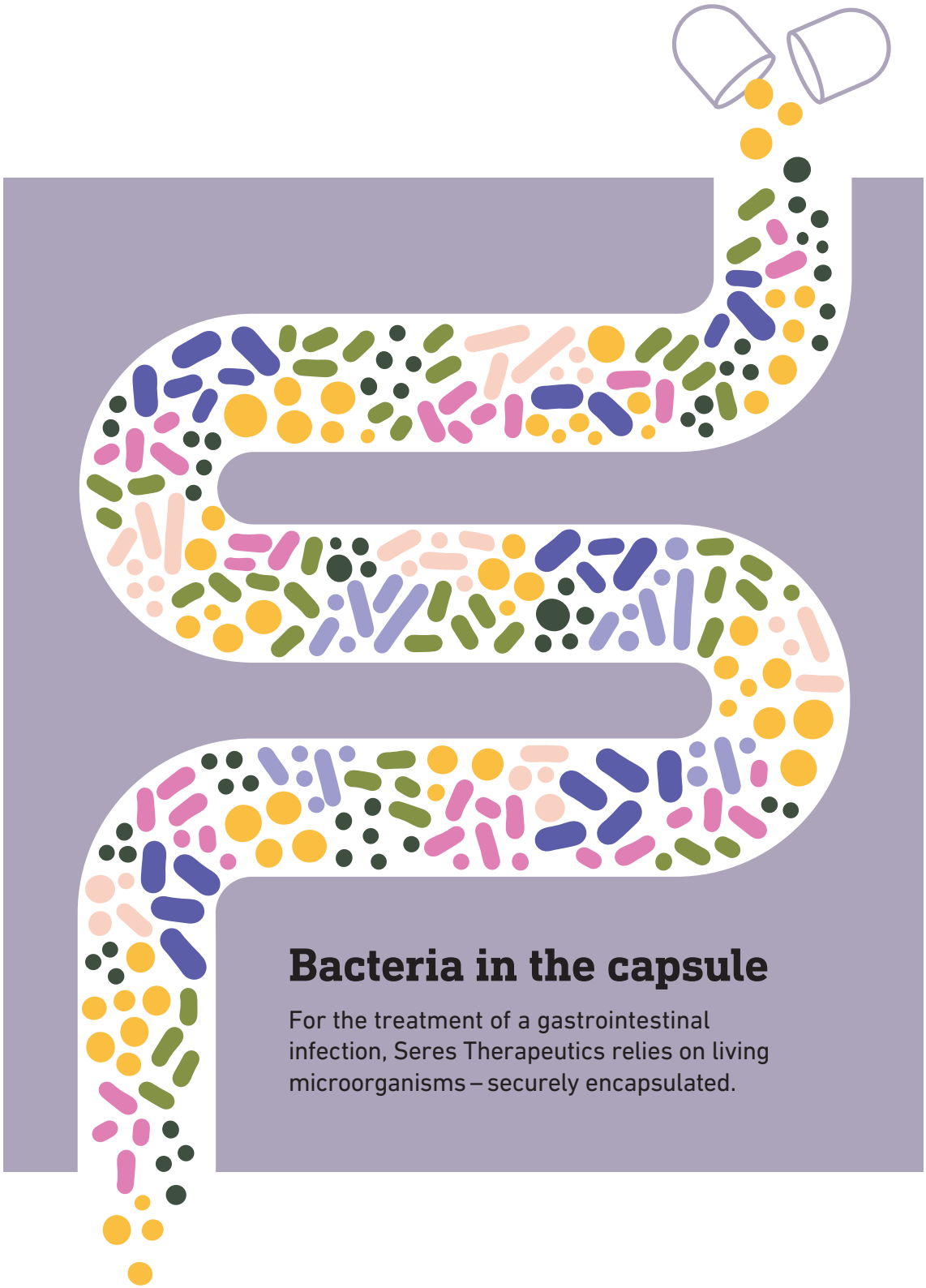
HARRO

The Customer Magazine by Harro Höfliger

Edition 14 | 2023



Bacteria in the capsule

For the treatment of a gastrointestinal infection, Seres Therapeutics relies on living microorganisms – securely encapsulated.

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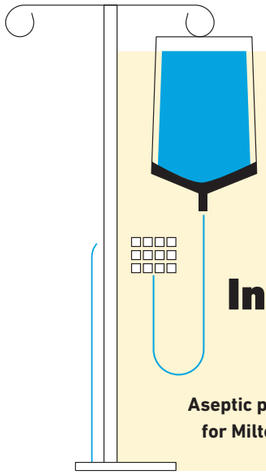


Helmar Lunig

EDITORIAL

Dear Readers,
dear Business Associates,

In this magazine, we dive into the exciting world of research and many more topics. The opportunities that the latest scientific discoveries and the field of biotechnology open up for treating patients are enormous. This, for instance, involves personalized cell and gene therapies. They are set to revolutionize medicine, as they offer huge potential for serious diseases that were largely deemed incurable until now. The targeted use of living microorganisms in drugs can also contribute to aiding people in their recovery.

The development of process competencies for handling, dosing and packaging of sensitive products must go hand in hand with the development of innovative therapies. We are well positioned for this at Harro Höfliger. Numerous successful projects over many years have given us the expertise to develop aseptic processes and suitable high-tech solutions that are necessary, for example, in filling aseptic bags (see article starting on page 8).

But we also set the bar high when it comes to our own capacity for innovation in other areas: Be it the software platform for pharmaceutical production developed by PYNR – our corporate startup – or a special forming process for producing water-soluble pouches.

But read for yourself. And enjoy it.

Your

Thomas Weller,
CEO at Harro Höfliger

10 years of HH India

Harro Höfliger's Indian subsidiary opened its new facility in Bangalore with a traditional ceremony. Not only the relocation to new premises was celebrated, but also HH India's 10th anniversary. Now almost 1,200 square meters of space is available to the 45 staff at present. Besides generously dimensioned offices there is also sufficient space for the spare parts warehouse – this offers the best prerequisites for fast, independent processing of orders on site and further growth.

Trade fairs

CPHI
October 24 to 26, 2023 – Barcelona

COMPAMED/MEDICA
November 13 to 16, 2023 – Düsseldorf

P-MEC INDIA
November 28 to 30, 2023 – Greater Noida

DDL
December 6 to 8, 2023 – Edinburgh

ATX West
February 6 to 8, 2024 – Anaheim

FESTIVAL OF BIOLOGICS
April 15 to 17, 2024 – San Diego

ACHEMA
June 10 to 14, 2024 – Frankfurt/Main

New managing directors

In April 2023, Harro Höfliger's Supervisory Board has appointed Alexander Herb (on the left) as the new Chief Financial Officer (CFO). He succeeds Turgay Güngormus. With effect from April also, Thomas Heckner (on the right) complements the management team around CEO Thomas Weller in the newly created position of Chief Operating Officer (COO). Heckner will successively be taking over the responsibilities of Heinrich Havenstein, Managing Director Production, who will leave the company in fall 2024.

Cooperation for pMD inhalers

Pressurized metered dose inhalers (pMDI) play an essential role in the treatment of various respiratory diseases. They contain active ingredient and propellant; when the device is actuated, an inhalable aerosol is released. Together with Koura, a leading manufacturer of medical propellants, and the pMDI expert Pharmatec Solutions, Harro Höfliger is working on a special dosing technology. In this two-stage filling process, the container is first filled with the solid active ingredient and only in the second stage with the propellant. This enables exact dosing of API and facilitates the use of new, more climate-friendly propellants. The main focus of the collaboration is on joint proof-of-concept trials, with particular emphasis on process simplification and scalability.

