HARRO

The Customer Magazine
by Harro Höfliger

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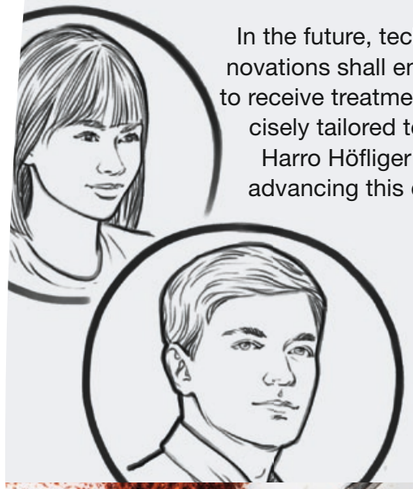
Back to the future

Since 1988, AstraZeneca has been producing one of its oncological drugs on machines made by Harro Höfliger and has improved the syringe continuously. Now a new, state-of-the-art line is ready for operation.

Harro Höfliger

Medication made to measure



In the future, technological innovations shall enable patients to receive treatment that is precisely tailored to their needs. Harro Höfliger‘s experts are advancing this development.

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It‘s all in the mixture

The Pharma Services team developed their first powder for a capsule-based inhaler.

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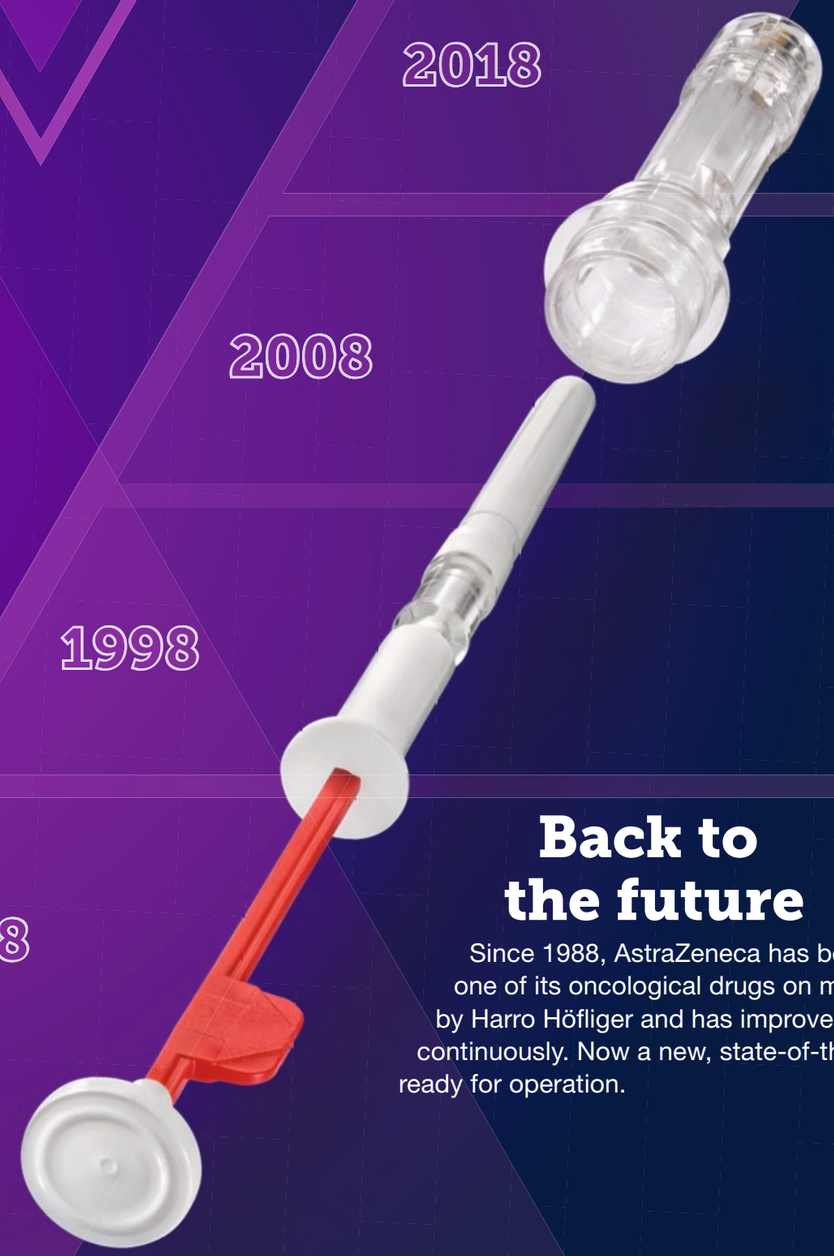

Back to the future

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Dear readers,
dear business associates,

Corona has plunged the world into a deep crisis. But a large number of companies quickly took the initiative: Research on medicines and vaccines is being conducted all over the world. Even beyond Covid-19, time does not stand still. Internationally, experts continue to work intensely on innovative drugs and technologies that keep people healthy, cure them – or make their lives easier.

Together with our customers, we pursue future-oriented trends and support the development of new dosage forms with our technologies. An example is the Accordion Pill® by Intec Pharma: A folded, multi-layer polymer film in a hard capsule releases the active ingredient in a controlled manner. For the biopharmaceutical company Zosano Pharma, we designed a fully automated line for the high-precision coating of titanium microneedles. They form the centerpiece of a patch that is supposed to provide faster relief for migraine patients in the future. In addition, we have taken a major step in the field of future-oriented vaccination technology using microneedles. Our long-standing development work with Vaxxas is moving on to the next stage: The manufacture of a pilot line for the new microneedle device with the support of organizations such as the Gates Foundation, PATH and the WHO.

Personalized medicine is a topic that could revolutionize the pharmaceutical industry. In this field, too, we are expanding our network of specialized partner companies and are advancing the technological development of these trends. For instance, we recently entered into a strategic partnership with DiHeSys Digital Health Systems – together we develop solutions for 2D and 3D printing to enable personalized production of medicines.

“Together we are strong” has been our motto not just since Corona. We have been living it for decades with reliable, trusting partnerships. As early as 1988, Harro Höfliger received the first order for the aseptic assembly of syringes for a world-leading oncology drug from AstraZeneca. The cooperation has been continuing until today.

The future holds many challenges in store for us. Let us overcome them together.

Stay healthy, your

Thomas Weller,
CEO at Harro Höfliger

Medical Device Assembly at Experic

The US-based company Experic supports clinical trials for pharmaceutical companies, for instance with manufacturing, filling, and labelling services as well as global logistics management. The latest addition to their technology portfolio includes the assembly of medical and pharmaceutical devices.

Since May 2020, an Assembly Lab expands the Harro Höfliger technology portfolio at Experic. The semi-automatic assembly machine can be flexibly customized for various devices, including autoinjectors, pens and patch injectors. In addition, the batch size can be determined individually – a clear advantage in early phase clinical studies, where small batches are required.

State-of-the-art dosing equipment from Allmersbach im Tal has been in place for capsule filling and micro-dosing since the Experic facility was commissioned in July 2019. For Harro Höfliger, the cooperation with Experic builds upon its promise to support customers from the product idea to market launch and well beyond.

The Assembly Lab complements the technology portfolio at Experic.

Eco-Design Award 2020

The Respimat® re-usable inhaler by Boehringer Ingelheim has won the Eco-Design Award at the Pharmapack 2020 in Paris. With this award, the jury honored the re-usable version of the established Respimat® inhalation device for its environmental compatibility. Now that multiple filling with an active ingredient cartridge is possible, according to the company, around 776 tons of plastic could be saved by 2025 and the carbon footprint could be significantly reduced The history of the Respimat® is closely linked with Harro Höfliger. First project studies already began in 1997. In the following years, the machine manufacturer supplied technology for pre-assembly, spray jet and function control as well as for the final assembly of the inhaler and of the active ingredient cartridge. The production systems for the re-usable inhaler and its cartridge were also developed in close cooperation between Boehringer Ingelheim and Harro Höfliger.

The Respimat®re-usable inhaler has received the Pharmapack Eco-Design Award 2020.

