Annual Report 2020

BREAK-THROUGH

HSE·AG

“BECAUSE THE HISTORY OF EVOLUTION IS THAT LIFE ESCAPES ALL BARRIERS. LIFE BREAKS FREE. LIFE EXPANDS TO NEW TERRITORIES. PAINFULLY PERHAPS EVEN DANGEROUSLY. BUT LIFE FINDS A WAY.”

Michael Crichton, Jurassic Park

Contents

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Dear Clients and Partners
Dear Employees
Dear Shareholders
Dear Stakeholders

HSE·AG continued to develop successfully in its extremely eventful fourth year of existence. In terms of new client business, we gained several life sciences and diagnostics companies as well as startups. In parallel, we also expanded our business with existing clients. The covid pandemic was undoubtedly the defining event in 2020. It placed the life sciences in general, and diagnostics in particular, at the heart of public interest.

The basis for the continued increase in business is HSE·AG's consistent focus on automating and simplifying workflows for sample preparation and analysis of nucleic acids, proteins and cells. Due to the clear focus, the competencies and, therefore, the added value for clients are immediately evident. Furthermore, HSE·AG can clearly and successfully set itself apart from the competition.

Pioneering projects

2020 was a pivotal year for the life sciences as a whole. The corona pandemic has made the crucial role of both molecular biology and automating its methods clearer than ever. Virus detection and global infection testing can only be carried out using efficient molecular PCR methods. Automation of sample preparation and analysis is crucial to facilitate handling of the enormous testing volumes. Systems such as QIAsymphony, which were essentially developed by HSE·AG employees, now play a central role in virus testing worldwide. HSE·AG is currently working with global companies to bring the next generation of these systems to market.

In 2020, we were very excited to have the opportunity to develop the Resolve Biosciences spatial transcriptomics system. In just nine months, a fully functional prototype was produced that automates the entire process of so-called molecular cartography. The revolutionary method of Resolve Biosciences enables the genes that are active in tissues to be visualized on a sub-micrometer scale. Correlation with the phenotype opens up a new world of possibilities for treatment of diseases such as Alzheimer's and cancer, or for understanding infections and other molecular processes in and between cells.

Domain knowledge is our core competency

Thanks to a profound domain knowledge, HSE·AG can develop systems that not only convince technologically, but also have market success. Successful project implementation is based on an application-oriented standpoint from which the requirements are defined. The primarily plastic-based consumables are derived from the process flow. Handling of the consumables, the reagents and the laboratory environment then determine the requirements for the automated system based on their mutual dependencies and interactions.

Engineering expertise is a required prerequisite for the development of successful laboratory systems. However, the crucial difference is the deep understanding of biological and medical applications in the laboratory context. Over the last few decades, the HSE·AG team has combined their expertise from technology and science to yield a unique understanding of the system. This is also evident, among other things, in the use of liquid-handling and microfluidics components, which are now at the heart of many life sciences and in vitro diagnostic systems. In this respect, HSE·AG also strengthened its relationships with existing and new clients in 2020.

The deep understanding of market needs allows HSE·AG to identify promising projects and product ideas quickly and accurately. Our clients benefit from a correspondingly greater market success. However, as a strategic innovation partner, we do not only develop the requirements specification and the specification of products and develop the respective devices from this. HSE·AG also organizes cost-transparent production and guarantees technical support throughout the entire lifecycle, including global repair services.

Market success

In 2020, HSE·AG entered into a long-term development and licensing contract for an HSE·AG innovation with a large laboratory automation company, among other things.

Business with the proteome purification device PreOn, which HSE·AG is driving forward with Munich-based PreOmics, was expanded in 2020. However, sales figures are below target due to the massive restrictions in laboratory operations at universities, research institutions and in pharmaceutical laboratories, plus travel restrictions.

It is rewarding to note that new client business grew by 63 percent compared to the previous year, despite global travel restrictions. In 2020, we also acquired several global life sciences players and start-ups as clients.

Employee development

Relying on the personal responsibility and self-determination of our employees has proved to be very effective, especially under the pandemic conditions. As soon as the first signs of an increased risk of infection became apparent, we transferred our operations to home offices wherever possible. Our current IT infrastructure enabled us to maintain the workload and realize ongoing projects on schedule with our employees, some of whom are located internationally. The decentralized mode of operation was practiced throughout the year without any negative impact on the course of business. Electronic communication has not only allowed us to continue to communicate with our clients, it also deepened relations in intercontinental projects.

“IT IS REWARDING TO NOTE THAT DESPITE THE GLOBAL TRAVEL RESTRICTIONS, NEW CLIENT BUSINESS GREW BY 63 PERCENT COMPARED TO THE PREVIOUS YEAR.”

Our corporate culture was able to fully leverage its qualities due to the particular circumstances of the pandemic year. Through personal responsibility and self-determination, we achieve personal satisfaction at work and a deep respect for our colleagues. Transparent company goals and status inspire great confidence and enable everyone to utilize the activities and decisions for the company's success.

Looking ahead

The pandemic has triggered massive momentum throughout the life sciences and diagnostics industries. With the increasing availability of vaccines, the pandemic is expected to be largely contained across the globe in 2021. It is currently difficult to assess how the unusual growth in the past year will affect development activity in the life sciences and diagnostics industries in the coming months.

The foreseeable decline in test volume for corona is expected to result in excess capacity that will need to be reduced over time. However, at the same time, the additional capacity will also promote new molecular tests and dispense with older test procedures.