Koura An Orbia business. | Pharmatec Solutions Ltd. | HH Harro Höfliger

Tomorrow's experts

29 apprentices and dual students have started their professional career at Harro Höfliger in fall 2023. Regardless of their chosen apprenticeships, they are learning basic skills in metal processing, as well as electrical and control technology for mechanical engineering during the first few weeks at the company's own training center – the Academy at the Allmersbach im Tal headquarters,

Our customer magazine is also available online:

www.harro-magazine.com

New subsidiary in Switzerland

Since September 1, 2023, Harro Höfliger has been represented by its own sales and service company in Switzerland. From Uhlmann Höfliger Schweiz GmbH – a joint subsidiary of Uhlmann Pac-Systeme and Harro Höfliger founded in 2005 – two independent companies have emerged: Harro Höfliger (Schweiz) AG in Reinach near Basel, and Uhlmann Schweiz GmbH in Arlesheim. Harro Höfliger's team will continue to support Swiss customers in all matters of production processes and services, and plans to continue its successful growth.

Tom Philippi

DIGITAL ASSISTANT

PYNR develops digital solutions precisely tailored to the demands of pharmaceutical production. Falk Pfitzer, Senior Sales Manager of Harro Höfliger's corporate startup, offers insights into the new software platform.

How did the idea for the new platform emerge?
In multiple discussions with customers, we identified a great need for digitization directly at the machine in pharmaceutical production. And this is precisely where our new platform comes in: on the shop floor, where the data arises. "Tapping the source" enables rapid response to events in real time, among other things. This way the platform helps analyze machine data, detect problems early on, provide guidance as a digital assistant, and much more besides. In a nutshell: It improves machine handling and boosts efficiency. The apps are usable on all internet-capable devices, even with smart glasses.

How is the system structured?
The linchpin is our app manager. It offers pre-installed tools like the audit trail, which completely documents changes to data. What's more: You can extend the manager to include individual functions and organize it according to your own needs. Another highly individual feature is the integrated user management. A machine operator, for instance, is often interested in different data than the production manager. The platform contains information individually tailored to each of them. We connect customer systems for user management via an interface.

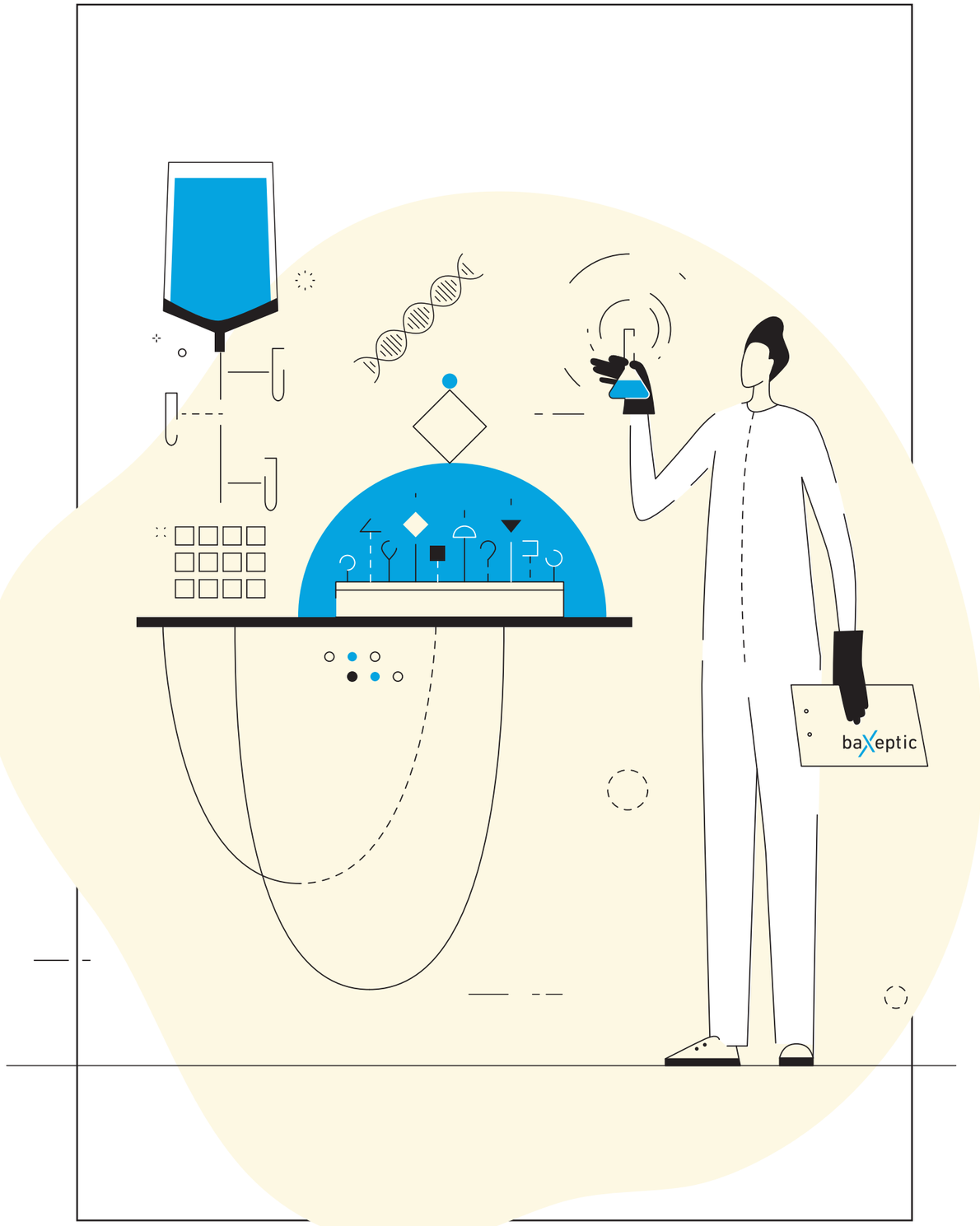
What is a specific use case?
"Guided troubleshooting" provides operators with step-by-step instructions, enabling them to correct errors. This reduces downtimes and conserves resources. Such real-time responses on the machines also reduce scrap, which benefits the environment. A guided approach is not only suitable for troubleshooting, however – customers can also use it for efficient format changing and for machine maintenance, as examples. Our platform perfectly complements our Customer Service applications.

PYNR BY HARRO

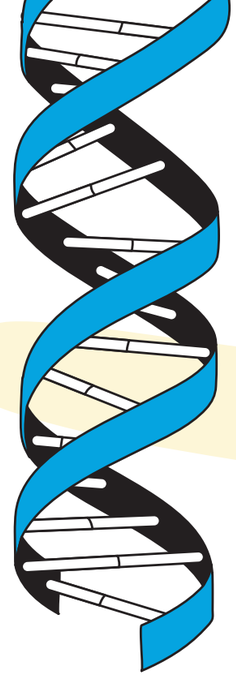
Falk Pfitzer
Senior Sales Manager at PYNR

A legion of little helpers

Trillions of bacteria live in every human body. Many of these strains are crucial to our health and vitality. For example, bacteria in our gut support digestion, strengthen the immune system and produce metabolites essential for human health. US company Seres Therapeutics has just launched a new, oral microbiome drug, VOWST™, that delivers healthy bacteria to treat patients with recurrent Clostridium difficile infections.
You can read more about this new product and the collaboration with Harro Höfliger on page 18.