Trade shows and events

Stay up-to-date which trade shows and conferences we are represented at, and have a look at our current overview on **www.hoefliger.com/en/newsroom/events**

Helmar Lünig, Experic, Boehringer Ingelheim microParts GmbH, Adobe Stock/Eva Bocek

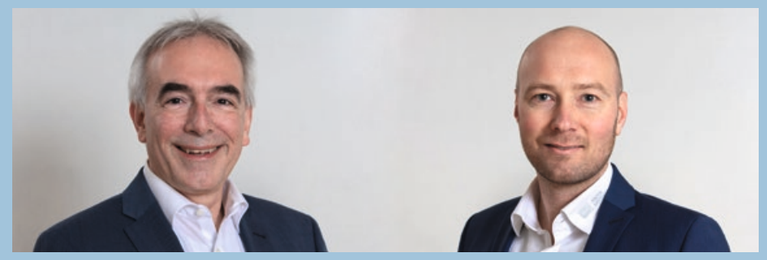
"The trend goes towards small batches"

General Manager Roberto Zürcher and Sales Manager Jan Paetzold tell us what the future of the Swiss pharmaceutical and medical market looks like.

When was the location near Basel established?
Zürcher: Uhlmann Höfliger Schweiz GmbH has been existing since 2005. It was the first sales and service company that Harro Höfliger founded together with Uhlmann and thus an important pioneer for the Excellence United alliance, which was established six years later. At that time we started with two people, later a service technician joined us. Meanwhile we are seven colleagues at the site.

What characterizes the pharmaceutical market in Switzerland?
Paetzold: The pharmaceutical industry has changed considerably in recent years. Suppliers have relocated their mass production of relatively easy to manufacture products to other countries. In Switzerland, the focus is increasingly on "small volume & high value products". This means that complex powder filling technologies, small batches and development projects involving highly complex products such as pens, autoinjectors or wearable pumps are our daily business these days. With our consulting, device and pharmaceutical services, we support start-ups and small companies in quickly building up know-how in order to develop devices. We also help large companies to launch new products as quickly as possible.

What does the changeover to small batches mean for Harro Höfliger?
Zürcher: The focus on small batches places new demands on our machines. It is no longer important how fast a machine can run, but how flexibly it can be retrofitted for batch sizes from 10 to 200 pieces. In the medical field, too, development due to personalized medicine is increasingly moving towards small batches. One extreme example is cell and gene therapy, where a drug is produced for just one person. That requires the patient's blood to be taken, modification of certain cells and subsequent re-injection. These are one-off therapies that can completely cure diseases and spare the patient a lifetime of medication. The large pharmaceutical companies located in Switzerland are already working intensively on this new form of therapy.



For Roberto Zürcher (left) and Jan Paetzold, the future lies in personalized medicine.

Where do you see further growth potential?
Paetzold: Although Switzerland is a country with high wages, there are still many companies in the medical sector that map processes manually, because the processes involving implants or surgical instruments are simply very complicated. New technologies will enable us to automate processes that until now were regarded as impossible to automate. As an example, today we have camera systems with deep learning software that allow us to identify things that were considered undetectable only yesterday.

Medication made to measure

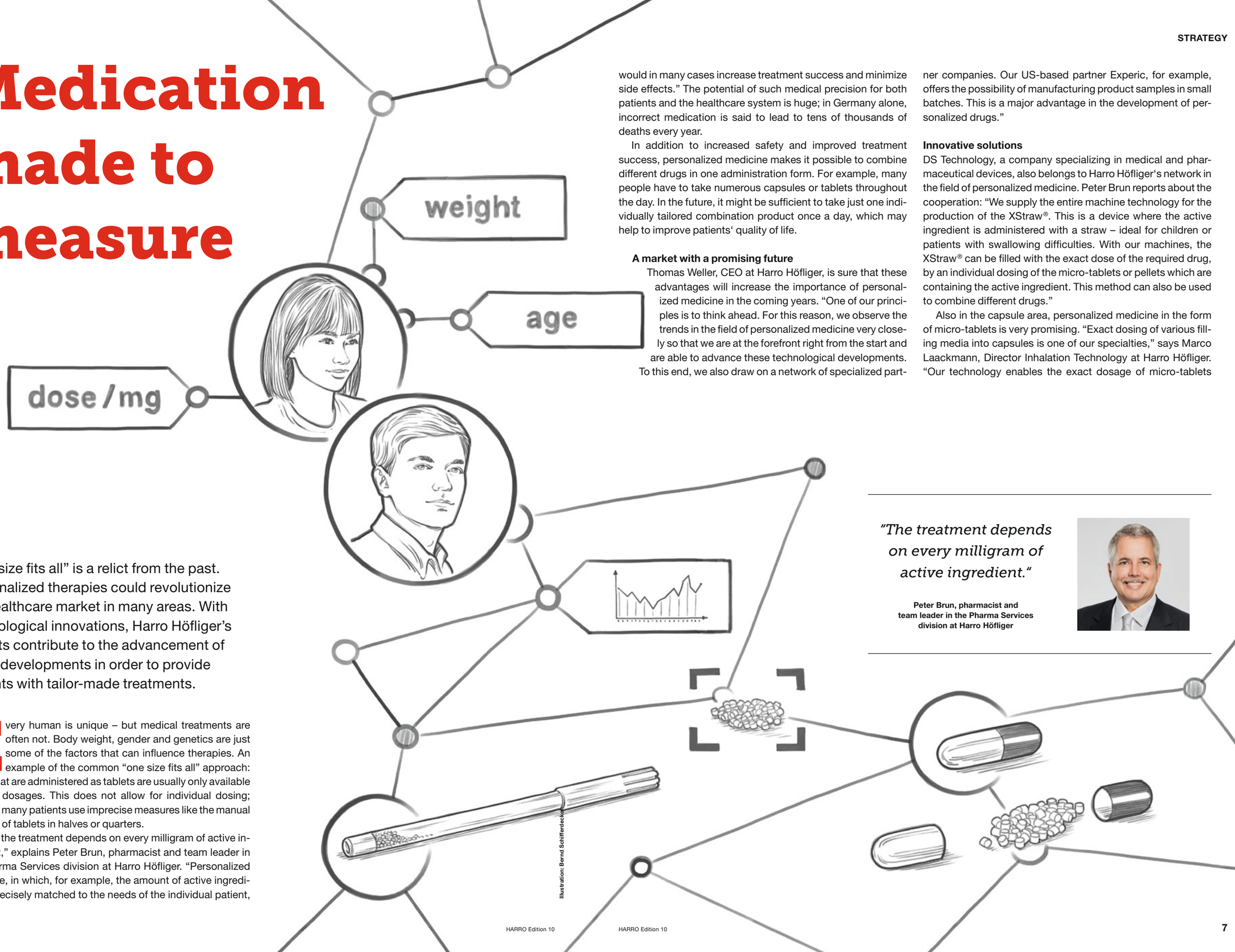


Illustration: Bernd Schifferdecker

“One size fits all” is a relict from the past. Personalized therapies could revolutionize the healthcare market in many areas. With technological innovations, Harro Höfliger’s experts contribute to the advancement of these developments in order to provide patients with tailor-made treatments.

Every human is unique – but medical treatments are often not. Body weight, gender and genetics are just some of the factors that can influence therapies. An example of the common “one size fits all” approach: drugs that are administered as tablets are usually only available in fixed dosages. This does not allow for individual dosing; instead, many patients use imprecise measures like the manual splitting of tablets in halves or quarters.

“But the treatment depends on every milligram of active ingredient,” explains Peter Brun, pharmacist and team leader in the Pharma Services division at Harro Höfliger. “Personalized medicine, in which, for example, the amount of active ingredient is precisely matched to the needs of the individual patient, would in many cases increase treatment success and minimize side effects.” The potential of such medical precision for both patients and the healthcare system is huge; in Germany alone, incorrect medication is said to lead to tens of thousands of deaths every year.

In addition to increased safety and improved treatment success, personalized medicine makes it possible to combine different drugs in one administration form. For example, many people have to take numerous capsules or tablets throughout the day. In the future, it might be sufficient to take just one individually tailored combination product once a day, which may help to improve patients‘ quality of life.

