement systems and processes that meet the precise needs of our clients.

PROMISES

1 We focus all of our energy not only on meeting our clients’ expectations, but also on exceeding them whenever possible. They should receive the greatest possible added value and the best possible quality.

2 The consistent application of our clearly defined processes and the uncompromising implementation of all requirements of our clients and regulators ensure the safety and performance of our products and services.

3 All of our employees at all levels are required to comply with all applicable specifications of our clients and the authorities and to ensure effective quality management at all times. We want to make a clear difference for our clients through our high-quality services.

4 To continue to boost our performance, we embrace continual improvement methodologies in compliance with regulatory requirements. We set objectives for the systematic management of these processes and review them regularly.

Clever integration of vital pre-analytics

Sample concentration and quality are crucial success factors for all nucleic acid technologies. However, measurement of these has mostly been carried out in external stand-alone devices up to now. With Colibri, HSE·AG has now developed a concept for a module that can be easily integrated into any liquid handler. This enables a seamless process that not only saves time, but also reduces costs. Device manufacturers can test the method with an evaluation kit and choose between several business models.

It doesn't matter if the context is medical, for example detection of circulating tumor cells, if next-generation sequencing and quantitative PCR methods are being used in research or if performed prior to cloning and transfection experiments, quantification and determination of the purity of the nucleic acids in a sample are among the most important pre-analytical procedures. If the sample quality cannot be determined reliably, this places a question mark over the validity of the results and experimental success.

Established methods but a lack of integration

Nowadays, a variety of devices on the market fulfill these tasks. Most rely on measuring UV absorption in the wavelength range between 230 and 320 nanometers, where nucleic acids and proteins have different absorption maxima.

But although they provide reliable results, almost all current devices have one major drawback: they are stand-alone solutions that are not integrated into the rest of the analysis process. Either each sample must be measured individually in a spectrometer or aliquots of the samples are transferred to plates that are then read in an external instrument. This break in the process requires time and additional consumables and, as always, results in a loss of the usually scarce samples.

HSE·AG has invested in implementable solutions

"We have encountered this obstacle in workflows in a variety of client projects", explains Konstantin Lutze, HSE·AG's Chief Technology Officer. "This is why we addressed the issue with our Innovation Guild." The in-house innovation team first carried out a detailed market analysis to highlight the gap in the processes of various equipment manufacturers. Then, in an iterative process, solutions were generated and these were then condensed into implementation variants.

The current result of this multi-stage development work is functional models with which all crucial steps and their feasibility were checked. The determination of quality and concentration can be easily integrated into any liquid handler by means of a special module. This requires just a small area on the workdeck and does not consume a single microliter of the samples.

Pipette tips transport the cuvettes

Special UV-capable cuvettes are at the heart of the patent-pending process. They are automatically attached to the pipet tips of a liquid handler and transported with them between the sample vessels and the sensor unit. Designed as consumables, the COC (cyclic olefin copolymer) cuvettes with their rectangular shape guarantee an exceptionally reliable and reproducible optical path in the sensor unit. Thanks to a well thought-out process, the measurement volumes of just a few microliters required for each sample can be pipetted back into the sample vessel without risk of contamination, or used directly for subsequent pipetting procedures. With the Colibri process, named after the intelligent nectar-drinking hummingbird, none of the sample is lost.

Furthermore, the modules can be easily adapted to the requirements of specific applications. Dilution steps can be seamlessly linked to the concentration determination or the process can be parallelized for efficient processing of entire racks.

Added value for clients with lower costs

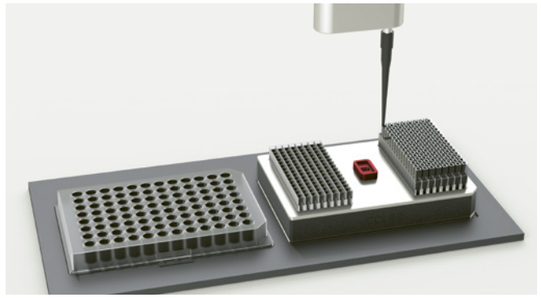
With the Colibri solution, liquid handler manufacturers can offer their customers extremely attractive added value. The module accelerates the analysis process and ensures maximum reliability and reproducibility of the results. At the same time, costs can also be saved compared to an additional stand-alone solution. Instead of a full-blown reader, only a slim sensor unit is required. And by using standard pipet tips as transport vehicles, the cuvettes as the only consumable can be of a very small size and their manufacturing costs can be kept correspondingly low.