INNOVATION



Finding therapies for serious diseases – this has been the driving force behind Miltenyi Biotec for over three decades. The company also focuses on the dynamically growing field of cell and gene therapies.

INNOVATION IN EVERY CELL

Cologne, 1989: The physics student Stefan Miltenyi has an ingenious idea. He coats small iron particles with antibodies and couples them to the receptors of certain cells. By applying a magnetic field, he succeeds in isolating these cells from a sample, so "Magnetic Activated Cell Sorting" (or MACS for short) is born, which is used worldwide today in biopharmaceutical and medical research.

With this technology, Miltenyi lays the foundation for his own company – Miltenyi Biotec – which he founds in Bergisch Gladbach near Cologne in 1989. More than three decades later, he still runs the company that bears his name. Since then, it has become a frontrunner in biotechnology.

HOPE FOR SERIOUS DISEASES

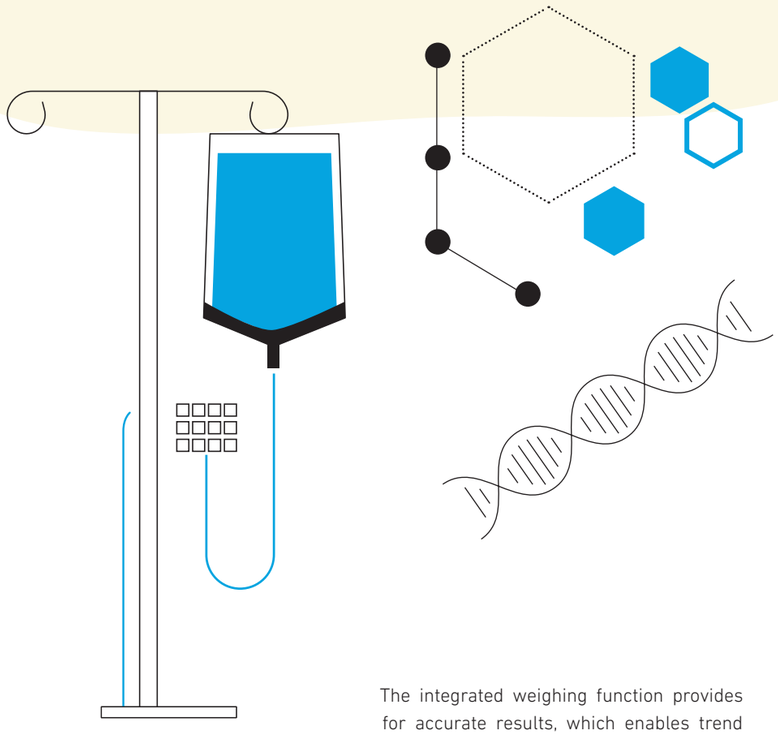
Around 4,700 employees work for Miltenyi Biotec worldwide, almost 25 % in R&D – so the passion for new technologies still drives the company, just as it did the young student back then. Miltenyi Biotec's declared goal is to contribute with its technologies to the treatment of cancer, autoimmune and neurodegenerative diseases. The company is also involved in clinical studies relating to cell and gene therapies. These therapies are set to revolutionize medicine, as they also offer huge potential for serious diseases previously deemed incurable.

CELLS IN FOCUS

Cell therapies with living cells are often used to replace the body's damaged or defective cells. In this process, cells are taken from a donor or the patient, proliferated outside the body, and subsequently re-administered. Stem cell therapy is a prime example.

"As the cell products are administered to patients, aseptic processing is a top priority."

Reiko Jennerjahn
Manager Liquid Solutions
at Miltenyi Biotec



Gene therapies, however, are designed to adapt genetic material – a faulty gene sequence can be replaced or repaired. DNA or RNA is introduced into body cells to achieve this. Prior to this therapeutic administration, the engineered cells must also be cultivated outside the body.

In both – cell and gene therapies – it is essential to proliferate cells in a controlled way. Only then is there sufficient material for effective therapy. This cell proliferation also features in one of Miltenyi Biotec's current projects.

STERILE FILLING OF BAGS

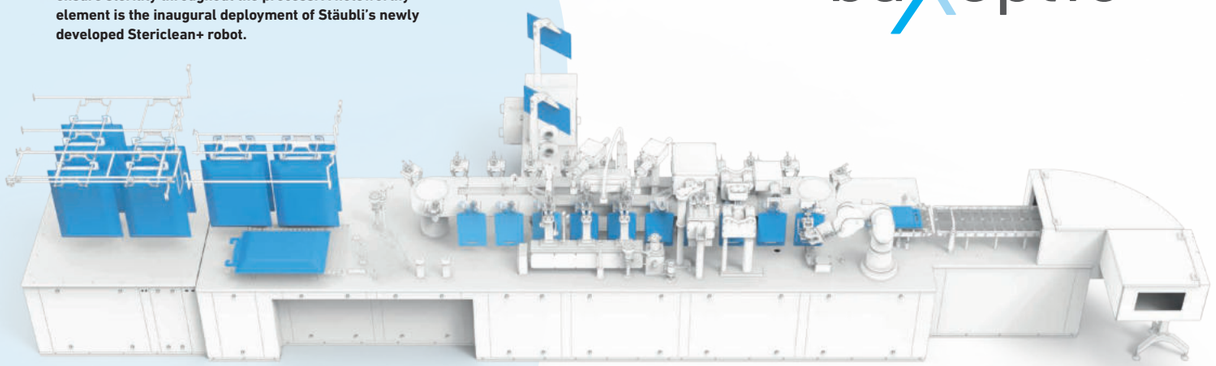
"This project is about filling cultivation medium for cells into bags. The medium is subsequently used for growing the cells," Reiko Jennerjahn, Manager Liquid Solutions at Miltenyi Biotec, explains. "As the cells are administered to patients, aseptic processing is a top priority. While looking for available automated filling solutions, we came across Harro Höfliger, and its experience in aseptic bag filling raised our interest. We got in touch in May 2022 and together we conducted our first filling trials soon after."

TAILOR-MADE THERAPIES, TAILOR-MADE SYSTEM

This resulted in a system that aseptically fills about 360 bags an hour. Depending on requirements, up to three bag formats with different volumes can be produced. Several measures ensure sterility throughout the process. Reiko Jennerjahn says: "The pre-sterilized bags are passed through a VHP airlock to ensure sterility. In addition, an isolator from our partner Franz Ziel GmbH is integrated to shield and control the process environment. Multiple bags are filled simultaneously, whereby a single-use system reduces the risk of contamination." The integrated weighing function provides for accurate results, which enables trend control of the filling station. After filling, the bags are sealed, followed by 100 % Container Closure Integrity Testing (CCIT).

With its individually coordinated process steps, the system perfectly exemplifies baXeptic. Harro Höfliger offers solutions under this brand name for aseptic bag applications. Reiko Jennerjahn sums up: "Cell therapies are very promising, not least because they are individualized to patients. A tailor-made system to facilitate tailor-made treatments – it's a perfect match."

The system fills about 360 bags an hour. Several measures ensure sterility throughout the process. A noteworthy element is the inaugural deployment of Stäubli's newly developed Stericlean+ robot.



baXeptic

"A SECOND LIFE FOR THE LINE"

A line for dosing inhalation powder into blisters had been out of service at AEROPHARM GmbH in Thuringia for some time and appeared to be a candidate for dismantling. Over a cup of coffee, the idea was born to make it fit for a new product with a different filling system. Account Manager Benjamin Jung reports on how Harro Höfliger's Customer Service succeeded in this quest.