A market with a promising future

Thomas Weller, CEO at Harro Höfliger, is sure that these advantages will increase the importance of personalized medicine in the coming years. “One of our principles is to think ahead. For this reason, we observe the trends in the field of personalized medicine very closely so that we are at the forefront right from the start and are able to advance these technological developments. To this end, we also draw on a network of specialized partner companies. Our US-based partner Experic, for example, offers the possibility of manufacturing product samples in small batches. This is a major advantage in the development of personalized drugs.”

Innovative solutions

DS Technology, a company specializing in medical and pharmaceutical devices, also belongs to Harro Höfliger‘s network in the field of personalized medicine. Peter Brun reports about the cooperation: “We supply the entire machine technology for the production of the XStraw®. This is a device where the active ingredient is administered with a straw – ideal for children or patients with swallowing difficulties. With our machines, the XStraw® can be filled with the exact dose of the required drug, by an individual dosing of the micro-tablets or pellets which are containing the active ingredient. This method can also be used to combine different drugs.”

Also in the capsule area, personalized medicine in the form of micro-tablets is very promising. “Exact dosing of various filling media into capsules is one of our specialties,” says Marco Laackmann, Director Inhalation Technology at Harro Höfliger. “Our technology enables the exact dosage of micro-tablets

“The treatment depends on every milligram of active ingredient.“

Peter Brun, pharmacist and team leader in the Pharma Services division at Harro Höfliger

into hard capsules. This not only enables us to precisely adjust the active ingredient in small, patient-specific steps – different dosing stations also make it possible to administer any number of different drugs with just one capsule."

Printed medicine

DiHeSys (Digital Health Systems), with headquarters in Ulm, also pursues the vision of a treatment that is precisely adapted to the individual patient. However, instead of dosing technology, the company focuses on medication printing. "With the help of 2D printing, we produce personalized thin films, where we apply an exact amount of one or several active ingredients to a carrier material," explains Dr. Markus Dachtler, CEO at DiHeSys. "For the individualized printing of tablets – also with several layers for different active ingredients – we use GMP-compliant 3D printers."

DiHeSys chose Harro Höfliger as a partner for the manufacture of these pharmaceutical printers: "Thanks to this cooperation, our customers receive printers, cartridges and the digital infrastructure for an optimized treatment from a single source. Personalized medicine – based on a patient's personal data such as weight, height and lifestyle habits – could soon be prescribed by physicians, and directly printed in the pharmacy."

Individual by tradition

Thomas Weller is convinced that Harro Höfliger with its strong network, innovative engineering and corporate philosophy is well prepared for further developments in the field of personalized medicine. "One of our major advantages is a broad range of core technologies, for example for dosing, assembly and web processing applications, which we combine and tailor to each individual product. Focusing on individual needs is therefore a tradition at Harro Höfliger – and in my opinion, this provides us with the best prerequisites for contributing to the success story of individualized medicine."

"Thanks to this cooperation, our customers receive printers, cartridges and the digital infrastructure for an optimized treatment from a single source."

Dr. Markus Dachtler, CEO at DiHeSys

Illustration: Bernd Schifferdecker, DiHeSys, Intec Pharma Ltd.

Laminated, folded, encapsulated

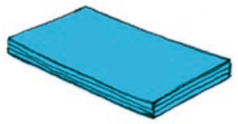
So much for capsules can only be filled with powders, pellets, microtablets or liquids! The Accordion Pill® by Intec Pharma Ltd. is a drug delivery system that uses active ingredient containing polymeric films, which are folded into an undulated shape. This system combines an efficient gastric retention and specific release mechanism. The manufacturing technology for this innovative product was developed in close cooperation with Harro Höfliger.

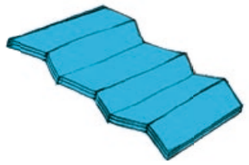
It is a problem that affects millions of patients around the world: After the intake of drugs, the level of active substances rises in the blood, reaches a peak and then subsides. To ensure that the level of active ingredient in the body is always within the appropriate concentration range, it is necessary to take the medication at regular intervals. For many patients, however, this poses an enormous challenge in coping with their daily routines, and reduces their quality of life. Due to the fluctuation range, the optimal level of active substances is often available for a limited period only.

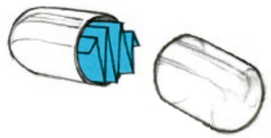
The Israeli enterprise Intec Pharma has addressed these issues by developing the Accordion Pill® platform. The Accordion Pill® looks like a normal capsule, however, its interior contains a small folded GRDF, short for "Gastro Retentive Dosage Form", which consists of several layers of biodegradable polymeric films and the active substance. The Accordion Pill® is named after the characteristic folding of the GRDF, which is reminiscent of the musical instrument.

The Accordion Pill®

The Accordion Pill® is a unique delivery platform based on folded multilayer films. It provides a better treatment by improving the pharmacokinetics of drugs with narrow absorption windows or poor solubility. Furthermore, it allows fixed-dose combinations. Safety and efficacy have been tested in more than 30 clinical studies, with tens of thousands of administrations.







substances lasting usually for only two to three hours when taken orally.

The Accordion's production is as complex as the innovative nature of this dosage form. "Depending on the type of application, different web materials must be laminated and welded, followed by punching and folding of the GRDF before it is encapsulated," explains Ronny Reinberg, Vice President of Technology Affairs at Intec Pharma.

"It was a long way to today's completely automated production."

Ronny Reinberg, Vice President Technology Affairs at Intec Pharma

From manual stations to a state-of-the-art line

Development was equally complex. "In the initial stage, we manufactured the Accordion Pill® in a completely manual process by using a self-designed folding unit, among other things. It was a long way to today's completely automated production," says Ronny Reinberg.

In 2013, when Harro Höfliger was commissioned with the development of a pilot-scale system for the production of clinical supplies of the Accordion Pill®, the company could draw on the experience gained with the manual stations. "When it comes to complex products and special solutions such as the Accordion Pill®, it always makes sense to start with smaller machines in order to acquire production experience," explains Frank Erbach, Senior Sales Director at Harro Höfliger. "This is why we designed a PML version – our small web processing machine – which was precisely tailored to the expertise gained with the manual machines."

In 2017, this was followed by the order for a high-performance line. While the web material on the pilot-scale line was still processed in intermittent mode and on two lanes, the high-performance line is operated in continuous motion on ten tracks and achieves an output of up to 360 products per minute.

The centerpiece of the line is the PMK, a production platform for web processing. As with the PML machine, the various GRDF layers are first joined together. Folding stations then fold the GRDFs into a compact format before encapsulation with a Modu-C machine. The line is completed with the Accura-C, a capsule weighing system for quality assurance.

Ronny Reinberg is very satisfied with the cooperation: "Our Accordion Pill® is by no means an ordinary product. For this reason, Harro Höfliger carried out tests, for example extensive proof-of-principle of the critical stations. Thus, we have jointly succeeded in making the leap from manual machines to pilot-scale equipment to high-performance production."