Depending on the needs: OEM, licensing or asset deal

Several business models can be selected for the use of Colibri. In the typical OEM model, HSE·AG produces the components and cuvettes and delivers them to the device manufacturer ready for use. If a client wants to produce these themselves, they can do so by means of a license model. Finally, exclusive use of the technology is possible via an asset deal in which all rights are transferred.

Many years of experience in innovations for the entire industry

Mr. Lutze still has many plans in petto with his innovation team: “Our long, extensive experience with DNA and RNA puts us in an excellent position. The successful COVID PCR testing and sequencing and the mRNA vaccines have created tremendous additional momentum in the field of nucleic acid technologies. We can be very effective in helping manufacturers leverage these technologies for their applications and products.”



About the author

Konstantin Lutze has more than 25 years of experience in the development of laboratory automation and in vitro diagnostic systems. After originally training to be an electrical engineer at the University of Stuttgart, he took on the position of CTO at HSE·AG right from the start. Previously, as VP Instrument Development at QIAGEN, Lutze was responsible for the successful development and market launch of a next-generation sequencing platform, among other things. As CTO, he is now responsible for technology management and drives innovations in the analysis of nucleic acids, proteins and cells with which HSE·AG provides its clients with significant added value.

Interdisciplinary kneading of ideas in the Innovation Guild

Successful innovations do not fall into your lap, and only a small proportion of them are the result of ingenious ideas. For innovations to be successful on the market, they must provide clients with a specific benefit. This is achieved through a combination of brainwork and practical tests, with which the feasibility is continuously checked. “For an idea to become a product innovation, it has to be kneaded intensively,” as Konstantin Lutze, Chief Technology Officer, figuratively describes the process HSE·AG uses to drive new developments like Colibri internally.

This kneading of ideas until they are formed into functional models or prototypes is handled at HSE·AG by the so-called Innovation Guild. In this team, five to eight specialists from all areas of expertise analyze market gaps, generate concept proposals and condense these in an iterative process. For Lutze, the key to this is not to apply filters too early: “Good approaches not only need to be recognized, they then need to be developed up to a certain point. In doing so, you have to prevent ideas from being written off too quickly because of obstacles that arise.” HSE·AG engineers do not focus on the obstacles, but on the question of what needs to be changed for an idea to work.

The innovations that HSE·AG develops in its own projects always benefit equipment manufacturers and suppliers of analytical methods. They address – as in the example of Colibri – either individual breaks in the automation workflows of the applications, or – as in the case of the PreOn cell protein sample preparation device developed for PreOmics – they are incorporated into the overall development of a novel solution for the client.

Benchtop analysis scaled down to the size of a handheld case – and made ready for the field

The closer life sciences applications are to the end customer, the greater the impact they have. This applies not only to medical tests, but also to analysis of pollen quality in agriculture. By means of a microfluidic chip in a robust handheld case, HSE·AG has made the groundbreaking impedance flow cytometry technology of Amphasys portable and ready for use in the field. To achieve this, the complex laboratory technology was scaled down to a minimum and operation was simplified to such an extent that even personnel without special knowledge can reliably perform analyses on site.

Pollen quality is critical for crop yields. This applies to seed production and crop breeding as well as to the production of fruits and nuts, which is supported by artificial pollination. Breeding success and crop yields depend directly on the vigor and quality of the pollen. Amphasys has developed a groundbreaking technology that can reliably and quickly determine the condition of pollen grains.

The technology from Amphasys is based on a microfluidic chip that can distinguish minute changes in the electrical resistance of biological cells. Because live and dead pollen grains differ in their impedance behavior, this measurement can accurately determine both the proportion of live pollen grains and their size and number. This makes it possible, for example, to identify the optimal pollination time and the most suitable pollen batches. Or it can be used to investigate and monitor the influence of humidity, temperature or pesticide use on pollen quality.

Simple measurement on a microfluidic chip

The major advantage of the Amphasys technology is that, unlike previous applications, it does not require fluorescence technology with sophisticated optics, toxic chemicals and time-consuming staining steps. The electrical resistance is measured directly in the sample solution in a narrow space in a flow capillary. Up to 60,000 pollen grains per minute can be analyzed. As a result, users save a huge amount of time and money on consumables.

Portable application increases effectiveness

In addition, the effectiveness of the method can be increased by performing the measurement directly in the field rather than in the laboratory. This eliminates the need to transport the samples from the plantations to the central laboratories of user companies, and the measurement results can be incorporated directly into the work on site. This is all the more important, because many agricultural areas are very remote and the various plantations are also usually far apart. Portable on-site testing allows for much better monitoring, especially for crops with short-lived pollen such as wheat, rice or corn.