Helmar Lünig

Mr. Jung, what did the conversion project involve?
Sustainability and the responsible use of resources are becoming increasingly important. This also includes using machines for as long as possible and yet keeping them fit for the future. As Customer Service, we deliver a wide variety of customized solutions to extend the lifecycle of the line or adapt it to new requirements. Modernizations and upgrades of every kind, from retrofits to complete machine conversions, are included, of course. Rebuilding the MSP – a machine for filling blisters with inhalation powder – of AEROPHARM GmbH was the biggest project of its kind that we had implemented in Customer Service to date.

What was specifically required?
The MSP with drum dosing system had served reliably for years, filling blister strips for a dry powder inhaler with powder containing active ingredient. Due to a product changeover, our customer had taken the line out of service some time previously. I've served this pharmaceutical company for about 15 years in various roles at Harro Höfliger. Over a cup of coffee, Pierre Solcher, Head Service & Qualification, and Dr. Sebastian Moritz, PD Group Head, and I got to talking about whether it would be possible to breathe new life into the line with a new filling system and retrofitting options. It turned out to be possible!

Benjamin Jung, Account Manager Customer Service at Harro Höfliger, accompanied the MSP modernization.

How did you go about it?
My colleagues and I took a close look at the requirements. The line consists of three modules: for forming, filling/sealing and for cutting. With the conversion of three drum fillers to a new dosing system, it was necessary to completely replace one module and modify the other stations. At the customer's request, space was also to be created inside the containment for an optional X-ray system for filling control – this meant extending the line by 1.5 meters. For dosing, we had one of our other filling principles in mind, which was established on the market and was in a position to meet the special requirements of AEROPHARM GmbH. In order to determine whether this represented the best dosing solution for the product and which format parts were required, we proceeded in much the same way as we do with a new machine and had our Pharma Services carry out powder analyses and filling experiments with active material in the cleanroom.

Where did the conversion take place?
A logistics company brought the line back to Allmersbach to the plant in which it had once been constructed. Project management was in the hands of Customer Service and we accomplished the design, installation, electrical installation, control engineering and technical documentation with our own resources. But of course we worked hand in hand with the various specialist departments on-site, for instance with regard to validation, containment or camera control. After commissioning and the factory acceptance test in our production plant, the site acceptance test was also completed successfully at the facility of our customer, with whom cooperation had been excellent.

The heart of the MSP: dosing inhalation powder into aluminum blisters.

Were there any other changes besides the new stations?
The MSP was converted in this process to a more advanced control technology – from PacDrive M to PacDrive 3 – and the operating system was upgraded from HMI 1.0 to 2.0. This gives our customer the assurance of being able to use their line for many years to come without any potential problems with discontinued components, a matter particularly close to our hearts in Customer Service.

Which advantages, beyond assured spare parts, does a conversion offer?
Conversion or retrofitting, in which a machine is improved or reconfigured to meet current requirements, is a sustainable, future-proof alternative to purchasing new and often entails lower investment costs. Apart from the complex measures on the MSP as described, the majority of the line remained unaffected. The extended service life of a machine not only saves on resources, but also usually reduces the effort required for the customer to retrain the operating personnel, as the familiar basic functionality remains. Giving a line a second life, so to speak, inspires me and our experts from Customer Service every time anew.

For the conversion, the line was transported back to Allmersbach im Tal.

Pierre Solcher
Head Service & Qualification,
AEROPHARM GmbH

"Already during the initial project phase, it was clear that we needed a competent partner to help us implement the complex project requirements. So we turned to Harro Höfliger with whom we have a long-standing business relationship. It didn't take long before the idea of upgrading an existing machine was born, knowing full well that this wasn't going to be an easy task and would involve a certain amount of effort. In summary, it's true to say that it was the right decision."

AEROPHARM GmbH
Helmar Lünig

Disassembly of the MSP. The modernized line has since started production in the AEROPHARM GmbH cleanroom.

"The overall concept convinced us not only in terms of the economical use of resources, which also plays an enormously important role for us. We received competent support from Harro Höfliger in all project phases and the work was always solution-oriented. We're looking positively to the future and are well equipped for upcoming challenges."

Dr. Sebastian Moritz
PD Group Head,
Pharmaceutical Development
AEROPHARM GmbH

INTERVIEW

5 QUESTIONS FOR NATALIE WITTLINGER

Natalie Wittlinger is Project and Sales Manager in the Packaging Technologies division. In this interview, she answers questions about current developments.

1

Everyone's talking about sustainability – how is this reflected in packaging?

One important aspect are the inserts: Products like pens, syringes and auto-injectors are secured inside the cartons by placing them in such an inlay. As they are often made of plastic, there's a trend to use cardboard instead. Yet they aren't suitable for every product. Both types are still used in our projects depending on the requirements, especially as developments are heading towards "green" plastics – we remain flexible here. But sustainability also means minimizing the space requirements and energy costs of production lines. We're well positioned here with our side-loading cartoners. As the name says, the products are inserted into the carton horizontally. Cartons that the user opens from the top can also be processed with our side-loading/top-opening concept.

2

The new version of MKT is such a side-loader. What sets it apart from the previous one?

Firstly, we managed to increase the output of this intermittent cartoning machine up to 150 cartons per minute. Nevertheless, it still remains very space-saving. Another important aspect was to achieve the high output without compromising product protection. For this reason, decentralized servo-drives control the individual stations, allowing the machine to run very smoothly even at high speeds. Last but not least, it is extremely flexible due to the easy format changeover and multiple closure solutions in one machine.

3

Flexibility – what are the trends in the packaging industry?

There is a clear trend toward product diversity. This means that a line should be able to package very diverse products, also in different quantities. Taken to an extreme, this even means changing to batch size 1, i.e. every single product has its individual packaging. This development shows why easy format changeover is so important, as it prevents prolonged downtimes when switching between different products.

But flexibility is also important to us in another sense: Harro Höfliger's packaging machines are never off the shelf, but are always individually adapted. For instance, in a recent project, we completely customized the machine. It packages beyond the conventional format range and products can be fed to the line either standing upright or turned by 90 degrees. Its shape is also unusual: Space was limited at the production site, so the line with its packaging machine, MQS quality module, through to the palletizer, is configured accordingly. For larger lines like this, we also excel with our ability to take care of the entire system integration.

4

What does system integration mean?

We procure all machines, including those from sub-suppliers, and combine them on-site at our facility. Rather than having to communicate with different companies, the customer then has a single contact who takes care of all topics. This way, all line qualification and validation activities can take place at the same location. With the line completely built and tested at Harro, the risk of interface related issues is reduced, so the line can go into production more quickly once it is installed. This approach is true to our credo as a turnkey supplier providing everything from a single source. Our processes are not only implemented during packaging, but often much earlier.

5

Can you give an example to illustrate this?

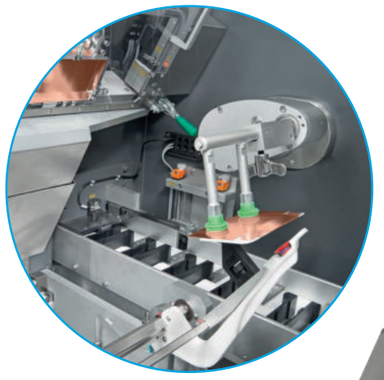
There are for instance medical devices such as auto-injectors and pens. Although we have separate, specialized departments for assembly and packaging technologies, we really benefit from each other. The assembly division, for instance, has in-depth knowledge of the device composition, which of course affects the packaging process. On the other hand, the packaging specialists can for instance develop an optimal transfer solution to the packaging machine. Thanks to the different departments, we illuminate tricky processes such as labeling from more than one perspective and then develop perfect solutions together.