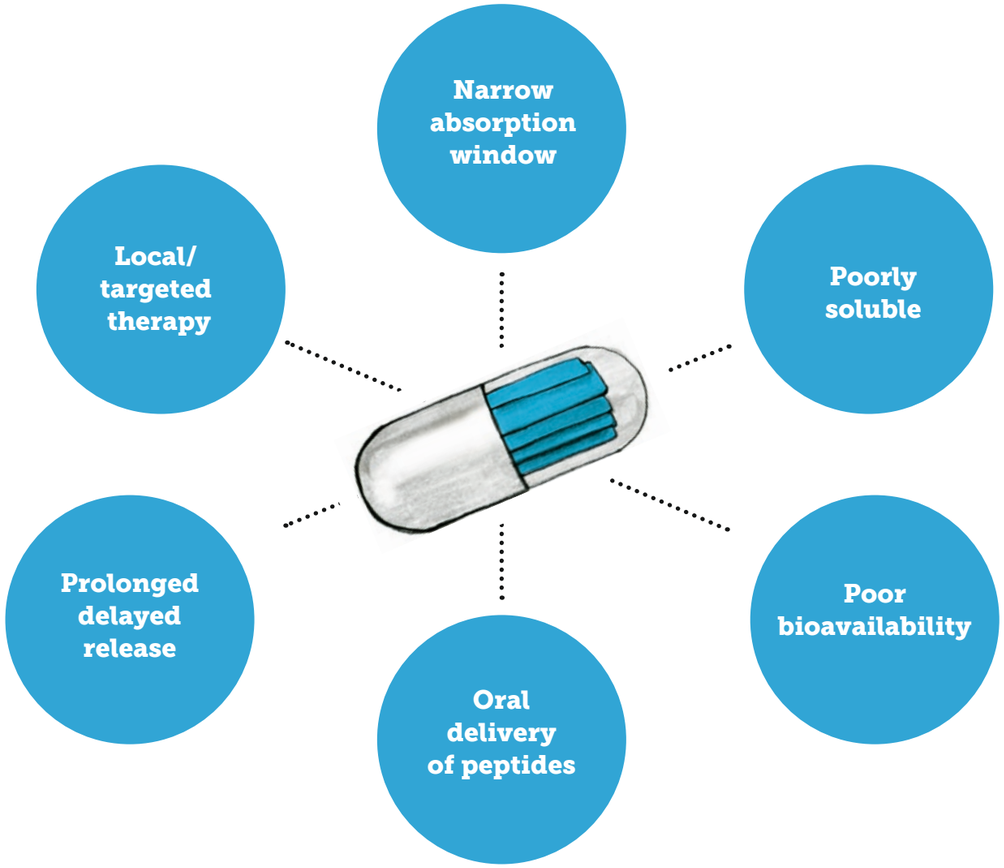
After taking an Accordion Pill®, the capsule dissolves in the stomach, the GRDF unfolds and releases the active ingredient continuously over a period of eight to twelve hours. This also applies to

About Intec Pharma Ltd.

Intec Pharma Ltd. is a biopharmaceutical company focused on developing drugs in the clinical stage on the basis of its proprietary Accordion Pill® platform technology.

Intec Pharma Ltd.

A solution to challenging pharmacokinetics



Twice as good

The two-story PMK in Mikkeli, Finland, is an impressive vertical project. On this line, Mölnlycke produces and packages medical dressings that are gentle on the skin.

It was exactly 30 years ago that the Swedish company Mölnlycke launched its Safetac® technology for dressings. A contact layer with silicone adhesion ensures that the patch rests firmly on the skin, but can be removed gently. Removing the patch is less painful for the patient compared to conventional adhesive products. When removing the dressing, there is no tissue trauma either, which is beneficial for wound healing.

Mölnlycke Health Care produces more than 100 million multilayer border products of the Mepilex® product line per year – mainly in Maine, US and in Mikkeli, Finland. The location in Finland, about a two-hour drive from Helsinki, is rich in tradition, and in recent years it has become a state-of-the-art, high-performance production facility, in particular for high-tech products for dressing wounds. Every day, containers full of wound dressings leave the facility and are sent all over the world. Mikkeli has also a research and development department in order to implement product improvements in close cooperation with and proximity to production.

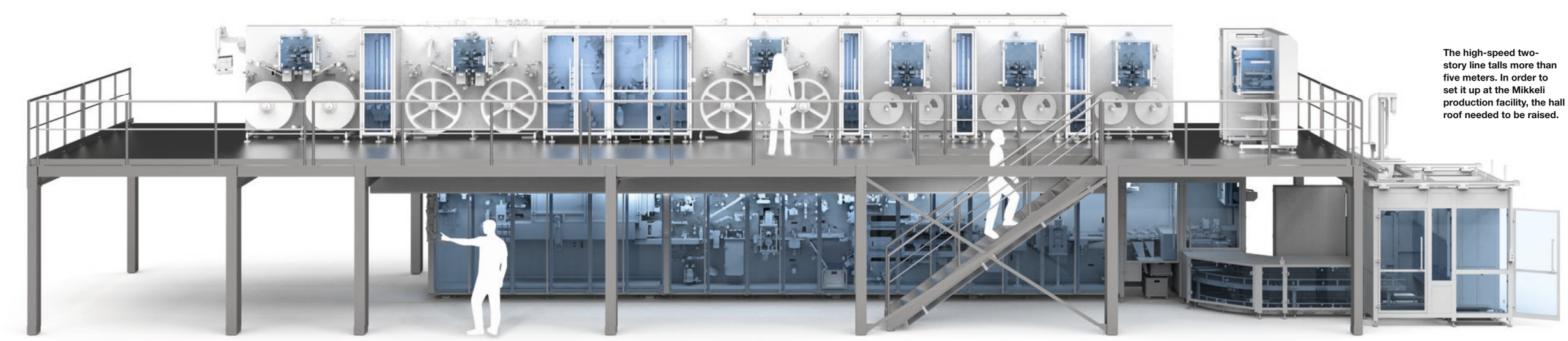
"For the production and packaging line, it was important for us to have a lot of flexibility in the configuration, a wide variety of possible formats and short changeover times in order to switch quickly between our various products," says Timo Saahko, General Manager and Managing Director of the Mikkeli production facility. "Time to market is of essence, therefore the line should be easy to modify so that we can process the materials of the future as well as today's products at any time. We have been working with Harro Höfliger for more than a decade, and we are sure that the company is the right partner for this task." Future viability has always been a specialty of Harro Höfliger's modular PMK setup. What is new about this line, however, is its layout: To accommodate in as compact a space as possible the numerous stations for the complex production and packaging processes, the decision was made for a two-story system.

The high-speed line is more than five meters tall. On the upper floor, the various web materials are automatically unwound and wound up: multilayer laminate, wound pads made of foam material, Safetac® wound contact layer, release liner and the packaging material for the sachets. Packaging takes place in the lower area. The wound pads are cut out exactly using cut & place and placed on the carrier film. After lamination of the different layers of film and confectioning, the patches are individually packed in pouches. Numerous camera stations monitor the processes and ensure, among other things, that the pouches are correctly printed with all batch-relevant data and with the UDI code for track & trace. At the end of the line, all products in perfect condition are stacked and moved to packaging. For Timo Saahko the high-tech two-story line is an investment in the future of Mölnlycke: "To set up the system, the hall roof had to be raised. It was worth it: The line is efficient and, thanks to its modular setup, offers us long-term production reliability for our current and future patch products."

Mölnlycke has since acquired additional two-story lines from Harro Höfliger, each of which effectively can produce border products in three shifts.

"We have been working with Harro Höfliger for more than a decade, and we are sure that the company is the right partner for this task."

Timo Saahko, General Manager and Managing Director of Mölnlycke's Mikkeli production facility



The high-speed two-story line talls more than five meters. In order to set it up at the Mikkeli production facility, the hall roof needed to be raised.

Border products

Border products have a self-adhesive edge that allows the dressing to be securely applied to the skin. In the case of Mölnlycke's Mepilex® products, the Safetac® technology is used to make sure that the dressing can be changed without damaging the wound or the skin, or exposing the patient to additional pain.

Helmar Lünig, Mölnlycke

About Mölnlycke

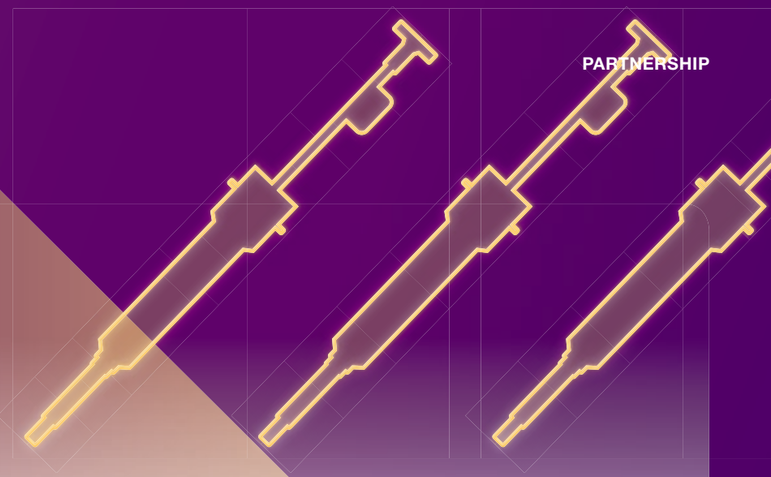
Mölnlycke, a global company with a Swedish heritage, is a world-leading medical products and solutions company that equips healthcare professionals to achieve the best patient, clinical and economic outcomes. Customers use their solutions in almost 100 countries – and the company owns operations in more than 40 of them. Mölnlycke's headquarters are in Gothenburg, just a short distance from the town of Mölnlycke, the place where the company was founded in 1849.