Scale down the technology and simplify operation

Two key requirements had to be mastered to achieve the target goal. Firstly, the entire mechanics and liquid handling system of the previous benchtop device had to be scaled down from the volume of a large, fully automatic coffee machine to such a size whereby everything – together with a powerful rechargeable battery and an evaluation console – fits into an easily transportable handheld case. On the other hand, user operation had to be drastically simplified and the software had to be optimized for the 7-inch touchscreen evaluated. The Amphasys software team took on this task. The resulting error-prone project interface was managed excellently by the team by means of short communication channels. Simplifying the software and graphical user interface is particularly important so that employees in the field who do not have any special laboratory training can also perform analyses independently and reliably.

What remains: 3 tubes, 1 pressure sensor, 4 valves and a manifold

To achieve the goals that were set, the entire fluidics – with the exception of the supplied Amphasys measuring chip – had to be redeveloped. For this purpose, the liquid handling system was integrated into a so-called manifold. The component, which is milled in synthetic resin, contains the entire system through which the samples and reagents flow on an area of just a few square centimeters. As a result, the dead volumes are kept to a minimum and the device contains only three tubes, one pressure sensor and four valves for the fluidics.

Cheaper maintenance thanks to fluidics expertise

Integration of the fluidics system into the manifold also significantly minimizes the sources of mechanical faults and the amount of maintenance required. This not only reduces operating costs. When used in remote agricultural areas, the risk of the work being interrupted for a prolonged period of time is also reduced in case the device needs to be repaired at a distant service center.

The technical solution developed for Amphasys emphasizes the unique competencies of HSE·AG in development of plastic fluidic components. The engineers can find the optimal solution for a wide variety of applications, reconciling even contradictory requirements – such as mechanical simplification, minimal size, cost-effective production and maintenance.

Touchscreen with battery permitted in checked baggage

A touchscreen was built into the case and intuitive software was developed for easy operation. Today, a commercially available system-on-a-module solution replaces the laptop that was required to control the previous benchtop device and for data evaluation. The battery capacity is designed for approximately 6 hours of full operation thus ensuring that measurements can be carried out for a full day in the field. If a full battery charge is not sufficient, a new fully charged battery can be inserted in a few simple steps (cordless screwdriver principle).

In addition to the self-explanatory operating software based on touch commands, sample handling has also been greatly simplified. All the user needs to do is take up pollen in the sample liquid, place the sample tube in the appropriate holder and insert the correct microfluidic chip. After that, everything from measurement to evaluation is automated. This ensures that less qualified users in remote fields can perform measurements on their own.

Field tests show practicability

The practicability of the portable system was tested with four identical prototypes by key Amphasys customers. The innovative system received extremely positive feedback from all sides. Thanks to the valuable feedback, the device was optimized and developed further to series-production readiness. A significant detail for the practical application of the portable analyzer is the option of removing the battery from the case. This allows the device to be transported as checked baggage on a passenger aircraft. This is a feature that not all potential customers may need. However, quite a few will greatly appreciate it.

Life science applications are becoming portable

With the recent successful launch on the market of the portable system under the name “Ampha P20”, Amphasys is one of the trendsetters in life sciences analysis.

Whether as point-of-care devices in doctors’ offices or pharmacies or as home testing applications, more and more analytical tests are being carried out on a portable basis, i.e., as close as possible to end customers and, whenever possible, by end customers themselves. This reduces the effort required for the measurements and dramatically reduces the waiting time for test results. Accordingly, measures can be derived from the measurements more quickly and there is a greater chance of these measures succeeding.

Scaling down technologies to portable dimensions and simplifying operation to make an analysis device suitable for lay persons requires very specific know-how and corresponding experience from the development engineers. With the “Ampha P20”, HSE·AG has once again proven these competencies.

About the author

Michael Steck graduated with an MSc in Mechanical Engineering from ETH Zurich in 2017. Before and during his studies he worked part-time for several diagnostic companies such as Roche and Tecan. After completing his studies, he worked as a consultant in aerodynamics and as a Project Manager for large-scale ICT projects.

Since joining HSE·AG in 2019, Michael has a dual role as Senior Project Manager and Mechanical Engineer. With his strong focus on project management and his technical and customer-oriented background, he leads several R&D projects with different interdisciplinary project teams.

Rapid development of economically optimal consumables

Rapid prototyping minimizes risks in the development of plastic consumables. To ensure that all issues can be addressed quickly and conclusively, non-additive processes such as precision milling and rapid injection molding with aluminum molds must also be considered, emphasizes Felix Westhoff, HSE•AG's Head of Projects and Quality Management. The advantages of the individual technologies are fully realized when the development engineers have established a partner ecosystem that encompasses the entire range of processes.