THE NEW MKT

Intermittent, reliable, space-saving – Harro Höfliger presents the new version of its MKT cartoning machine. Along with higher performance, it stands out by virtue of its many other advantages.

Ingenious

The cartons are opened using a sophisticated cycloid system.



Clearly arranged

The use of safety glass eliminates the need for intermediate supports. This enhances accessibility. It also avoids clouding and static charging.

Flexible

Format changeover is quick and easy with plug-and-play and servo-driven adjustment.

Smart

The individual stations on the line are controlled by decentralized servo-drives.

Productive

The new version of the cartoner packages up to 150 products per minute.

Compact

The MKT features space-saving design.

Efficient

Low maintenance requirements and ease of operation ensure maximum line availability.

Helmar Lünig

BACTERIA IN THE CAPSULE

The targeted delivery of living microorganisms opens up a new class of therapeutics. Seres Therapeutics' VOWST™ is the first FDA-approved, orally delivered microbiome product to treat recurrent Clostridium difficile infections. Working closely with Harro Höfliger, a customized system was developed for filling microbes into capsules.

The Modu-C LS Containment is set up to protect the operator while handling living organisms.

Every human body is home to many trillions of microorganisms, like fungi, viruses and bacteria. Together they form the microbiome whose composition is as individual as a fingerprint. But for all its uniqueness, every microbiome has one thing in common: It plays an important role in health. Our intestinal bacteria support digestion and protect against pathogens, for instance.

So the problem is all the more serious if this sensitive ecosystem gets out of balance. This could lead to a variety of health problems – like digestive disorders and inflammation.

"Live biotherapeutic products have the potential to treat a wide range of diseases."

Michael Philbrook
Senior Director of Formulations at Seres Therapeutics

DRUGS WITH MICROORGANISMS

Live biotherapeutic products – LBPs – are based on specific strains of bacteria or other microorganisms. Their purpose is to restore balance. The US biotech company Seres Therapeutics specializes in such microbiome therapies. Its new drug – VOWST™ – is used to combat rCDI, a serious gastrointestinal infection. Michael Philbrook, Senior Director of Formulations at Seres Therapeutics, explains: "Recurrent CDI can occur after taking certain antibiotics, because while they fight harmful bacteria, beneficial bacteria are also significantly impacted. In a disrupted microbiome, the bacterium C. difficile can multiply and produce harmful toxins that cause severe inflammation of the colon and debilitating diarrhea." Although antibiotics are necessary to kill the toxin producing C. difficile bacteria, they do not address the disrupted microbiome, which may increase the risk of reinfection.

That's why Seres Therapeutics developed VOWST™ for such recurrent forms of infection: A capsule containing a mixture of different live bacterial strains which produce metabolites that end the cycle of recurrent C. difficile.

CAPSULE FILLING, A TRICKY BUSINESS

The process for producing this promising drug is demanding. Michael Philbrook: "The bacteria are obtained from a healthy donor's stool sample which is then purified, cleared of potential pathogens, and formulated to a target concentration. The process results in a stable bacterial spore suspension which is then filled into capsules." These capsules are then over-encapsulated into a slightly larger size.

Harro Höfliger is the partner for all aspects of encapsulation. "This was based on our proven Modu-C LS Containment machine," explains Daniel Müller, Sales Director in the Capsule Technologies division. This includes a trolley system. Which means: The dosing systems are mounted on mobile carriages, making them interchangeable. This allows both processes to run on one machine.

Helmar Lunig

TWO NEW DEVELOPMENTS

The first dosing station is for filling the liquid into the smaller capsule. Müller: "We've developed a dosing system that maximizes the filling efficiency so none of the valuable product is wasted." Specialists then inspect each capsule outside the machine before over-encapsulation takes place again.

The second dosing trolley is now used for this purpose. "This is also a customer-specific development and an absolute novelty in the market," says Daniel Müller. "So far, it was like this: When one capsule is filled into another, there was usually a two capsule size difference, e.g. a size 1 capsule in a size 00 capsule. This buffer did not exist here, however, because we are filling a 0 capsule into the next larger 00 capsule. In close coordination with Seres specialists, our engineers developed a perfect solution for this."

HIGH-TECH CLEANING

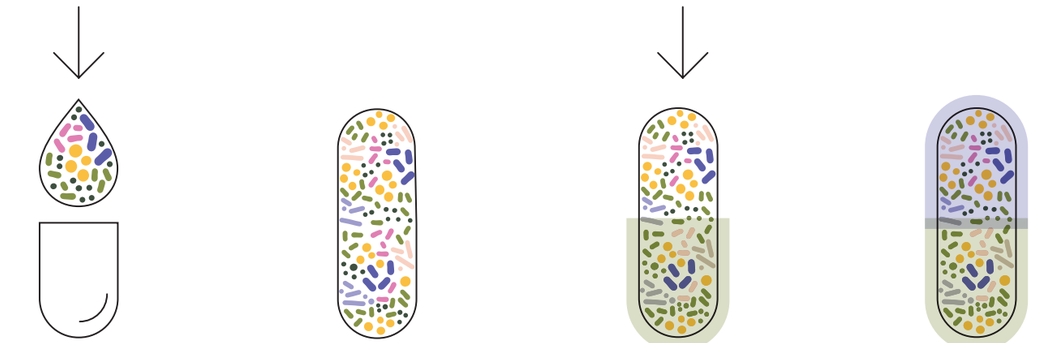
Handling living organisms requires special protection. Daniel Müller explains the background: "Even the slightest amount of bacteria left behind after one batch could contaminate the next one. Measures to prevent this include disinfecting with vaporized hydrogen peroxide (VHP). During this process, you can run the machine slowly with the doors open – thus ensuring that the gas reaches into every corner of the machine. A scanner is also integrated to check the area in front of the Modu-C for safety reasons. If it detects a person, the machine stops immediately."

"In close cooperation with Seres, we have developed two special dosing systems."

Daniel Müller
Sales Director Capsule Technologies at Harro Höfliger

"The equipment is tailor-made and precisely meets the exceptional requirements of this product," Daniel Müller summarizes. "The close partnership with Seres contributed to the success of this design. We are always interested in exploring applications where new technologies must be found."

FOUR STEPS TO THE PERFECT PRODUCT



Fill liquid into capsule

Close inner capsule

Fill capsule into capsule

Close outer capsule

Flexible like never before: A new transportation system opens up a wide range of options for Harro Höfliger in the design of future production lines. As MOT Flex, the tried-and-tested MOT platform demonstrates its strengths in the agile assembly of medical and pharmaceutical products, for instance auto-injectors.

Helmar Lünig

Magnetic force holds the individual shuttles on the guide rails.

Quietly buzzing servo-controlled shuttles speed around a central oval on guide rails – the so-called tracks. They accelerate, decelerate, group and arrange themselves with the components or products they have picked up before reaching the downstream processing station. At the end of this fascinating choreography there is a perfectly assembled auto-injector which allows patients to administer their drugs with a precise dose.