It is also expected that many research activities and medical examinations that were put on hold by the focus on the pandemic will resume. To maintain the growth of the pandemic, companies will try to capture new growth areas with existing and new products, triggering cut-throat competition.

HSE·AG therefore expects companies to drive their innovations while continuing to increase cost flexibility and cost outsourcing. As a specialized and focused service provider, HSE·AG can benefit from this trend.

HSE·AG expects a significant boost especially in the area of RNA immunotherapies, which achieved a breakthrough in 2020 with corona vaccines based on mRNA. In principle, any disease that responds to specific activation of the immune system – from infectious diseases through to all types of oncological disease and also Alzheimer's disease – can be treated with this. Molecular methods are crucial for the analysis and development of specific and some personalized therapies. With our proven competencies, we are optimally positioned for these tasks.

Hans Noser

Chairman of the Board

Michael Collasius, Ph.D.

Chief Executive Officer

“HSE•AG has been a competent partner for the development and innovation of our automated systems for many years. We can always rely on their know-how.”

Thierry Bernard, CEO QIAGEN

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.

An ODM model saves a huge amount of time and money

What has long been standard in the household appliance or automotive industry brings numerous benefits to the field of laboratory automation. Original design manufacturing (ODM) eliminates costly duplication, especially in the area of change management, and improves product quality. Based on its initial implementation experience, HSE·AG has built a framework for ODM partnerships that can be adapted to specific requirements and that ensures maximum certainty.

The roots and, therefore, the core competencies of most manufacturers of life sciences tools and diagnostic systems lie in the biological and chemical methods utilized in the devices and systems. For a number of years, these manufacturers have been working increasingly with specialists in the subsections of their portfolio that lie outside of their core biological and chemical know-how. This gives them flexibility and can reduce costs. These fields include, in particular, design and engineering and production of the devices. However, this division of labor automatically creates triangular relationships that involve communication and coordination efforts. And the more complex devices become, the more complex the collaboration becomes. The bottom line is that an ever-increasing part of the benefits of the partnerships is lost again.

No duplication or conflicts of competencies

The fact that this does not necessarily have to be the case is demonstrated by sectors such as automotive manufacturing and the household appliance industry. Both have been operating in global production chains for a long time and have optimized their organizational structures accordingly over the years. “It’s essentially about a company being able to benefit from the advantages of a networked division of labor with specialized partners while still achieving the same efficient integration of the various tasks as would happen in a complete manufacturer with a hierarchical structure,” explains Alexander Ferro, Chief Operating Officer at HSE·AG.

First and foremost, the responsibilities of all involved partners must be properly divided. This prevents duplication and conflicts of competencies – and saves a huge amount of time and money.

Hierarchical structure with design at the heart of this

In the triangular relationship of manufacturer, design and production, change management is central from an organizational perspective. To prevent the communication required for the coordination from becoming overwhelming, it is not just the lead management that needs to be implemented unambiguously in a hierarchical manner. Proper positioning of all three partners is equally as important. The ideal way of doing this can be seen in companies that do everything internally. In these, design is always responsible for change management. There are obvious reasons for this. In contrast to business, the engineers understand the technical and functional dependencies of operation and manufacturing of the devices in detail. And, in contrast to production, they are also familiar with the business requirements as they have already implemented them in device engineering.

ODM automatically divides responsibility in the right way

However, the realities of today's division of labor in the laboratory and analytical instrumentation sector almost always turns this natural division of responsibilities on its head. Change management remains with the manufacturer and, therefore, business, with the predictable negative consequences such as shifting responsibility, unnecessarily long decision-making processes and a frequently reduced product quality.

The more experienced automotive and household appliance manufacturers show how this can be reliably prevented. The ODM model has become established in these manufacturers to divide responsibility efficiently. As in an internal organization, the design partner also assumes responsibility for change management, including management of the production partner. The manufacturer therefore only needs to maintain one interface with design and can concentrate on developing its product portfolio further, and on its core competencies in biological and chemical methods. They no longer need to worry about the production details or technical equipment service.

Successful ODM model for a proteomics solution

HSE·AG has already successfully implemented a configuration of this kind in the laboratory automation environment with several clients, including Munich-based PreOmics. They have invented a revolutionary method for preparing samples for analysis of all proteins present in a cell at a given time. As a design partner, HSE·AG not only developed an automation solution for the process, but also took responsibility for the production of the devices. As a result, the young company can now concentrate fully on the further development and marketing of its method. At the same time, HSE·AG can carry out change management directly and, therefore, much more efficiently, ensuring a maximum level of quality.

Flexible framework for optimal partnerships

Building on this experience, HSE·AG has now developed a framework for ODM partnerships that can be flexibly adapted to individual cases. "The specific partnerships have shown us in detail what is important in building a successful collaboration in the laboratory automation environment," Ferro explains. In particular, the framework helps to regulate legal and risk issues in a transparent manner. It provides a variety of tools for this purpose.

Insurance policies and contracts that become effective, should they be required, make the financial and operational risks manageable for everyone involved. The financial sustainability of production risks is covered by business insurance and product liability insurance. The exact procedure in the event of changes in the ownership structure and also the manufacturer's right of recourse, including a complete design transfer should necessity require this, can be regulated in exactly the same way in subcontracts, as requested by the manufacturer. Tried and tested standard procedures are now available for this purpose, including ESCROW agreements.