Mr. Westhoff: Rapid prototyping in the development of consumables – isn't that using a sledgehammer to crack a nut?

Actually, the reverse is true. In many applications today, the consumables are a crucial factor for the cost-effectiveness of the entire solution. The advantages and disadvantages in their design add up with each analysis performed – from the unit cost of plastic goods to the efficiency of processes to reagent consumption. Furthermore, the market launch is subject to additional costs and delays if a new injection mold is required because design errors have to be corrected.

What methods are typically used in the development of consumables?

We do not just use individual methods, but cultivate an evolutionary approach instead. This means that we gradually refine the granularity of the problem during the development process and also work out increasingly sophisticated functional models. The prototyping method that is best suited for the specific problem is used for each iteration step.

Can you be more specific?

As a first step, the spatial conditions and interfaces in the instrument, such as contact points for gripper systems, are most interesting. For these, we can work with fast procedures such as stereolithography in the first step. In the same way, the plastic does not yet have to meet any special requirements at this stage. This changes when, in further steps, specific functions such as fluid paths, mounting methods, tightness of closures, optical transparency or thermal conductivity are to be tested.

Are as many functions as possible integrated into a functional model to be able to test as efficiently as possible?

No, experience shows that it is more efficient on balance if the questions are kept as simple as possible. If only one requirement is addressed per functional model, the results are unambiguous, and questions can be answered more quickly. In addition, the process and plastic material can always be optimally adapted to the individual requirement. Therefore, only the minimum effort is required.

A huge number of different rapid prototyping processes are available today. How can you master all of these at HSE•AG?

We have a stereolithography device in-house. This allows us to create initial functional models overnight and define, for example, the dimensions and interfaces to the other system components. In addition, the resins are being continuously developed further. This is why more and more functions can be tested with this method. For example, we can now also use elastomers to print seals or ceramic resins that greatly expand the range of available mechanical and chemical properties.

“IN MANY APPLICATIONS, THE CONSUMABLES ARE THE CRUCIAL FACTOR FOR THE COST-EFFECTIVENESS OF THE ENTIRE SOLUTION. THE ADVANTAGES AND DISADVANTAGES IN THEIR DESIGN ADD UP WITH EACH ANALYSIS PERFORMED – FROM THE UNIT COST OF PLASTIC GOODS TO THE EFFICIENCY OF PROCESSES TO REAGENT CONSUMPTION.”

But not everything can be made using stereolithography?

If greater accuracy is needed or more demanding plastic materials need to be used, more complex processes such as selective laser sintering are required. We work closely with a specialized partner for these procedures. Together, we can continuously push the boundaries of these technologies a little bit further. And, if necessary, several methods can be combined to answer a specific question with the desired accuracy.

Can prototyping be achieved nowadays just using additive processes?

For tasks that require a very high degree of precision, such as small threads that must seal tightly, additive processes are often still too imprecise. In this case, we work with a microtechnology service provider who is proficient in precision milling. And if absolutely clean surfaces are required, for example if optical detection is to be tested, this can often only be achieved using injection molding processes. For this, too, we have an established collaboration with a partner specializing in rapid injection molding who not only delivers the quality we demand, but also works with us to explore the possibilities of the process. For me, precision milling and rapid injection molding are as much a part of the rapid prototyping palette as laser sintering and stereolithography.

But aren’t they much more time-consuming than additive methods?

Each process takes a certain amount of time. This is taken into account when deciding which method is to be used for which question. Our in-house stereolithography device provides a result in a few hours. Our partner’s delivery time for laser sintering is about two days and precision milling takes about a week. Rapid spraying processes are a bit more time-consuming. However, by working today with partially prefabricated aluminum molds into which only the specific cavities have to be milled, delivery times of a few weeks can be achieved.

Is rapid prototyping completed when all functions that the plastic component must fulfill are tested?

Not quite. At the end, the entire workflow must be brought together. For this purpose, either a prototype is produced that integrates all functions or – because integration is often not possible before production injection molding – the entire process is simulated using various functional models. In this final step, it is important, firstly, to have a clear understanding of the strengths and weaknesses of each rapid prototyping method and to be able to interpret their results correctly. On the other hand, you also need a lot of experience with the special effects that can occur in injection molding production. For example, the plastic parts shrink at different rates depending on the cooling rate and on the exact orientation of the molecular chains at different points. Furthermore, the positions where seams may occur must also be included in the planning. The behavior of injection molding in production can never be predicted down to the last detail, even with the most modern simulations. However, practice shows that our approach fully verifies the function of the consumables during development and, thus, guarantees the desired behavior of the series products.