With its new intelligent transportation system, the tried-and-tested MOT assembly platform offers significantly more flexibility in production. Individually controllable shuttles based on linear drives move individual parts and the end product quickly and flexibly from one station to the next. Magnetic force keeps the highly dynamic transport vehicles securely on track. The system software always ensures sufficient safety clearance between the shuttles and prevents them from colliding. Special track switches enable agile splitting and merging of product streams. This flexibility also gave the new Harro Höfliger assembly platform its name: MOT Flex.

"The drive system offers us a multitude of new options and has what it takes to fundamentally change the design and operation of production lines," says Rainer Wolbers, Operations Director Assembly Technologies. "The MOT Flex is characterized by a small footprint and an economical workflow. The infeed and outfeed of products can also be reconceptualized, because it is possible to connect trayloaders and palletizers directly to the intelligent transportation system without pucks."

VARYING SPEED

Format changeovers can be carried out much more easily and quickly than with conventional chain drives. This allows for assembly of diverse medical and pharmaceutical devices, such as pen injectors, auto-injectors, inhalers and many more, on one line. "Depending on requirements, parallel processing stations, buffer zones and much more can be realized for our customers," Rainer Wolbers explains. "The capability of varying speed and acceleration between processing stations allows the shuttles to be distributed to multiple stations in time-critical processes. The effort required for less demanding tasks like presence monitoring, however, can be kept to a minimum."

The new MOT Flex with the innovative shuttle system was first used in a line for the final assembly of auto-injectors. The core task in this project was to insert the drug-prefilled syringes into the syringe housing with high precision and to press them in reliably according to the manufacturer's instructions. Printing the auto-injector with laser technology was also part of the process. Special attention was paid to efficient handling and gentle, smooth transport of the syringe without any glass-to-glass contact.

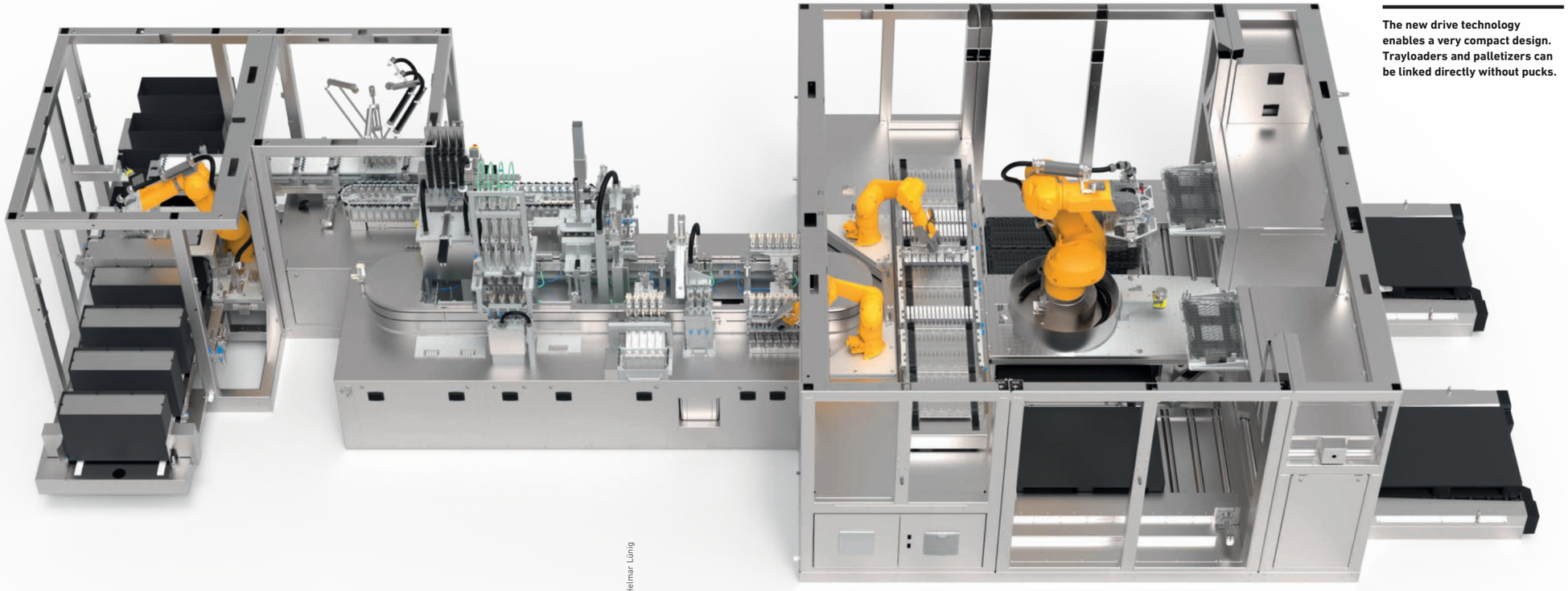
"The transportation system sets completely new standards in terms of flexibility."

Rainer Wolbers
Operations Director Assembly Technologies
at Harro Höfliger

On this line, two robotic arms accurately grip the pre-assembled syringe units from the tray, which is fed via Harro Höfliger's TS Pallet Euro palletizer, and places them in the shuttles. These speed along with their transported load to the first processing station. Here the syringe unit is separated again and the drive unit for triggering the injection is removed in order to insert the prefilled syringe. Then the device is reassembled in the steps to follow. After the subsequent quality control, the nimble transport vehicles deliver the fully assembled auto-injectors back to the robot station: The gripper arms carefully pick up the end products and load them in the finished trays, which are automatically placed on pallets.

MULTIPLE OPTIONS

The shuttles have already started the next round and are whizzing around the oval with a new load. "The transportation system sets completely new standards in terms of flexibility," says Rainer Wolbers. "This makes it easier than ever to assemble completely different products on one line."



Helmar Lünig

The new drive technology enables a very compact design. Trayloaders and palletizers can be linked directly without pucks.

LOOKING FOR A TRAVEL COMPANION?

It's a long journey before an inhalable API powder comes onto the market. So it is a good thing that Harro Höfliger has experts who know exactly where the journey is going. They use their experience and expertise to explore the fastest and safest way to reach the destination.

For some time now, growing numbers of pharmaceutical companies are focusing more on distributing rather than researching and developing pharmaceuticals themselves. They are increasingly buying semi-finished or finished formulations from smaller companies or startups. The reasons for this are fairly obvious: The initial development of new drugs is laborious, cost-intensive and risky. Nobody knows whether there will be an approved and marketable drug at the end of the road. One of the more common stumbling blocks relates to process development, which may be inadequate or comes too late. Smaller companies often lack the necessary expertise and technical options for this task. Harro Höfliger has both: The specialists accompany and support customers with a bundle of services on their way to turning an idea into a product – quckly and with minimal risk. We'll show you how such a shared journey proceeds by taking the example of an inhalable powder.

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WHERE ARE WE HEADED?

Marco Laackmann is one of THE inhalation experts at Harro Höfliger. As a sales representative, he is the first point of contact for customers in many cases. In his discussions it is important for him to understand the wishes or ideas and find out where the journey should actually go. "Sometimes there's merely a concept, but often the customer already has a sample of the powder they've developed. We also have cases where the focus isn't on the API but on the route of delivery, such as a novel inhaler. And then there are customers who need our support in developing the powder itself," Laackmann explains. Regardless of the starting situation: Together with the customer and experts from Harro Höfliger, he focuses on process development at an early stage, thus setting the course for the success of their project.

Marco Laackmann
Sales Director Inhalation Technologies at Harro Höfliger

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HOW MUCH CONSULTATION IS REQUIRED?