Transparency as the basis for long-term benefits

In addition to unambiguous contractual regulations, the degree of transparency between the manufacturer and ODM partner is also crucial. "For example, the choice of contract manufacturer and also any changes should definitely be made together," emphasizes Ferro. "This builds trust and puts the partnership on a sustainable long-term footing." This is important, among other things, because ODM partnerships demonstrate their advantages more effectively over time. The organization can be continuously improved and mutual investments become more and more fruitful.

Defining the goals together – and then achieving them

The specific structure of a partnership depends on many details, as Ferro knows from experience. A startup, for example, has very different needs to an established company. Furthermore, the willingness to take risks can vary greatly. Therefore, a specific solution always needs to be derived by means of mutual exchange. "We have developed a flexible concept with which we can specify the goals of the partnership together with a manufacturer and then achieve them," Ferro points out. "The best way for a company to convince itself is to challenge us!"

Rapid automation of the spatial analysis revolution

Resolve Biosciences is spearheading the start of the next life sciences revolution. Its Molecular Cartography platform illuminates individual mRNA molecules in cells, both temporally and spatially, at the sub-micrometer scale. HSE·AG Engineering automated the cutting-edge laboratory method in just a few months. As a first step, the Resolve Biosciences CEO, Jason T. Gammack, now intends to set up service centers in Europe, the USA and Asia. In the future, proteins and metabolites will also be analyzed and the instruments will be further developed into integrated series products.

The life sciences are still developing at a breathtaking speed. Having shrunk from mammoth scientific projects to mass benchtop applications in less than 20 years, genome sequencing tools are now poised for the next step – visualization of biomolecules in a cellular context. The aim is to no longer obtain only two-dimensional gene sequence information from individual cells, but to visualize the 3D distribution of biomolecules and metabolites in a biological process.

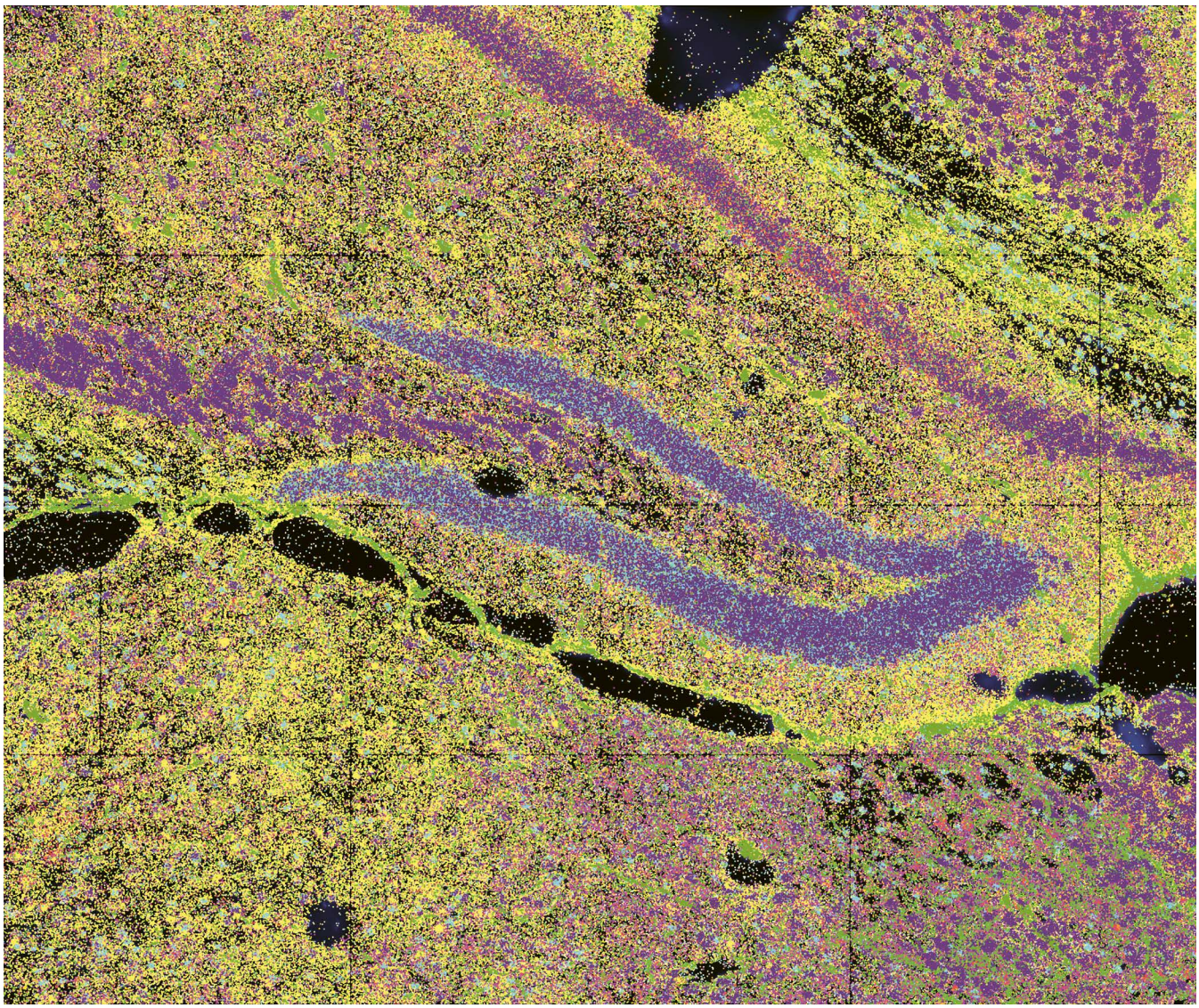
The prime focus is mRNA. In January, the journal Nature named "spatially resolved transcriptomics" method of the year. Spatially and temporally resolved visualization of a variety of mRNA transcripts in tissue enables detailed observation of molecular processes within and between cells. Jason Gammack, the CEO of Resolve Biosciences, is convinced that these technologies will take cancer research, neuroscience or even the understanding of infections to a completely new level. But his company's Molecular Cartography platform is not just limited to mRNA. "In the future, our technology will also allow proteins and metabolites to be analyzed in a cellular context."