What are the bottom-line success factors in rapid prototyping of consumables?

For me, the two most important success factors are experience and partnerships. Experience is required in both the prototyping processes and analytical laboratory applications in which the consumables are used. It allows development to proceed in a much more targeted manner and, thus, more quickly and effectively. On the other hand, partnerships in which communication takes place on equal terms ensure that clients always get the most out of the technologies currently available. This is the only way to minimize the technical and financial risks involved in investing in a complex injection mold.

About the author

Felix Westhoff has worked as a project manager in medical technology and laboratory automation in diagnostics and the life sciences for more than 15 years. The range of experience of the Head of Project and Quality Management at HSE·AG includes, in particular, system, consumable and process development in regulated environments (ISO 13485; ISO 9001; ISO 14971; 21 CFR Part 820), as well as extensive technical expertise and management of international and multi-site project organization.

Rapid, cost-efficient automation of a start-up technology

Lino Biotech has developed focal molography – a novel technology. This raises analysis of the interactions of biological macromolecules to a whole new level. HSE•AG is automating the method. The requirements for this are very stringent. Reliable and efficient processes must be developed for a novel technology while, at the same time, strict requirements in terms of costs must be fulfilled. To achieve this, HSE•AG developers work very closely with method experts from the start-up and with a company specializing in measurement optics.

The life sciences are developing at a breathtaking speed. The driving forces here are start-up companies that use novel technologies to open up previously inaccessible areas of medicine and biology. These trendsetters include lino Biotech. The start-up company, which emerged from a collaboration between the Roche Innovation Center and the Laboratory for Biosensors and Bioelectronics at ETH Zurich, wants to take measurement of interactions between biological macromolecules to a new level with a novel technology.

Focal molography analyzes complex molecular interactions in a biological context without upstream sample purification steps and in a label-free manner. Therefore, it avoids signal interference due to temperature changes or non-specific binding. This opens up a whole range of new applications; from medical diagnostics and drug efficacy research to the control of biotechnological manufacturing processes and, especially, for rapid and cost-effective quality control in the production of cell and gene therapies.

Partnerships with start-ups drive HSE•AG forward

HSE•AG is not just helping lino Biotech to automate the process quickly and effectively. The start-up's solution must also be financially viable. "For us, collaborations with start-ups like lino Biotech are strategic. Each time, we push the boundaries of what was previously possible and expand our application expertise. At the same time, start-ups usually have only limited financial resources," says Kai Hassler, Principal Scientist who leads the lino project at HSE•AG. "This combined challenge brings us a few steps further each time, both in terms of technology and project implementation."

Competencies must be a good fit and the technology must convince

For this reason, HSE•AG chooses its start-up partners carefully. On the one hand, the specific needs of the company must match the engineering competencies of HSE•AG. On the other hand, HSE•AG must also be convinced of the technology innovation. lino Biotech fulfills these requirements perfectly. Focal molography is a completely new method that enables analyses of interactions between macromolecules, such as nucleic acids or proteins, that were previously impossible.

The technology is based on a sensor chip made of glass. Chemical binding sites are applied to the chip in a special pattern of lines by means of nanolithography. Binding partners of the biomolecules to be analyzed can be bound to these sites. When the biomolecules in a sample bind to these binding partners on the chip, they form regular grid lines. Like a lens, these focus light of a specific wavelength that illuminates the sensor chip. By analyzing the focused light, precise conclusions can then be drawn about the binding between the molecules and, for example, the binding constants can be determined or the binding kinetics can be studied in detail.

Efficient and economical

The foundation was laid in the 1990s at the Roche Innovation Center in Basel by Christof Fattinger, who is now a member of the Scientific Advisory Board of lino Biotech. From 2014 to 2020, he worked together with the research group of Janos Vörös at ETH Zurich to develop the method to application maturity. lino Biotech is the first spin-off from this development cooperation to turn the method into marketable products.

HSE·AG ensures, among other things, that the product will bring clear advantages economically and also in terms of performance. The objective is to automate the method in such a way that the analyses can compete in cost with SPR spectroscopy (surface plasmon resonance). Although this technology is much less powerful, it has been established for a number of years. To ensure the success of this, HSE·AG works very closely with the method experts at lino Biotech and with an optics specialist. In addition, a supplier specializing in flow cells and an industrial design company are also involved in the project.

Weekly fixed day at HSE·AG

The setting for the cooperation of the three main partners is a weekly fixed day at HSE·AG in Hombrechtikon. For Hassler, the close networking with regular meetings at short intervals is an important success factor in the project: “We hold a joint half-day work meeting with lino Biotech once a week in Hombrechtikon. Because this setup enables us to exchange information informally in an uncomplicated way, we make rapid progress.”