Mölnlycke®

Back to the future

Zoladex is one of AstraZeneca‘s leading oncology drugs worldwide. Since its market launch in the 1980s, systems from Harro Höfliger have been ensuring that syringes are automatically filled with the depot, assembled and sterile-packed at the plant in Macclesfield, England. Now Harro Höfliger is involved in the next generation of equipment with a new state-of-the-art line.

HARRO Edition 10



Let us rewind back to 1988: the world dances to the songs of Michael Jackson. The World Wide Web known as the Internet experiences its first virus epidemic. The first digital camera is presented, which – what a sensation! – offers storage space for up to ten photos. And Harro Höfliger receives the first order for the HH20 assembly machine, which is to be delivered to Macclesfield. The machine automatically opens the pre-assembled syringes, checks the depot length and presence, inserts the delicate implant containing the active ingredient, closes the syringes and transports them to the removal point. 20 high-quality syringes per minute are produced in this way – a major step forward compared to the previously purely manual production.

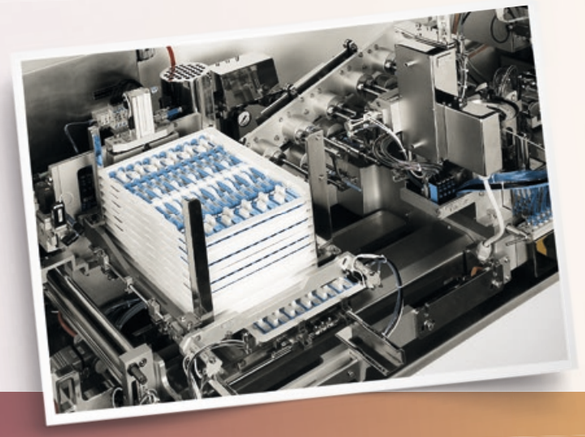
Inserting the brittle depot manually into a syringe was a tricky, time-consuming operation. 24 pre-assembled syringes arrived in a tray to the “Grade A” laminar airflow cabinet. The operator removed a single syringe, separated the top and bottom halves, measured the depot in a template, inserted it into the bottom half of the syringe using forceps, reassembled the syringe, closed and sealed it in a table mounted jig. The wrap-around self-adhesive label was also applied by hand. The syringe was then passed to the next station for hand insertion into a pouch and subsequent final sealing.

The challenge of aseptic production

The product at that time was still an oncology product of former British chemical giant ICI (Imperial Chemical Industries). The implant releases the active substance over a period of around four weeks as it dissolves within the body. Wolfgang M. Rauch, founder of Raupack Ltd., which was to become a 100 percent subsidiary of Harro Höfliger in 2012, recalls initial talks with ICI in the summer of 1988. “We manufactured a rig for separating and sorting the approximately 10 mm long depots and presented a successful station in autumn.”

This was a milestone because it was the first aseptic project in Harro Höfliger‘s history and it was to lay the foundation for today‘s profound know-how in the field of sterile production. With the HH20, the operator loaded the tray and all 24 syringes were automatically removed and processed one after the other.

Following on from the success of the HH20 Syringe Filling & Assembly Machine, Harro Höfliger went on to develop an automated pouch filling and sealing system, a cartoner with a feeding and seal-



The HH20 allowed production of 20 syringes per minute. The trays were presented to the machine by the operator and each syringe was automatically removed, opened and passed on to subsequent operations.

ing station and an automated labelling system: a complete turnkey line was created.

Raupack drew up the requirement specifications for ICI and later the first validation and qualification documentation. Here, too, Harro Höfliger broke completely new ground. In close cooperation with ICI, the necessary documentation was developed for presentation to the regulatory authorities. “When he saw the documentation package, company founder Harro Höfliger’s comment was that it weighed nearly as much as the equipment itself. He said that his company was in the business of building machines, not paper mountains,” recalls Dr. Neil Calder of HH Packaging Systems Ltd. with a smile. “Little did we know back then, how important the validation and qualification package would become to supplying equipment into the pharmaceutical industry.”

When ICI transferred all of its pharmaceutical business to the Zeneca Group in 1993, Harro Höfliger had already supplied four HH20 lines. In 1999, when Zeneca merged with the Swedish company Astra, the number of machines had increased by several more lines.

State-of-the-art

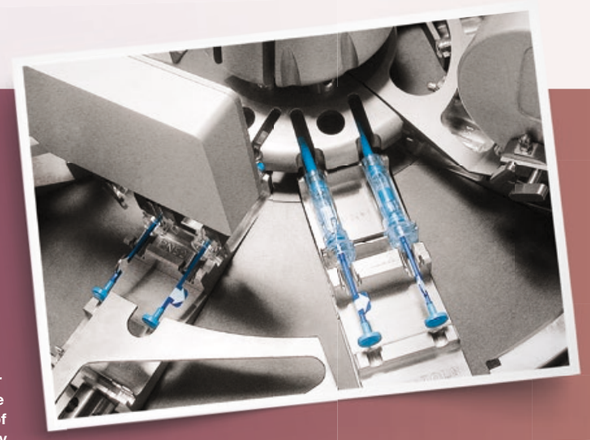
In view of the ever stricter regulatory requirements for aseptic production, and as the product was increasing worldwide sales, AstraZeneca and Harro Höfliger were faced with the challenge of developing a new, faster generation of equipment. A walk-in laminar airflow unit was devised. In 1992 the HH60 was born, a state-of-the-art line for fully automatic filling, assembly, labelling, pouching, and packaging targeting 60 syringes per minute. It took into account modern aseptic processing, reducing the risk of microbial contamination by separating the operating staff from critical areas of manufacture. A total of four HH60 lines have been supplied to AstraZeneca and these turnkey lines have gone on to produce millions of filled syringes.

Over three decades, the syringe design has been modified several times due to regulatory requirements. One example is the syringe shield, which is designed to counteract the hazard of needle-stick injury. All HH60s were successfully converted to incorporate this new technology.

30+ years of partnership

Harro Höfliger is also involved in the next generation of equipment to support production at Macclesfield. This involves a new state-of-the-art line, including closed Restricted Access Barrier System (cRABS) technology, incorporating integrated decontamination with vaporized hydrogen peroxide (VHP). Automatic inline 100 % leak testing of the “final sterile barrier sealed pouch” will be carried out to ensure that the line meets the highest standard of sterile production for years to come.