Groundbreaking and mature methodology

It is no coincidence that Resolve Biosciences, based in Monheim am Rhein, Germany, is leading the technological forefront of this groundbreaking method. The core team already started work in 2016. The co-founders include QIAGEN's former CEO Peer Schatz and Jason Gammack, who was responsible for QIAGEN's life sciences business at the time.

The technology is based on three pillars. At the heart of this is chemistry that enables visualization of individual molecules with extremely high specificity and sensitivity at a resolution of just 0.27 micrometers, limited only by the power of light microscopy. Using fluorescent dyes, hundreds of mRNA transcripts can be distinguished in multiple rounds of staining and imaging (see illustration on p. 16). The second pillar is microscopy that pushes the limits of what is physically possible in terms of resolution, imaging the sample in a way that builds a three-dimensional map of the transcripts at subcellular resolution. Informatics tools that can be used to extract meaningful scientific information from the vast amounts of data, several terabytes per sample, form the third key pillar.

After five years, the methodology is now robust and one of the first in the world to be ready for commercial use. Thanks to the development partnership with HSE·AG, the technology is already fully automated and available at the push of a button. This not only reduces the time required for each analysis and increases sample throughput, but also optimizes reliability and reproducibility. The first pilot customers have already achieved spectacular results with the platform. For example, a research group in Austria has succeeded in visualizing how SARS-CoV-2 spreads in infected tissues.



Productive instruments in record time

Automation is crucial for successful commercialization of the Molecular Cartography platform, as Jason Gammack points out. And it had to succeed quickly, because time to market is a key competitive factor in what is probably the hottest new life sciences sector. Thanks to the collaboration with HSE·AG, it was achieved in record-breaking time. The project kicked off in March 2020 and a working prototype was already in operation by September. In the meantime, the first instruments are in productive operation as part of an early access program.

To achieve its goal efficiently, HSE·AG divided the laboratory process into individual modules for liquid handling, biochemical processes and microscopy. These were connected by robotics. As far as possible, standard components were used as the basis for the individual modules. “These had to be adapted to a large extent, though, because nothing about our method is standard,” Gammack emphasizes.

Domain knowledge enables efficient new developments

The slide handler is a completely new development. The cell and tissue samples are hybridized with the fluorescently labeled molecules in multiple staining steps in this key part of the method. Rapid tilting and pipetting processes are used to save as much time as possible in the many individual steps required for this method. The tray used to transport the sample slides through the process steps and the control software also had to be developed.

"HSE·AG has extremely competent and experienced engineers," Gammack points out. "Not only are they proficient in their disciplines, but they understand the molecular biology that happens inside the instrument, and they understand the reality of the laboratory." This domain knowledge is crucial to quickly find solutions that not only work on their own, but also work together, even when additional functionality needs to be added later. Furthermore, HSE·AG also goes the extra mile if needed, as a matter of course.

Great demand from industry and universities

At the moment, the first market launch steps are pending. Resolve Biosciences is setting up service centers for this purpose in Europe, in San José, California, and in Singapore, using instruments developed by HSE·AG. In a first step, the technology is made available as a service via these service centers. The main target groups are pharmaceutical companies and universities. "Demand is not the problem," says the CEO. "The orders on hand are sufficient for more than a year, even before the official launch."

For example, the industry is using the technique to look for biomarkers that show who will respond to a particular drug and who will not. These findings could help to personalize cancer therapies, among other things. In contrast, academics tend to use the platform to test hypotheses for molecular mechanisms at the cellular level.

Either way, users can benefit from a unique advantage of the technology from Resolve Biosciences – the method leaves the examined tissues intact. This means that several hypotheses can be studied using the same sample and the temporal patterns of intra- and intercellular processes can be observed.

Continuous development and new markets

The collaboration between Resolve Biosciences and HSE·AG only started with the first instruments. Currently, the processes are being refined further. The molecular biology, image acquisition and bioinformatics tools are being continuously optimized. Accordingly, the instruments also need to be continuously adapted. In the future, Resolve Biosciences also plans to make other biomolecules visible in cells. The main focus is on proteins and metabolites, both of which can be labeled by specific antibodies.

But it's not just technology that will continue to evolve in the next few years. Market access will also change. "The appetite of the life sciences has been whetted," as Gammack knows from his years of experience. "As the number of spectacular research results grows, demand from companies and research centers for their own equipment will automatically result." The instrument design needs to be adapted for this. The current platform and data analysis are still too complex for independent use by external users.

Original design manufacturing all the way to series product

It will be some time before the Resolve Biosciences method reaches the final stage in the lifecycle of a life science technology and becomes a mass benchtop application, like sequencing technologies are today. However, HSE·AG can accompany the dynamic company on this journey. As an experienced ODM (original design manufacturing) partner, the engineering company also assumes overall responsibility for instrument manufacture. Life science innovators like Resolve Biosciences can, therefore, concentrate fully on developing their pioneering processes further.