Particularly high demands were placed on the optics module that is used to analyze the focused light. In this, two lasers generate light with two different wavelengths. Detection then takes place via three channels. One measures the actual mologrames, while a second and third channel record the fluorescence of the chip surface and the scattered light. These data provide additional information on the mology and improve process control. lino Biotech has invested heavily in correction algorithms over the past few years. Using these, much more information can be gained from the evaluation process.

Tiny spatial conditions with no scattered light

The challenge with the flow cell lay primarily in the precise bonding of the mology chip to the plastic cell, in which all the microfluidics are incorporated. At the same time, the spatial conditions are tiny. 54 different binding sites on a chip need to be connected via a channel system that the chemicals and biological samples flow through. In the final flow cell, the narrow channels and inclusions in the bonded areas should not lead to scattered light.

To ensure that this is successful not just in the prototypes but also later in production, a particular focus was placed on the adhesive application process. The sensor chip and plastic components are now bonded, after being pressed together precisely, using an adhesive that is hardened with UV light.

Gene and cell therapies are the first to benefit

Now that lino Biotech has successfully tested the first customer applications with the functional model of the biosensor device, work is currently underway to develop the first prototype devices.

Cell therapy manufacturers are the first main target market for the technology. The quality of the cells is crucial for this rapidly growing biomedical field of the future. Mology chips don’t just enable 54 different samples to be tested at once. Likewise, fluorescence labeling and sample purification are no longer required. The measurements can be performed directly with materials from production. In addition, the measurements are much less sensitive to temperature changes or non-specific binding than the SPR technology used up to now. Therefore, cell therapy providers can use this rapid assay from lino Biotech to simultaneously reduce their production costs and increase the treatment success of their therapies.

Huge potential and strong implementation partner

However, a technology for rapid and cost-effective quality control for production of gene and cell therapies is just the beginning. The interactions of macromolecules form the basis of the communication between the X trillion cells in our body. Gaining insights into the highly complex cellular communication networks is an essential prerequisite for understanding many diseases and then curing them. With focal mology, the life sciences now have a technology for measuring molecular interactions that can shed light on nature’s intricate communication pathways. With HSE·AG, lino Biotech has a partner for the transition to marketable products that has wide-ranging application experience and technological expertise in the field of biological macromolecules.

About the author

Kai Hassler graduated from University of Vienna, Austria in Theoretical Physics MSc in 2001 and from EPFL Lausanne, Switzerland in Biomedical Optics PhD in 2005.

Since joining HSE·AG in 2017, Kai is facing a role as Principal Scientist. With his strong skillset in advancing technologies such as Fluorescence Optics or Next Generation Sequencing and Laboratory Automation, he leads several R&D projects with different interdisciplinary project teams within HSE·AG.

Facts & Figures for the 2021 financial year

HSE•AG was able to significantly expand its client base once again in the financial year 2021, and also retain the clients it has acquired to date. Revenues increased by 18% to CHF 12,49 million. The service business grew by 15%. The gross profit to operating profit ratio EBITDA increased to 12%. HSE•AG's financial strength increased further, with the equity ratio rising from 32% to 42%. Liquidity factor 1 is 47, previous year: 113. The calculation includes normal accruals and depreciations, where necessary.

Key figures

In 2021, HSE•AG achieved sales of **CHF 12,49 million,** a growth of 18% compared to the previous year. This resulted in a net profit of **CHF 502,339** (2020: 287,768).

These business results gave rise to the following key figures:

4.07 %

Previous year: 2.65 %
Return on sales

47

Previous year: 113
Liquidity factor 1

42 %

Previous year: 32 %
Self-financing ratio

Appropriation of profits

		2021	2020
Retained earnings, beginning of the fiscal period	CHF	1'509'518	1'221'749
Net profit	CHF	502'339	287'768
Available retained earnings	**CHF**	**2'011'857**	**2'011'857**

The Board of Directors proposes to the General Meeting that the profit be appropriated as follows:

		2021	2020
Payment of a dividend of	CHF	0	0
Allocation to the legal reserves	CHF	0	0
Allocation to the free reserves	CHF	0	0
Carried forward to new account	CHF	502'339	1'509'518
Available retained earnings	**CHF**	**2'011'857**	**1'509'518**

Audit of the financial statements

The annual financial statements of Hombrechtikon Systems Engineering AG for the financial year 2021, which covers the period from January 1, 2021 through December 31, 2021, were audited on April 11, 2022 by Treucontrol AG as external auditors in accordance with the Swiss Standard on Limited Audits.