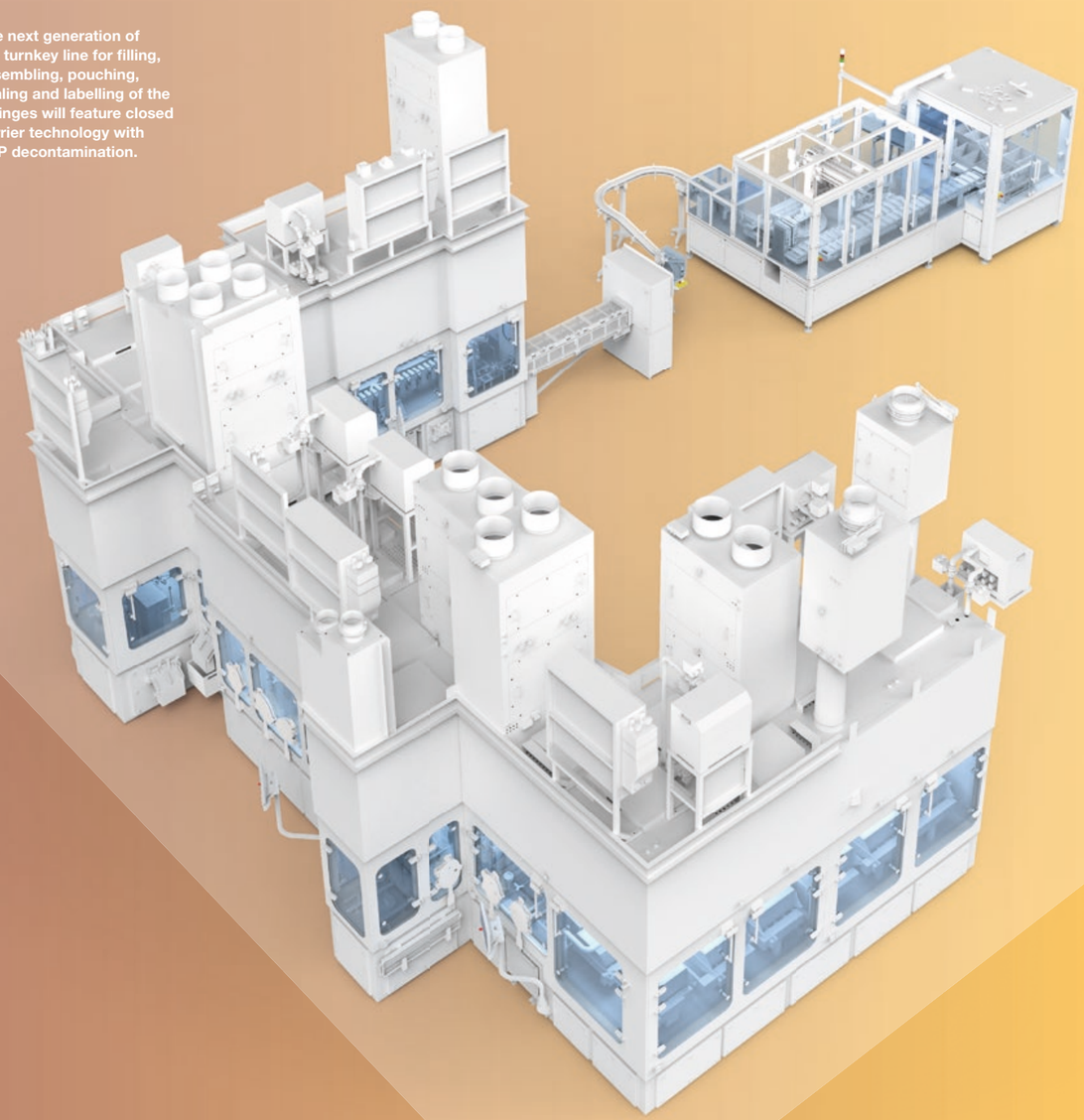
Harro Höfliger in conjunction with AstraZeneca are striving to ensure that patients all over the world continue to be supplied with Zoladex.



Assembly of the syringe shield. Harro Höfliger converted all HH60 lines to incorporate technology for the protected needle syringe to counteract the hazard of needle-stick injury.

In the course of more than 30 years, the syringe design for AstraZeneca’s successful product has been modified several times.

Helmar Lünig



The next generation of the turnkey line for filling, assembling, pouching, sealing and labelling of the syringes will feature closed barrier technology with VHP decontamination.

About AstraZeneca

AstraZeneca

AstraZeneca is a global biopharmaceutical company that focuses on the discovery, development and commercialisation of medicines, primarily for the treatment of diseases in three therapy areas: Oncology; Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide.

Microneedles to tackle migraine

At first sight it looks like an ordinary adhesive bandage on the skin. What is unique is below the patch: a tiny metal array consisting of over 1,800 microneedles. If Zosano has its way, patients will soon be able to use it for systemic delivery of drugs – for example during a migraine attack – via the skin.

The Californian biopharmaceutical company Zosano Pharma is one of the pioneers in the field of intracutaneous drug administration using MAPs (microarray patches) as an alternative to oral delivery. These microneedle systems penetrate the uppermost skin layer, allowing a more rapid absorption of active ingredients into the bloodstream than with oral administration. Zosano has developed its own device, a proprietary intracutaneous microneedle system. "The core of our technology consists of almost two thousand drug-coated titanium microneedles," explains Hayley Lewis, Senior Vice President of Operations at Zosano Pharma. "The patch is about the size of a two-euro coin and is applied to the skin using a reusable handheld applicator. To make the application as convenient and safe as possible, the microneedle patch is mounted in two polymer rings. The patient snaps the outer ring onto the applicator. Once pressed downward, the applicator applies the patch with a precisely defined energy onto the skin, while the ring assembly remains attached to the applicator."

Zosano Pharma, shutterstock.com/Tatiana Barinova

Prior to application, the patch ring assembly is snapped onto the handheld, reusable applicator.

Novel processes and precise mechanics

In the uppermost layer of the cutis, the epidermis, the drug coating is reconstituted and quickly available for absorption. "Our triptan-coated patch for the acute treatment of migraine, for which we filed an NDA to the FDA at the end of 2019, can be removed and disposed of after just 30 minutes. Wear times of our system are considerably shorter than those of traditional transdermal systems, which also have the drawback that delivery of the active ingredient is typically slow, as well as inefficient," says Hayley Lewis.

Manufacturing an innovative device such as the intracutaneous microneedle system required a series of novel processes. One of the challenges was to find a dip coating technology for applying tiny amounts of formulation on each microneedle. This is where Harro Höfliger, with their experience in the field of microneedle systems and dosing processes in micro quantities, came in as a partner for development and scale-up. Hayley Lewis: "A microneedle is only about 340 µm in height – precise mechanics and high-end control systems are essential for coating accuracy and uniformity. Our first joint milestone was a laboratory-scale coater for proof-of-principle (PoP). Harro Höfliger has scaled up the principle of a rotating drum that creates a thin liquid formulation film for higher output."

The fully automatic line from Harro Höfliger not only coats up to 12 products per minute in a low bioburden environment. It also carries out the final assembly of the devices and packages them individually in heat-sealed, nitrogen-purged foil cups. The subassembly of adhesive backing, inner ring and array are loaded in tubular containers. These containers are fed by a walking beam construction to a robotic system where the parts are de-loaded and prepared for further processing. A separate robotic system distributes the components to four coating stations where the arrays are dipped several times into the formulation film at a controlled depth, and speed. A high-resolution camera then checks for integrity of the microneedles and uniformity of the coating. After coating, each subassembly is pressed into the outer ring. The final assembly is then transferred to a customized SSP2 machine for forming, filling and sealing of aluminum packaging.

About Zosano

Zosano Pharma Corporation, headquartered in Fremont, CA is a biopharmaceutical company focused on providing systemic administration of therapeutics to patients using their proprietary intracutaneous microneedle patch technology. Zosano is focused on developing products where rapid administration of established molecules with known safety and efficacy profiles provides an increased benefit to patients.

After forming, a retainer is sealed into the cups into which the device is inserted with the correct orientation, followed by printing the cover foil, purging with nitrogen, sealing and punching. Quality and traceability play a major role: The products are discharged on four lanes – one for each coating station.

"Harro Höfliger has an extremely technical and diligent approach to processes and challenges. We've come a long way together, and it has been a deep, collaborative experience," says Hayley Lewis. "We're both pioneering this new technology and have evolved in our understanding of it. It's always been a dialogue, never a one-way conversation."

Further information on the fully automatic line and photos can be found online at:
www.harro-magazine.com

"Harro Höfliger and Zosano are both pioneering this new technology."

Hayley Lewis,
Senior Vice President of Operations at Zosano Pharma

It's all in the mixture

The first pharmaceutical development for a capsule-based inhaler was a real challenge for Harro Höfliger's Pharma Services team. But the new options in the analytical laboratory paved the way for the perfect powder.

Suddenly there is no air to breathe, the chest feels tight and aches, agonizing coughs shake the body – asthma sprays help to prevent such episodes. Soon, patients shall be able to benefit from a new drug: An inhaler that treats symptoms with a combination of two active pharmaceutical substances (APIs). The generic drug is currently being developed by a pharmaceutical company together with Harro Höfliger. "The original product is a blister inhaler in which the two APIs are stored separately," says Dr. Elke Sternberger-Rützel, Division Leader of Pharma Services at Harro Höfliger. "For the generic drug, the customer had a special request: a capsule-based inhaler in which both APIs are combined in one powder."