Algorithmic methods deliver an optimal solution

With complex laboratory automation devices, optimizing each component individually rarely leads to the best possible system in practice. The most effective solutions are frequently found at the interfaces or in a peripheral area of functionality. Thomas Hanselmann heads HSE•AG's Algorithm & Data Analytics group, which uses an algorithmic and model-based approach to find solutions outside the box of traditional analytics technologies.

Mr. Hanselmann, you and your group pursue an algorithmic approach for problem solving that goes beyond conventional engineering methods. What do you mean by this?

We think out of the box. We understand algorithms in the conventional sense. That is, not just as a computer program, but in a general way as a sequence of step-by-step executable actions that can be used to solve a problem. We approach the problem to begin with by iteratively exploring the most important requirements and constraints. Based on this, we then define all requirements and interfaces and create a model of the entire system, on which we test our solution approaches. In doing so, we divide the problem into individual, definable subtasks and the solution approaches are dimensioned in such a way that they can overcome other more difficult situations. This model-based approach gives us robust complete solutions.

Isn't that how most engineers do it?

The difference in our approach has less to do with the basic principle, and more to do with the way we apply it. Engineers are usually specialized in certain fields. Therefore, they always approach a task from their specific perspective. In contrast, we deliberately leave out the technical "boxes" and first try to define from a broader perspective what the purpose of a task is when the entire system is taken into account. This opens up many additional solutions for us, which at first glance sometimes seem to lie outside the boundaries of the system.

What does that mean exactly? Can you give an example?

In an analysis robot, you must reliably ensure, among other things, that all positions in the pipette tip racks are filled. Up to now, laser systems that scan all racks row by row have been used for this. This is accurate but takes more than half an hour. A check using a method that can read out all the necessary information from a single high-resolution photo of the entire filling unit of the device would be much faster. However, what sounds good in theory, quickly reaches its practical limits. These include space constraints, unusual perspectives, extraneous light, reflections, or technical limitations such as limited bandwidths, available and affordable hardware, or maintenance requirements. Furthermore, the previously available software algorithms were, to a certain extent, very sensitive to certain kinds of image distortions such as shadows, reflections, edge distortions, or distortions caused by the light-conducting plastic materials that the sample containers are made of. The result is misinterpretations that can only be prevented in a fail-safe way with a lot of work, even with artificial intelligence and deep learning algorithms. Together with our specialized medical robotics camera manufacturer, we were able to demonstrate solutions that take object recognition performance to a new level. We use simple and maintainable parameterization of the objects to be recognized.

“AFTER ANALYZING ALL CONSTRAINTS IN DETAIL, WE CAME TO THE CONCLUSION THAT WE SHOULD APPROACH THE PROBLEM NOT SIMPLY AS A BAR-CODE RECOGNITION ISSUE, BUT AS A TRACKING CHALLENGE.”

Even if artificial intelligence doesn’t help, what was the key to success?

To solve the problem, we first had to take a step back. The crucial question is: What do you need for a good picture? We therefore started experimenting with factors such as the lighting of the unit and quickly realized there was great potential for optimization of the illumination. But even this approach did not lead to the desired result straight away. On the one hand, optimal illumination of all corners of the tip racks with several diffuse lighting panels had to be worked out experimentally. On the other hand, many test scripts that check a variety of properties such as color, brightness, or saturation in a modular fashion for each tip position were required for image analysis to then come to a robust overall decision analogous to a checksum. To prevent the volumes of data to be transmitted from exploding, modular verification of the various criteria also had to take place on the camera itself.

How does this solution benefit the device user?

Laboratory automation devices are becoming more and more complex as new functionalities are continuously being integrated. This also increases the work required to ensure that all samples, reagents and consumables have been filled correctly. Errors cannot really be tolerated here because they lead to incorrect analysis results. In practice, test procedures are taking up more and more time and are, therefore, becoming an important cost driver for device users. Our solution reduces the time required to fully check a filling unit from around 30 minutes to just under one minute.

What do you think is the crucial factor in finding a highly efficient solution like this and then being able to develop it to product maturity?

In addition to having the most versatile and in-depth technology know-how possible, the understanding of laboratory processes is particularly crucial. The more precisely an engineer understands not only the process from sample collection to analysis of results, but also the chemical and biological reactions and the measurement technology, the more specifically the important questions can be asked. Another example illustrates this very well. To reliably check the loading of an analysis robot with sample tubes using a camera, we first needed to find the right perspective for the question.

Was there anything unusual about your perspective?

After analyzing all constraints in detail, we came to the conclusion that we should approach the problem not simply as a barcode recognition issue, but as a tracking challenge. As a result, we were able to reliably identify and interpret 2-D codes despite the limited memory capacity of the camera and the large differences in speed of sample insertion into the system. Our system does this by predicting where a barcode should appear in the next image based on a physical model of the whole process we have created. Thus, the system immediately detects a change in speed and because multiple barcodes are visible in each frame, missed codes can be found with certainty and interpreted in surrounding frames in a post-processing procedure.

Has this tracking system been developed from scratch?