Risk assessment

In the first year of its existence, HSE•AG established a quality management system in accordance with ISO 13485:2016 for the development of IVD (in vitro diagnostic) systems. This was successfully recertified in November 2021. Risk management is an integral part of this system. To identify both risks and

opportunities at an early stage, HSE·AG regularly reviews internal and external factors across the entire corporate environment. The financial data determined for the financial statements in accordance with the Swiss Code of Obligations and the risk-related financial figures in accordance with the regulatory requirements form the basis for this review.

Employee competencies

HSE·AG has an exceptional breadth and depth of expertise among its staff. Its employees come from **8 different countries.** Their competencies cover the entire spectrum of technology and project implementation requirements for the development of life sciences and diagnostic solutions based on molecular biology. In combination with many years of experience, they represent a crucial competitive advantage for HSE·AG.

Employee development

In 2020, the workforce increased from 51 to **52 employees.** The workforce includes 3 apprentices (one commercial apprentice and one IMS trainee), which results in an apprenticeship quota of around **5.7%.**

The turnover rate remained below 10%. This means that in its third financial year it is already at a standard industry level. The fact that all vacancies due to turnover have been filled and additional employees have also been brought on board shows that HSE·AG is well positioned in the extremely competitive international labor market for highly skilled professionals. Furthermore, HSE·AG employed six contractors in the second half of the year.

Employee participation program

An important cornerstone for the long-term business success of HSE·AG is the employee participation program launched at the end of the first financial year. Selected employees can acquire participation certificates through this program. The value of these is strongly linked to the success of the company. The purpose, detailed participation conditions and calculation of value of employee participation are documented in the program regulations.

After the fifth financial year, the value of the participation certificates is 33.46 times (2020: 33.17 times) the original nominal value of CHF 0.01.

Employees will be able to acquire further participation certificates in 2022. Around 80% of HSE·AG employees have taken the opportunity to participate in the company to date. This high proportion shows that employees also have great confidence in the sustainability of the HSE·AG business model.

52
Employees

3
Trainees

80 %
of employees have a stake in HSE·AG

“We quickly arrived at an elegant solution by trying many different ideas for the design with low risk and within aggressive timelines.”

Crystal Stephens,
System Development Lead, Roche

LUDWIG MARTINA TOBIAS NICHOLAS ANTONIO JEAN PASCAL MIKE STEVE
DIRK JAKOB ALMA URS LENA UDO ANGELA REINER JONAS MEIKE INGO
MARTA AXEL MARIJA RON FRAUKE HIAM ALEXIS HANS CHRISTIAN ALEXANDER
MOHAMMAD MARIO JOHN JANE MARGARET LINUS GIULIANO STEPHANIE
FINOLA ANDREAS SIMON PATRICK ANTOINE CLEMENT MICHAEL AXEL CLAUDIA
FRANCESCO ANDRES RÉMY ALEXANDER JEKYLL MOHAMED KASPAR
MARCO MATTEO PIT MARC ROLAND SIMONA MARIANA METIN WINFRIED
NIKLAS ATTILA JOACHIM VASYL RETO CLÉMENCE MARCO SEBASTIAN
ANGELA HELGE WENDY OSKAR ALASTAIR MAGNUS ULRICH PEDRO FREDRIK
STEPHEN RUEDI SUSANNE MANFREDO **DANKE** GERARD METEHAN HARALD
FREDEKE CARLOS KATARZYNA ALESSANDRO JANET GARWIN FABIO KLAUS
DIK SARAH JANINA HANS-JÜRGEN DIRK PETRA DORIS MARTIN HEIKO
SEBASTIAN ROHAN BERND JANINA HENRY PAUL KENNETH SAMUEL FELIX
RAIMUND CARLOS CLAUDIO KARSTEN DANIEL JACKIE URS PHILIPP KEITH
JODIE KIM TANJA JAKUB CLÉMENT BARRY BIRGIT DIANA MATTHEW
ALLISON IVO CHRIS WOLFGANG IRIS RICARD DANIEL NACHIKET REMZO SERGE
BENEDIKT BASTIAN FABIO JÜRGEN SELMA MARIO PETER ELMAR SACHIN
ANNEMARIE GIAN-ANDREA THIERRY ROGER NICOLE MATTHIAS QUI RÓISÍN
AARON JENNIFER DAVID HANSUELI ANJA CAROLINE PATRIZIA MARKO
SVEN BRUNO LAURA PATRICIA JULIE DAVID JULIA RAFAEL TOMMY
JAN-MARC STEFAN DENIS GARY MASAE JAN IULIA ANDI BARTHOLD
ACHIM NARENDRA VAHÉ HANS-ANTON JOSE SANDRA ANDREW LAURA
OLIVER MIHAI ALESSANDRO SASA JING ALEX FLORIAN FRANK VOLKER
PETRA NILS SANDRA MATTHIAS HILKE KATHRIN OLIVER THOMAS ANDREAS
SUNSEET NINA PEDRO THOMAS HENNA BOON SACHIN WON STEPHEN
SASCHA DANIEL HECTOR THOMAS JULIAN THOMAS ADRIAN ANDRÉ JONAS
VIJAY BRAADEN MARISSA CRYSTAL REBECCA ARCELY BENJAMIN JENS DANIEL