Protect the active substance

Not an easy task for the team, which now has to implement the first project in the field of inhalation powder development. Under no circumstances must the two APIs react with each other. „We had to protect one substance from the other, to prevent them from degradation," explains Dr. Sternberger-Rützel. How exactly this works was explored by the experts from Pharma Services in the new, state-of-the-art laboratory.

Mixing, filling, analysing

First, they selected the right lactose qualities for the powder mixture. This is important in order to enable dilution of the APIs in small dosages so that filling is possible, and to ensure that the patient feels an effect during inhalation. Since one of the APIs is degradated when getting into direct contact with lactose, the lubricant magnesium stearate was added to the blend. Mixing experiments then followed. This resulted in eight mixtures per API, which the experts filled and tested in the laboratory. In order to assess the quality of the powders, laboratory manager Karin Marek developed a six-step analysis.

Six steps for a perfect result

1

Flowability: Can this powder be used in the filling process?
First of all, the lab co-workers examine the powder's behaviour. Does it flow well or poorly? Can it be easily filled into capsules?

2

Water contact angle: Is the lactose coated with magnesium stearate?
Then they test whether the amount of magnesium stearate added to the lactose and the blending quality is correct. For this purpose, Harro Höfliger developed an in-house method: The researchers put a drop of water on the surface of the lactose. If it remains on the surface, the blend is correct.

3

Blend uniformity: Is the API uniformly distributed in the total mixture?
In order to check whether the two APIs are uniformly distributed throughout the mixture, the experts take samples and measure the concentration of the active ingredient. If the blend is not homogeneous, the blending parameters must be adapted in the next test.

4

Content uniformity: Does the capsule contain the correct amount of active ingredient?
If the blend in the total quantity is correct, the concentration in the individual capsules has to be verified. 25 micrograms of API 1 and 200 micrograms of API 2 should be contained in each of the examined capsules. By determining the concentration, it is possible to assess the quality of the filling process.

5

Emitted dose: How much API is released from the inhaler?
The next step is to check whether enough API is supplied to the patient. For this purpose the Harro Höfliger team uses a so-called "Dosage Unit Sampling Apparatus" (DUSA). The device generates negative pressure, thus simulating a patient's inhalation. What DUSA "breathes in", is flushed into a solution. A high-pressure liquid chromatograph (HPLC) determines the API level contained in the solution. "Some of the API always sticks to the capsule," explains Karin Marek. If the emitted quantity is not sufficient, either more API must be added to the capsule or the formulation needs to adapted.

6

Determination of aerodynamic particle size: Does the correct amount reach the alveoli?
Now the experts are measuring whether enough of the API is delivered to the alveoli. To this purpose, the Next Generation Impactor (NGI) is used – a kind of aerodynamic flow model of the lungs through which the particles are sucked with the help of negative pressure. Depending on their size, they come to rest in different sections of the model, corresponding to the bronchial tubes and alveoli. The lab technicians analyze how much of the API has settled, in which section. A correct distribution is prerequisite for a successful powder development.

Testing and adapting, again and again

Of course, the perfect blend is not achieved in the first trial. Adjustments to the process are always necessary. Despite all challenges, the team has made good progress within few months and the project is close to completion. "This is one of the major advantages when machine manufacturers are involved in powder development right from the start," says Karin Marek. "Project time is vastly reduced when all parties involved are located under one roof. Together with our colleagues from equipment development, the steps required for optimization can be initiated a lot faster." Dr. Sternberger-Rützel agrees: "We focus on the interaction between formulation, filling technology and device from the very beginning. This is the key to success for our Pharma Services."

All clear for Line 13

Preventive maintenance can help to avoid unscheduled downtimes and increase production output. The joint project of Harro Höfliger and Roche Diagnostics is picking up speed.

Angelo Alletto is a production engineer at Roche Diagnostics in Mannheim and his mission is clear: "His" line number 13 must be running in order to reach the required production output at the end of each week. In other words: 85 cycles per minute, 16 hours a day and ideally without interruptions. "The machine should only stop when we have planned it, not because something has broken," says Alletto. With the introduction of a Preventive Maintenance Plan this year, Roche and Harro Höfliger have set out on a shared path to achieve precisely this goal.

Roche's Elecsys®-Technology has been on the market for about 20 years. Laboratories all over the world use it in many areas of immunology. The successful diagnostic product consists of up to three components in separate plastic bottles, which Roche combines, labels and packages in different ways with Line 13. It is also constantly controlled by numerous cameras, sensors and checkweighers to make sure that only perfectly produced and therefore 100 % safe products leave the plant. "The many combinations and carton formats, as well as various packaging inserts with their tolerances, make the packaging process prone to errors," says Alletto and adds: "Together with Harro Höfliger's Customer Service we have been able to optimize many factors in recent years and in doing so have continuously increased our output."

14 machines work closely together

Line 13 consists of various machine types and includes trayloaders, an assembly unit, several labelers, carton erectors and a toploader cartoning machine. In addition, the line has numerous feeding and control systems – a complex array of 14 machines that work together in closely timed intervals. Maintaining the entire system in such a way that technical malfunctions can be avoided is what the Preventive Maintenance Plan shall make possible in the future. "We will no longer use our budget for unscheduled repairs between maintenance intervals, but for preventive and carefully prepared maintenance activities. This enables us to achieve a more stable production process that gives us the time and flexibility to identify and implement further optimization needs," explains the production engineer.

Together with Harro Höfliger, Angelo Alletto, production engineer at Roche, makes sure that "his" Line 13 is running.

But there is another reason for planning maintenance more precisely, Alletto knows: "Inspection authorities such as the FDA or even the TÜV (German Technical Inspection Authority) nowadays demand documentation that is more precise and goes far beyond the time of the actual approval. Ticking off maintenance checklists is no longer sufficient." Thanks to the maintenance plan and the associated documentation, from now on Roche will be able to provide transparent evidence as to which checks and maintenance activities were carried out and when they took place.

Maintenance needs preparation

In order to implement the Preventive Maintenance Plan, some initial preparation is required. In addition to the experience from previous maintenance work and daily operation, an evaluation of the machine serves as a basis. To this end, all machine components are analyzed by our technical experts and rated with regards to expected wear and tear, the probability of failure and the resulting effects", explains Sven Fischer, Service Manager at Harro Höfliger. Fischer has been responsible for Roche for many years and has played a key role in advancing the Preventive Maintenance Plan project.

"We maintain an open and honest communication with our customers. Roche's systems receive our utmost attention. As a result, we were able to develop individual solutions together with Roche which made it possible to continually increase production efficiency. We consider the Preventive Maintenance Plan a large sign of confidence and the result of our excellent teamwork," says Sven Fischer. A cooperation that will become even stronger. "Preventive maintenance is an ongoing process," explains Angelo Alletto. "Maintenance plans are living documents that we will continually refine and adapt. Together with Harro Höfliger, we are getting better and better and can continue to increase our production."

Electrical equipment checked

Pneumatic system checked

Safety-related functions checked

Line 13 consists of a complex construction of different machine types, feeding and control systems.

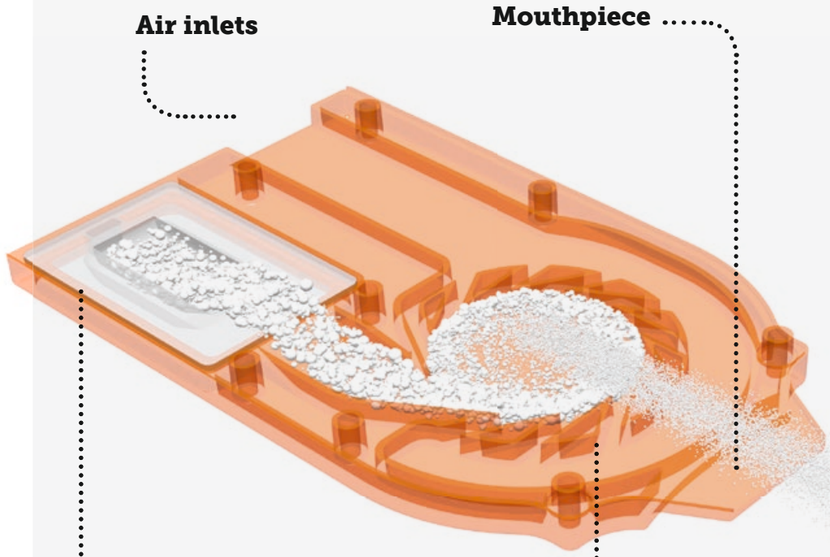
Error memory read out

Wearing parts replaced

About Roche Diagnostics

Roche Diagnostics GmbH is located in Mannheim and is a subsidiary of the Swiss company F. Hoffmann-La Roche AG which is headquartered in Basel. With about 8,300 employees, Roche in Mannheim develops products for people with diabetes or cardiovascular diseases. In addition, the company produces life-prolonging drugs against cancer and important products for in-vitro diagnostics, which are delivered from Mannheim to destinations all over the world.