From the basic concept point of view, no, but we devised a sophisticated specific implementation. Tracking technologies like this are used, among other things, to track aircraft positions at an airport using radars to prevent collisions. However, in our specific case, additional limitations then emerged. Thus, the computational load of the camera increased point by point. As a result, the model assumption that the frame rate was constant was violated in each case and tracking no longer functioned correctly. Thanks to our model-based design approach, a small extension of the predictive model was sufficient to solve this problem faster than it would have taken the camera manufacturer just to find the root cause. In many projects, this kind of problem could even have become a complete showstopper. However, in our approach, we always take into account that model assumptions may not apply, and we consider alternatives. Together with our in-depth understanding of laboratory processes and diverse technology know-how, this systematic, model-based approach enables us to find outstanding engineering solutions for our clients' challenges.

Determining the optimal transition to microfluidics

Microfluidics is the key to high throughputs and low consumable costs. The biggest hurdle is frequently the transition between the inevitably macro-scale reagent tubes and the fine structures in the flow cells and cartridges. Finding the optimal solution requires not only extensive experience in a wide variety of applications, but also a deep understanding of molecular biology and laboratory processes, as HSE·AG's Head of Engineering Technologies, Hans-Jürgen Tiedtke, explains.

Mr. Tiedtke, you have been developing fluidics systems for many years. What is the biggest challenge with modern micro flow cells?

The biggest hurdle is often not – as you might think – the construction of the small reaction cells. The most difficult problems arise at the transition between the reagents provided on a large scale and the reaction cells that have an extremely small volume. In extreme cases, the liquids must be taken from a milliliter vessel and transferred as volumes of a few microliters. By narrowing the diameters of the fluid channels, for example, either the pressure increases sharply or the flow rate is significantly slowed.

What are the most important economic constraints that impact problem solving?

The most important factors for users of automation solutions are time and reagent consumption. On the one hand, flushing very small channels can take a lot of time and, therefore, reduce the sample throughput of the device. On the other hand, the reagent costs can sometimes be very high. Therefore, it is often crucial to keep the tubes as short as possible and the flush volumes as small as possible.

You have found or analyzed very different solutions for this, from using geometry and capillary forces to mini-valves and finely drilled and milled plastic manifolds (see text boxes). Which criteria determine the best solution in each case?

The driver is always the application. The more closely the solution is tailored to the specific application, the more efficient the automation becomes. As an engineer, this requires you to understand as precisely as possible what the purpose of the flow cell and the entire device is in the context of the laboratory. For this, it is not enough to master only the engineering part. It also requires a deep understanding of the molecular biology that goes on in the reaction cells and of the entire laboratory process.

As a trained electrical engineer, how and where did you acquire this knowledge?

I worked on a hydrodynamic test system for artificial heart valves for my degree dissertation. As I joined QIAGEN in 2011 – and am therefore part of the original team that makes up HSE·AG today – fluidic systems are virtually part of my everyday life. In the meantime, I have developed countless different applications. Your know-how grows with each new project. This is especially true when it comes to understanding the molecular biology that goes on inside the devices.

Can any engineer acquire this knowledge for the life sciences domain?

With time, you can certainly acquire a lot of knowledge about biology and chemistry. However, at HSE·AG, there is an added feature that goes beyond personal experiential learning. We are not just engineers; we work together in multidisciplinary teams. In this way, I can also benefit directly from the knowledge and wealth of experience in biology and biochemistry of my colleagues – and they benefit likewise from my engineering expertise.

How does this multidisciplinary makeup of the development teams impact the project results?

The math is easy: The more experience there is from different disciplines and with different systems, the more conceptual options there are when finding solutions. And many pitfalls on the way to developing a productive device have already come to light by then. But the bottom line is that together we don't just find more efficient solutions that better meet market needs. Thanks to our extensive experience, we also know what is important during development and this enables a device to be manufactured and operated as cost-effectively as possible.

Applications and solution examples from microfluidics

VALVE AS CLOSE AS POSSIBLE TO THE FLOW CELL CONNECTIONS

A flow cell used for drug screening must be connected to a total of 16 fluidic connections for filling and flushing. The tubes are conventional tubes with small diameters that draw reagents from storage vessels with volumes of up to one liter. The flow cell was designed to keep the connections permanently attached during the analysis process. To exchange the reagents in the flow cell as quickly as possible, a way of connecting the 16 tubes to the flow cell in a very confined space was needed, while positioning the valves that open and close the various reagent tubes as closely as possible to the cell. A special adapter head solved the problem by integrating all tubes. The adapter head can be positioned precisely on the cell.

USE GEOMETRY FOR FLUID TRANSPORT

To determine the DNA concentration in a spectrometer, a flow cell was designed so that the liquids move automatically through the channels into the measuring cell from a filling funnel using capillary action. As soon as the measuring cell is filled, the channel becomes wider and the capillary action stops. At this point, the funnel is also completely empty, so that only minimal evaporation can take place at the thin capillary cross-section. With this intelligent cell geometry, it was not just possible to elegantly solve precise dosing of the samples. At the same time, sample consumption could also be minimized.

OIL-WATER SURFACE EFFECTS PRODUCE A THOUSAND PCR REACTIONS

Surface effects between oil and water were used to automatically generate the largest possible number of aqueous droplets in which PCR reactions can run in parallel. The aqueous solution containing all reagents for the PCR reaction is forced under pressure into the cavity between an oil film and a membrane. About a thousand droplets of the same size are produced, in which the PCR reaction is then carried out in parallel. Fluorescent markers enable visualization of positive results. If the initial concentration is selected smartly, the droplets that light up positively can be used, for example, to determine the exact virus concentration in a sample.