FRANK MANUEL MANUELA ANN SEAMUS JAMES JÖRG CATHARINA MIHA
MATTHIAS ROB REMI TRISTAN ISAAC PAOLO KONSTANTIN SUBHO BETTINA
ERNST MANUEL BRIAN RAHEL FABIAN HENNA SEAMUS KARL GERALD MEI
INGRID MARC-ANDRÉ THOMAS JOHN BEAT CHRISTIAN ROBERT ROGER KAI
ANDREA MARKUS CHRISTOPH KATJA SANDRO DIETRICH MICHA UTE ASTRID
PRAHLAD TAMAR ANTON SAMUEL WILLEM RENÉ JÖRG RAINER CLAUDIO
BRUNO DANIEL FABIENNE ADAM MYRIAM ULF HILKE TZU-HSIANG NILS
MICHAEL NEIL RUSSELL FRANZ GEORG WULFF ANDREAS KATRIN MEINHARD
ADRIAN MIRJANA STEVE CHRISTINA JEFF WOLFGANG GERHARD BORIS
LINE MAGDALENA THORSTEN HARALD DENNIS TOBIAS RALPH FABIEN NICOLE
RENÉ JENS GARY NIK MEVLAN MARIUSZ BARBARA MARCEL JOACHIM
LAWRENCE JENNY MORITZ JAN-PETER NICOLAS LUKAS ARMIN STEPHAN
JOO SIANG TIM AI BEN KERSTIN ALEXANDRA MARION DIVYA BRAD SUBHO
ÉTIENNE ERGÜN SANDRA MARTA ONDREJ RAMA NICOLAS HELEN PATRICK
MICHAEL ANNA UWE PEER REGINA LAURENT JERZY CHEUK FAN YOLANDA
RICHARD MATHIAS RAFAEL EVA RICCARDO MARK TONI IZABELA DEREK
WOJCIECH STEPHAN FABIAN SABINE PHILIPP IGOR JEFF RUTH SASCHA SEAN
BOON CHIM WILLIAM KAROLINA MARIUS SUZY CAROLA KLAUS JONATHAN
THOMAS DEBORA MARKUS ANDREA FREDEKE GINTAS FABIAN STEFAN
CAROLINE KEN DONNA SIMONE JASON THOMAS DIMITRI BRIGITTE
MADSEN ACHIM WEN ANDRES TZU-LUN RALPH KAI ROLAND HADY
BENJAMIN SERGIO UWE ERIK ANDREAS CHRISTOPHER ANDRÉ LARS ALBAN
KLAUS CHRISTOPHER DANIEL BORIS VASYL CATHARINA SEBASTIAN GARY
JENS ULF ALEXANDER THOMAS VALCOUR JOHN WINFRIED AMAR HAKAN
JENNIFER WILLIAM MARC PRAHLAD MATTHEW JAMES MYRIAM ANTON KEN
BENJAMIN HAMZA GERT BIANCA DONALD SHELLY EEFAY JIL DAVID KRYSTYN
RENÉ CLAUDIO SASCHA DIETMAR JOACHIM RAVI CINDY SRINIVAS JOHN

Contact

Hombrechtikon Systems Engineering AG
Garstligweg 6
8634 Hombrechtikon
Switzerland
www.hseag.com
info@hseag.com

Head Office, North America
Boston, MA
USA

Imprint

Publisher
Hombrechtikon Systems Engineering AG,
Hombrechtikon, Switzerland

Concept / Design / Photography
Detail AG, Zurich

Content / Text
inhalte.ch GmbH, Zurich

Print
DAZ Druckerei Albisrieden AG, Zurich

Languages
German, English

The Hombrechtikon Systems Engineering AG 2021 Annual Report covers the financial year from 1/1/2021 through 12/31/2021.

Gender-neutral pronouns and role descriptions have been used whenever possible and are to be understood in all cases.