A little push in the right direction



Bottom plate of the Cyclops™ during the inhalation process.

Sometimes all it takes is a little push to get something big rolling. With their expertise in the field of dry powder inhalation, Harro Höfliger gave the Dutch start-up PureIMS the necessary push.

The start-up enterprise PureIMS not only develops dry powder inhalers (DPIs) but also produces them in their own GMP compliant cleanroom. All products are based on the Cyclops™ platform and are also characterized by another common feature: “The ’pure‘ in our company name means that we use as few excipients as possible in our formulations,” says Floris Grasmeijer, Principal Scientist at PureIMS. “The special dispersing technology of our platform makes this possible without affecting drug efficacy. In most cases, we only need a small percentage of an excipient for our formulations, in some cases we require none at all. This is ideal for high-dose applications.”

However, this specialization also poses particular challenges: “Commercially available formulations contain up to 95% lactose. This is what makes the powder flowable and enables reproducible dosing,” explains Grasmeijer. Pure formulations, on the other hand, have poor flow properties. Conventional filling techniques are therefore often not suitable for such powders.

The dry powder before (right) and after pressing into powder compacts (left).

PureIMS

Looking for options to scale and automate

“At the beginning, the entire powder filling process was done manually. The reproducible dosing of our cohesive formulations was not a topic at that time,” recalls Floris Grasmeijer. “Of course, the whole thing was very time consuming – and we rather wanted to spend our limited resources on development. So, we were looking for options to scale and automate the process. Already at that time we had good contacts with Harro Höfliger and thus came across the Omnidose dosing machine with drum filler technology.”

Numerous filling tests

The transition from manual dosing to the semi-automatic filling process was tricky: “The drum filler of the Omnidose forms the powder into small pellets and our inhaler platform was not yet adapted to this process,” explains Grasmeijer. “This is why we carried out numerous filling tests in Harro Höfliger‘s cleanrooms. With the support of the experts on site, we were able to adapt our inhalers in such a way that it became possible to process the pellets. Today we have our own Omnidose, which is a real eye-catcher in our cleanroom.”

Into the grown-up world

These extensive tests have paid off: “We now spend much less time on production and can focus more on development and the search for partners to finance the later development phases of our DPI products. The scalability of dosing processes and of course the well-established name Harro Höfliger have proven to be major advantages in discussions with potential partners.”

PureIMS has big plans for the future: “We are still a small biopharmaceutical company. But things may change very quickly. We have the right products, are continuously expanding our process knowledge in the field of drug development and also have the appropriate production equipment. So we are making our way into the grown-up world – even if we will never behave like them,” says Floris Grasmeijer, tongue in cheek. “And when we get there, we will of course remember the push in the right direction which Harro Höfliger once gave us.” ■

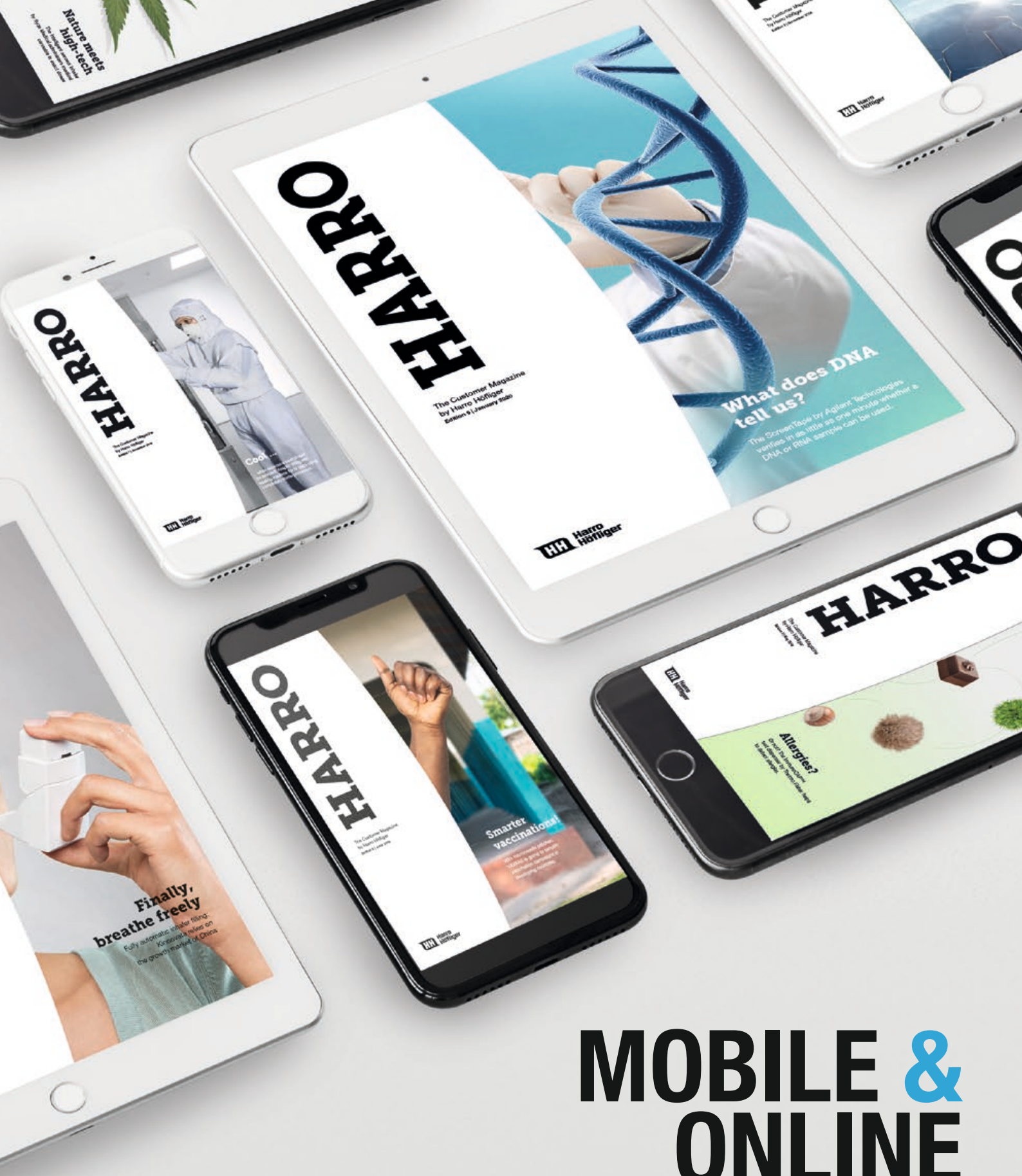
The PureIMS start-up team at the 2019 “Drug Delivery to the Lungs” exhibition.

“The drum filler of the Omnidose forms the powder into small pellets and our inhaler platform was not yet adapted to this process.”

Floris Grasmeijer, Principal Scientist at PureIMS

About PureIMS

Pure Inhalation Medication Systems (PureIMS) is a biopharmaceutical company based in Roden, The Netherlands. The core activities of PureIMS are: development, manufacturing and commercialization of inhaled drugs for patients with diseases such as Cystic Fibrosis, Tuberculosis, Parkinson’s disease and Anaphylaxis. Cyclops™, a proprietary disposable dry powder inhaler, forms the innovative heart of all the therapeutic products.



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