A VALVE FOR COMPLEX SAMPLE-TO-RESULT CARTRIDGE

To carry out complete sample-to-result PCR reactions, including DNA purification and concentration in a cartridge, a valve needs to be developed that enables specific liquid change. The solution was a small rubber part that can be closed and opened by a certain force using a miniature plunger. The second challenge was the large sample volumes that needed to be concentrated for the analysis. To fill them directly using a pipetting robot, a funnel was designed in such a way that it can be hermetically closed via pressure through the pipette tip. Thus, the sample can be easily injected.

MOVING THE FLOW CELL BETWEEN CONNECTOR GROUPS

One way of making a reagent change as efficient as possible is to move the micro flow cell backwards and forwards between different connector groups. This method was selected for a next-generation sequencing device. The big advantage: Virtually no expensive reagents are wasted. The downside: A small air bubble forms with each change and must be flushed out.

PLACE SINGLE CELLS VIA ELECTROMAGNETIC TAPPING

A fluidics system uses gravity and an electromagnetic tapping mechanism to separate individual cells and place them in microtiter plates. The channel through which the cell suspensions are filled tapers into a narrow silicon channel that is open at the bottom. An electromagnetic force is triggered to tap a silicon membrane, which enables droplets of the same size to be produced at the outlet. Using a camera, drops containing one, several or no cells can then be automatically differentiated and positioned accordingly.

MANIFOLD ALLOWS FOR SHORT DISTANCES AND FLUSH TIMES

The number of bacteria in a liquid can be accurately determined by the change in electrical impedance in a measurement channel. However, this requires the sample liquid to be forced through a measurement channel of only 15 micrometers. Even at high pressures, flow rates of just 30 µl/min are achieved. To minimize the time needed to clean the system before the next measurement, it is essential that the tubes to the flow cell are kept as short as possible and have a small internal diameter. Thanks to a so-called manifold, the additional volumes of liquid required in the tubes were limited to a few microliters. The channels, which are only 500 micrometers in diameter, were milled and drilled for this purpose in two plastic plates, which were then joined using a bonding process to form the functional manifold channel system.

Facts & Figures for the 2020 financial year

HSE·AG was able to significantly expand its client base once again in 2020, increasing revenue from new clients by 63 percent. However, business performance was impacted by the corona pandemic. Sales of OEM products, in particular, nosedived sharply and only recovered slowly toward the end of the year. In addition, the start of several development projects was delayed and business development was also hampered.

Key figures

In 2020, HSE·AG achieved sales of **CHF 10,873 million,** a reduction of 12 percent compared to the previous year. This resulted in an EBIT of **CHF 368,732** (2019: 658,532).

These business results gave rise to the following key figures:

113

Previous year: 47
Liquidity factor 1

35.55

Previous year: 13.59
Evaluation of participation certificates

32 %

Previous year: 28 %
Self-financing ratio

Appropriation of profits

		2020	2019
Retained earnings, beginning of the fiscal period	CHF	1,221,749.57	715,831.56
Net profit	CHF	287,768.87	505,918.01
Available retained earnings	**CHF**	**1,509,518.44**	**1,221,749.57**

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

		2020	2019
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	1,509,518.44	1,221,749.57
Available retained earnings	**CHF**	**1,509,518.44**	**1,221,749.57**

Audit of the financial statements

The annual financial statements of Hombrechtikon Systems Engineering AG for the financial year 2020, which covers the period from January 1, 2020 through December 31, 2020, were audited on April 19, 2021 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 again in November 2020. 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 **10 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

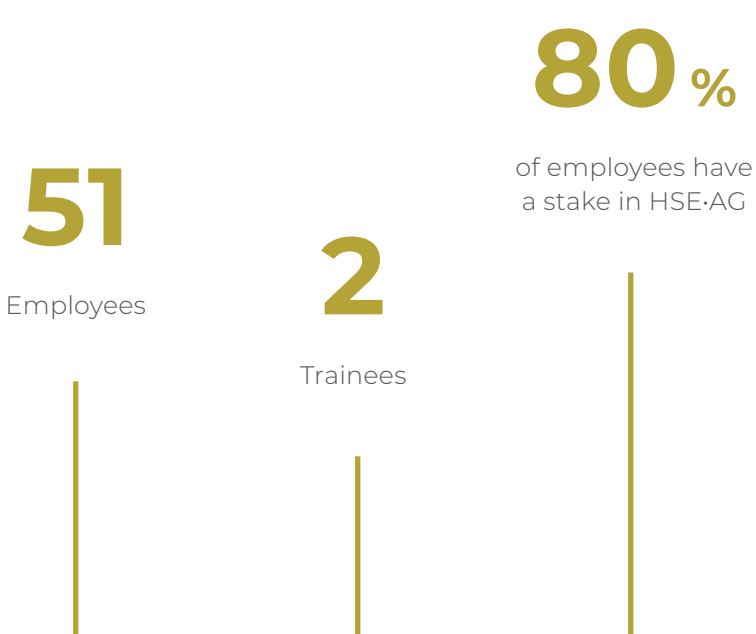
In 2020, the workforce was reduced from 56 to **51 employees.** The workforce includes two apprentices (one commercial apprentice and one IMS trainee), which results in an apprenticeship quota of around **3.9 percent.**

The turnover rate in 2020 remained below 10 percent. This means it is at a standard industry level. The fact that all vacancies could be filled in the year under review shows that HSE·AG is well positioned in the extremely competitive international labor market for highly skilled professionals.

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.