Harro Höfliger offers customers an entire catalog of consulting services. These range from analyzing the powder components and the subsequent production of the mixture, to searching for an appropriate filling technology and a suitable inhaler, up to developing a high-performance line for commercial series production of the finished product. Regardless of whether customers go for individual consulting modules or the complete package: The risk of errors in early process development is reduced, which increases the chance of quickly bringing a viable drug to market that can be produced in large amounts.

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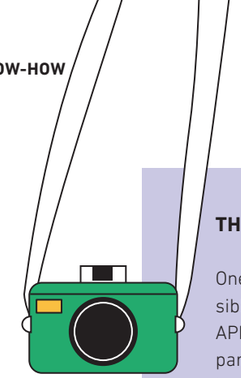
CAN THE DESTINATION BE REACHED? AN INITIAL APPRAISAL

The first stop in process development is with Dr. Elke Sternberger-Rützel, Division Leader Pharma Services at Harro Höfliger. Together with her team, she ensures that each powder can be processed perfectly and ends up where it is supposed to: firstly in the primary packaging material and later in the patient's lungs. Prior to starting the actual work, the safety datasheet of the API to be analyzed is reviewed and an identity test ensures that it matches the powder sample sent by the customer. The pharmacist then undertakes physical characterization of the powder. "Putting it simply, some are like sugar, so they're flowable. Others are more like powdered sugar, so they're cohesive, i.e. poorly flowable," says Sternberger-Rützel. Based on the analyses, the Pharma Services team creates metrics and compares them with the reference powders available in large numbers at Harro Höfliger. "At this point," Sternberger-Rützel explains, "we can already predict with a fair degree of confidence whether it is possible in principle to fill the powder on a large scale."

Andreas Dalferth



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THE QUEST FOR THE PERFECT MIXTURE

One of the trickiest tasks in process development is mixing the API with excipients like lactose and possibly magnesium stearate. At the end of the day, the mixture must have optimum flowability and an even API distribution. To achieve this, Elke Sternberger-Rützel and her staff need a ton of patience: "The main parameters we look at are the constituents, as well as mixing speed and duration. We have to adapt both to the particular API, because not every API can tolerate high shear forces during mixing, for example." Each mixing experiment is followed by sampling at ten different points. "Only when the same active substance concentration is present at each measuring point do we move on to the next step," says the pharmacist.

Dr. Elke Sternberger-Rützel
Division Leader Pharma Services
at Harro Höfliger

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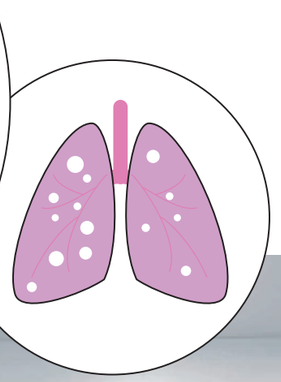
TIME FOR GOING SEPARATE WAYS

The core principle of dry powder inhalers is that the patient inhales and the air flow makes the powder disperse. The finer fraction ends up deep in the lungs. So what had first been mixed with care and patience must now separate again perfectly. With the aid of numerous tests, the experts determine the ideal interaction of inhaler and API particles. The interaction must be just strong enough for the particles to adhere to each other during filling, but reliably separate from each other again during inhalation. "We have a Next Generation Impactor (NGI) for the tests, which works like an artificial lung," Sternberger-Rützel explains. "With this device, we can accurately determine the aerodynamic particle size distribution during inhalation to ascertain whether the powder is separating as required."



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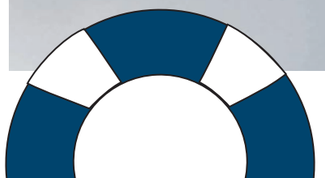

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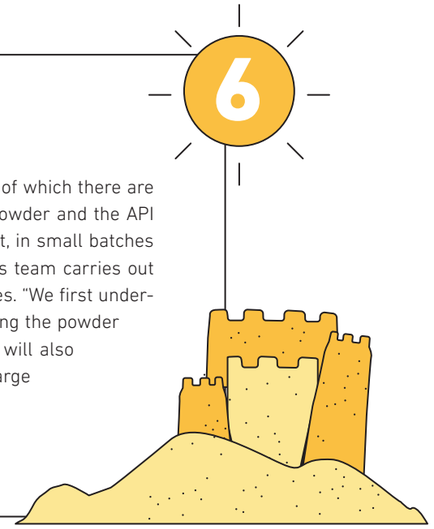
THE SUITABLE PRINCIPLE

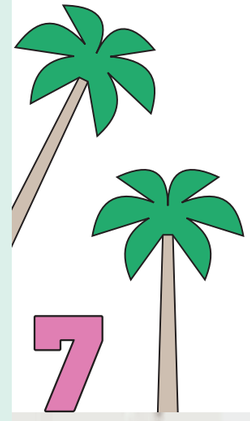
For each powder, it is necessary to select the suitable filling technology, of which there are around 15 at Harro Höfliger. Sternberger-Rützel says: "The amount of powder and the API concentration in every single dose must be perfectly suitable throughout, in small batches for clinical trials as well as for series production." The Pharma Services team carries out filling experiments with a pre-selection of two or three filling technologies. "We first undertake experiments manually with tabletop instruments and start with filling the powder into capsules. If precise dosing can be demonstrated here, the process will also work dependably and reproducibly when filling into other devices and in large amounts. This gives customers peace of mind before they enter into major investments."



EVERYTHING IS POSSIBLE NOW

Prior to and during the numerous analyses and tests that the powder has to undergo, experts from Harro Höfliger also advise customers on devices, on request. "We help turn ideas into real products," Marco Laackmann explains, adding: "Here, too, we have the expertise and technical prerequisites to carry out sound experiments." Elke Sternberger-Rützel, who documents all analysis and experimental results as well as the process parameters of the powder and makes them available to the customer, adds: "We take a holistic view of process development. Our approach is to bring formulation, device and filling technology together as early as possible to quickly arrive at the optimal process."

"The demand for consultation in process development is already high. And it is set to rise," Laackmann is convinced. "For instance, with the growth of biotech drugs and APIs like inhalable antibodies or mRNA, entirely new development challenges arise for all involved. We will not abandon our customers on this path. We accompany them on request – from powder development to the construction of a commercial production line."



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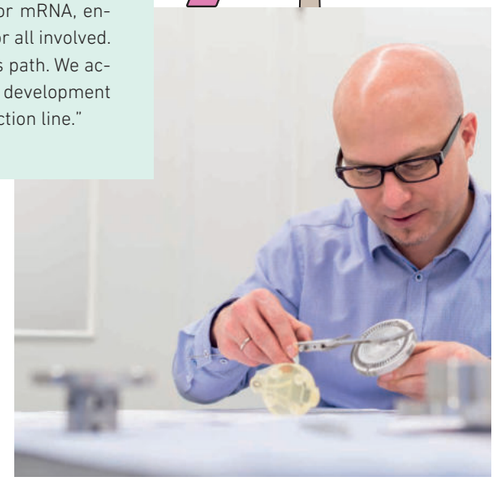


TAKE A DEEP BREATH!

Inhalable medication is essential with lung diseases. But not every active ingredient can be processed into a respirable medication. Now, a new thin film freezing (TFF) process developed by the University of Texas at Austin can tame even difficult substances. The US companies TFF Pharmaceuticals and Experic are collaborating on new powder formulations and processes for encapsulating TFF inhalable powders.