At the end of the financial year, the value of the participation certificates is 35.55 times (2019: 13.59 times) the original nominal value of CHF 0.01. Employees will be able to acquire further participation certificates in 2021. Around 80 percent 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.



“HSE•AG is a partner who autonomously solves complex and interdisciplinary engineering issues for us. Concepts, prototypes or designs ready for series production are included in the range of products offered.”

Jens Höhndorf,
R&D Manager Bruker Daltonics

LUDWIG MARTINA TOBIAS NICHOLAS ANTONIO JEAN SEAMUS JAMES JÖRG CATHARINA MIHA DIRK JAKOB INGO MATTHIAS JAN ROB REMI TRISTAN ISAAC PAOLO MARIJA RON FRAUKE HIAM ALEXIS HANS CHRISTIAN SEAMUS KARL GERALD MEI MOHAMMAD MARIO JOHN INGRID MARC-ANDRÉ THOMAS JOHN BEAT CHRISTIAN ANTOINE CLEMENT MICHAEL AXEL CLAUDIA ANDREA UTE ASTRID FRANCESCO ANDRES RÉMY ALEXANDER SAMUEL WILLEM RENÉ JÖRG RAINER CLAUDIO MARCO WINFRIED BRUNO DANIEL FABIENNE ADAM MYRIAM VASYL RETO CLÉMENCE MARCO SEBASTIAN MICHAEL MEINHARD ANGELA HELGE WENDY OSKAR ALASTAIR STEVE CHRISTINA JEFF WOLFGANG GERHARD BORIS METEHAN HARALD LINE MAGDALENA HANS THORSTEN NICOLE FREDEKE CARLOS KATARZYNA ALESSANDRO MEVLAN PETER MARIUSZ BARBARA MARCEL JOACHIM MARTIN HEIKO LAWRENCE JENNY MORITZ JAN-PETER BERND JANINA HENRY PAUL KENNETH SAMUEL FELIX DIVYA SUBHO RAIMUND CARLOS CLAUDIO KARSTEN SANDRA MARTA ONDREJ RAMA NICOLAS HELEN BRAD PETER BIRGIT DIANA MATTHEW MICHAEL ANNA UWE ALLISON IVO CHRIS WOLFGANG IRIS RICARD DANIEL EVA RICCARDO MARK TONI IZABELA DEREK BENEDIKT ELMAR SACHIN WOJCIECH STEPHAN FABIAN SABINE GIAN-ANDREA THIERRY ROGER NICOLE MATTHIAS QUI CAROLA KLAUS JONATHAN AARON JENNIFER DAVID DEBORA MARKUS ANDREA FREDEKE GINTAS FABIAN JULIA RAFAEL TOMMY CAROLINE KEN DONNA SIMONE DENIS GARY MASAE JAN IULIA ANDI BARTHOLD HANS ROLAND HADY ACHIM NARENDRA VAHÉ HANS-ANTON ANDREAS CHRISTOPHER ANDRÉ LARS ALBAN OLIVER

PASCAL MIKE STEVE FRANK MANUEL MANUELA ANN ALMA URS LENA UDO ANGELA REINER JONAS MEIKE MARTIN KONSTANTIN SUBHO BETTINA MARTA AXEL ALEXANDER ERNST RUEDI RAHEL FABIAN HENNA JANE MARGARET LINUS GIULIANO STEPHANIE BRIAN ROBERT ROGER KAI FINOLA ANDREAS SIMON PATRICK MARKUS CHRISTOPH KATJA SANDRO DIETRICH MICHA JEKYLL MOHAMED KASPAR PRAHLAD TAMAR ANTON MATTEO PIT MARC ROLAND SIMONA MARIANA METIN ULF HILKE TZU-HSIANG NILS NIKLAS ATTILA JOACHIM NEIL RUSSELL FRANZ GEORG WULFF ANDREAS KATRIN MAGNUS ULRICH PEDRO FREDRIK ADRIAN MIRJANA STEPHEN SUSANNE MANFREDO **THANK YOU** GERARD HARALD DENNIS TOBIAS MARTINA RALPH FABIEN JANET GARWIN FABIO KLAUS RENÉ JENS GARY NIK DIK SARAH JANINA HANS-JÜRGEN DIRK PETRA DORIS NICOLAS LUKAS ARMIN STEPHAN SEBASTIAN ROHAN JOO SIANG TIM AI BEN KERSTIN ALEXANDRA MARION DANIEL JACKIE URS PHILIPP KEITH ÉTIENNE ERGÜN PATRICK JODIE KIM TANJA JAKUB CLÉMENT BARRY PEER REGINA LAURENT JERZY CHEUK FAN YOLANDA NACHIKET REMZO SERGE RICHARD MATHIAS RAFAEL BASTIAN FABIO JÜRGEN SELMA MARIO HANS PETER PHILIPP IGOR JEFF RUTH SASCHA SEAN ANNEMARIE RÓISÍN BOON CHIM WILLIAM KAROLINA MARIUS SUZY HANSUELI ANJA CAROLINE PATRIZIA MARKO THOMAS STEFAN SVEN BRUNO LAURA PATRICIA JULIE DAVID JASON THOMAS DIMITRI BRIGITTE JAN-MARC STEFAN MADSEN ACHIM WEN ANDRES TZU-LUN RALPH KAI JOSE SANDRA ANDREW LAURA BENJAMIN SERGIO MIHAI ALESSANDRO SASA JING ALEX FLORIAN FRANK

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