Anyone who has ever tried to pour the contents of a saucepan into a narrow bottle opening will have a rough idea of the efficiency of oral delivery of many pulmonary drugs. Frequently, only around ten percent of the active ingredients reach their target. One of the reasons for this is the poor solubility of many drugs in water. This makes it difficult for the body to absorb the active ingredients, reducing efficiency. Delivery through dry powder inhalers is much more efficient and targeted, explains John Koleng, Vice President of Product Development and Manufacturing at TFF Pharmaceuticals. "The patient takes a deep breath, and the tiny particles of the engineered powder containing the active substance directly reach the deep pulmonary tissues without major loss. This only works with fine powders whose particles are aerodynamically smaller than about five micrometers. This rules out many highly effective substances from the start." Researchers at the University of Texas at Austin have succeeded in identifying a solution to this problem. They developed a technology which converts a coarse powder into a light and respirable one. TFF Pharmaceuticals has secured a license for the patented thin film freezing process technology.

FROZEN AND CONDITIONED

"Thin film freezing is a particle engineering process," explains Koleng. "We dissolve the drug in a solvent and then drop the liquid onto a stainless-steel drum cooled with liquid nitrogen, where the droplets are rapidly frozen. The frozen product is then freeze-dried to remove the solvent thus yielding the TFF powder." At the end of the process, the originally coarse and compact powder has been converted to brittle matrix particles that are highly porous, have a large surface area and a low bulk density. After conditioning, the result is a fine powder. This way, a dry powder inhaler is used to deliver up to 75 % of the active ingredient to the lungs where it is intended to act.

"With TFF technology, a coarse powder can be converted into a light and respirable one."

John J. Koleng, Ph.D., R.Ph.
Vice President of Product Development and Manufacturing at TFF Pharmaceuticals

LEVERAGING COMMON POTENTIAL

TFF Pharmaceuticals works closely with Harro Höfliger and its partner, Experic, in evaluating TFF manufactured powders and their subsequent encapsulation for use with a dry powder inhaler. Experic is a contract manufacturing and development organization that manufactures and packages clinical trial materials and specialty supplies primarily for small,

Experic, Avector/Adobe Stock

Since the beginning of 2019, the US company Experic has been offering contract services for the manufacturing, packaging, labeling and global logistics of clinical trial materials and specialty commercial supplies. Experic is focused on the small, midsize, and specialty pharmaceutical customer.

medium and specialty pharmaceutical customers. Justin Lacombe, Chief Scientific Officer at Experic, explains: "As a CDMO partner, we manufacture powders for TFF Pharmaceuticals and carry out tests with our Harro Höfliger filling machines. In this way we can test formulations for compatibility with the encapsulation machines at an early stage of development. This supports early success with initial clinical manufacturing and facilitates feedback that enables successful scale-up."

INFINITE POSSIBILITIES

The thin film freezing particle engineering process has a lot of potential, and TFF Pharmaceuticals and Experic are working together to develop new applications. One of these is TFF Pharmaceuticals' inhaled tacrolimus product, currently in Phase 2 trials. Tacrolimus is a natural compound that acts as an immunosuppressant. Inhaled tacrolimus is being studied as an alternative to oral tacrolimus for lung transplant patients where direct to lung delivery could potentially maintain the efficacy of the oral therapy while reducing side effects

"As a CDMO partner, we manufacture TFF powders and carry out filling tests with our Harro Höfliger machines."

Justin Lacombe, Ph.D.
Chief Scientific Officer at Experic

and drug-drug interactions. However, TFF developers are not just looking at repurposing existing drugs. Koleng explains that around one third of the most important drugs available worldwide are difficult to dissolve in water and that thin film freezing technology is suitable for many of them, as well as for combination therapies and the growing segment of biologics. "Inhalable powders are the future," he says, adding: "They can be accurately measured, don't require cold chain storage and distribution, and are significantly easier to handle than sterile syringes. We can give them a boost with TFF technology."

HOW THIN FILM FREEZING WORKS

1. Formulation: The thin film freezing process involves first combining a drug or drugs in a liquid carrier system, which can include agents designed to promote dispersion and avoid aggregation, as well as excipients to promote delivery to the target site.

2. Freezing: Controlled freezing the liquid material on the surface of a cryogenic drum results in brittle matrix particles: highly porous, large surface area, low-density particles

3. Drying: The frozen solvent is then removed by sublimation to yield a dry powder material that can be aerosolized to facilitate delivery to the lungs, nose, eyes and topically through the skin.

4. Finishing: The brittle matrix particles are then further processed to facilitate creation of the final dosage form for the targeted route of administration.

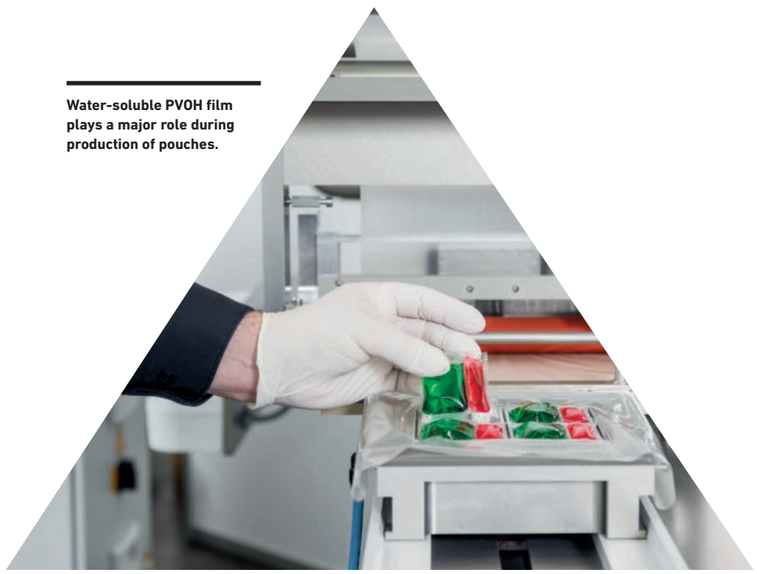
PERFECT IN FORM

Processing water-soluble film presents rather tricky challenges. Harro Höfliger is expanding their leading-edge technology using an innovative thermoforming method.

In many households, they already belong to everyday life: pre-portioned units (pouches) for washing machines or dishwashers that are convenient to handle. Quite often they are produced on machines made by Harro Höfliger. "The production steps sound simple: forming, filling, sealing and cutting. But this is misleading. The water-soluble PVOH film used comes with challenges," says Alina Nick, Sales Director Portion Packs.

A current example is the forming of the PVOH film. "Via a vacuum thermoforming process, it is formed into the desired shape," explains the expert. "The application of high heat and a rapid forming process using a high vacuum creates thin areas in the film. This is a real problem because, for the safety of the user, the pouches are supposed to dissolve in water only after a certain time."

As Sales Director Portion Packs, Alina Nick knows the challenges production processes may pose.



Water-soluble PVOH film plays a major role during production of pouches.

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This is where Harro Höfliger's special thermoforming method comes into play: "It is based on our patented continuous forming process in which heat and vacuum are optimally coordinated with each other. By heating the film more slowly, it gains elasticity without high temperatures, and the vacuum required is also reduced. Ultimately, this results in more film thickness, even when it comes to complex designs."

Another example for the department's innovative strength is the patented water sealing method: In this process, a print head applies water to the lid film with pinpoint accuracy and in a controlled manner. These water drops start to partially dissolve the film before it is pressed onto the base film for sealing.

Alina Nick summarizes: "With such processes, we not only shape perfect pouches – we also set new standards in this challenging field."

IMPRINT

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