HARRO

The Customer Magazine
by Harro Höfliger

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Smarter vaccinations!

With microneedle patches, VAXXAS is going to simplify vaccination campaigns in developing countries.

Harro Höfliger

Going automated

A fully automated turnkey line from Bausch+Ströbel and Harro Höfliger gives a big boost to the production of AstraZeneca's successful drug.
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The DPI experts from the far North

The start-up Iconovo develops the perfect combination of device and formulation.
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Smarter vaccinations!

With microneedle patches, VAXXAS is going to simplify vaccination campaigns in developing countries.

Our **Innovation Expo** will take place on June 25 and 26, 2019. All topics that are important for the Expo are marked with this logo in the magazin:

www.innovation-expo.com

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Dear Readers,
dear Business Associates,

when developing machines and processes for our customers’ products, risk minimization is our top priority. But when it comes to questioning the familiar and exploring new horizons, we do not shy away from the risk. Whether it is the optimization of products, devices and processes, or the development of brand-new technologies: Our experts are clearly at the forefront.

For years, for instance, worldwide research has been conducted on how vaccination campaigns in developing countries can be simplified. Microneedle patches could be a key to the solution, according to the World Health Organization (WHO). As an example, we are currently working with the start-up company VAXXAS to pave the way for this future technology to reach affordable large-scale production.

Good is not good enough – that is what spurs on our specialists in Engineering & Innovation Services. With the help of an innovative method for water sealing, they have not only succeeded in tightly joining water-soluble films. They have succeeded in optimizing impermeability and improving the safety of the packages.

We also look for ways to make the manufacturing process for your product safer and more scalable: With the expansion of our cleanrooms for trials, verification and process creation, we reduce risks. The enlargement of our laboratory space allows us to assist you as early as the formulation development phase. Using state-of-the-art equipment and high-level safety standards, we manifest our holistic “From Lab to Production” approach.

About 20 years ago we were the first machine manufacturer with in-house cleanrooms. This investment risk paid off a long time ago, and it will pay off this time: With added safety for our employees, better verification of process parameters, and with your confidence in our technology and expertise.

Yours,

Thomas Weller,
CEO at Harro Höfliger

Harro Höfliger

* April 24th,1937 † May 12th, 2019

Expansion of Aspach site

The production and logistics center in Aspach, which opened in 2013, has been expanded by a two-story industrial building with approximately 1,500 square meters per floor. In addition to a larger logistics area, the building offers space for a state-of-the-art machine park which will speed up order processing in the future. In May, the first production and milling machines will start to move in. This also includes a new five-axis CNC machining center for large-format parts, which were produced by outside manufacturers so far. The Aspach site supplies the main plant in Allmersbach im Tal and the workshops in Backnang and Satteldorf with components and materials.

In Aspach, orders can be processed even faster in the future.

"Technical service right on the spot"

Since 2014 Harro Höfliger has a branch office in Istanbul. Sales Manager Baykal Karadeniz tells us what makes this Turkish location special.

What distinguishes your site from other branch offices?
We are the first branch office worldwide that represents all companies of the Excellence United Alliance! Until 2014, local distributors were responsible for this market. As demand increased, we established this joint office. The alliance's Managing Director Fikret Uslu represents Glatt, Fette Compacting and Bausch+Ströbel. I am responsible for Uhlmann and Harro Höfliger as Sales Manager. Our focus is on the sale of new machines as well as after-sales service, which includes technical support by our three in-house and well-trained technicians. Local service is very important to our customers because it enables us to provide quick assistance at a reasonable price. Our technicians go to our customers on the day of the call or the following day.

What are the distinctive characteristics of the Turkish market?
So far, the Turkish pharmaceutical industry has mainly produced generics in large quantities at a very low price level. In addition, the medical sector imports many products from other countries, mainly from Southeast Asia. Gradually, however, the market is changing, medical technology is gaining in importance and pharma production is increasing. This is mainly due to a new law passed by the Turkish Ministry of Health, which promotes the local production of medicines and makes imports more expensive. Initially, this means that several international companies are relocating their production to Turkey by commissioning contract manufacturers. In the future, they will intensify their local investments. As a result, we are receiving an increasing number of inquiries for machines that are capable of producing medicines and medical technology.

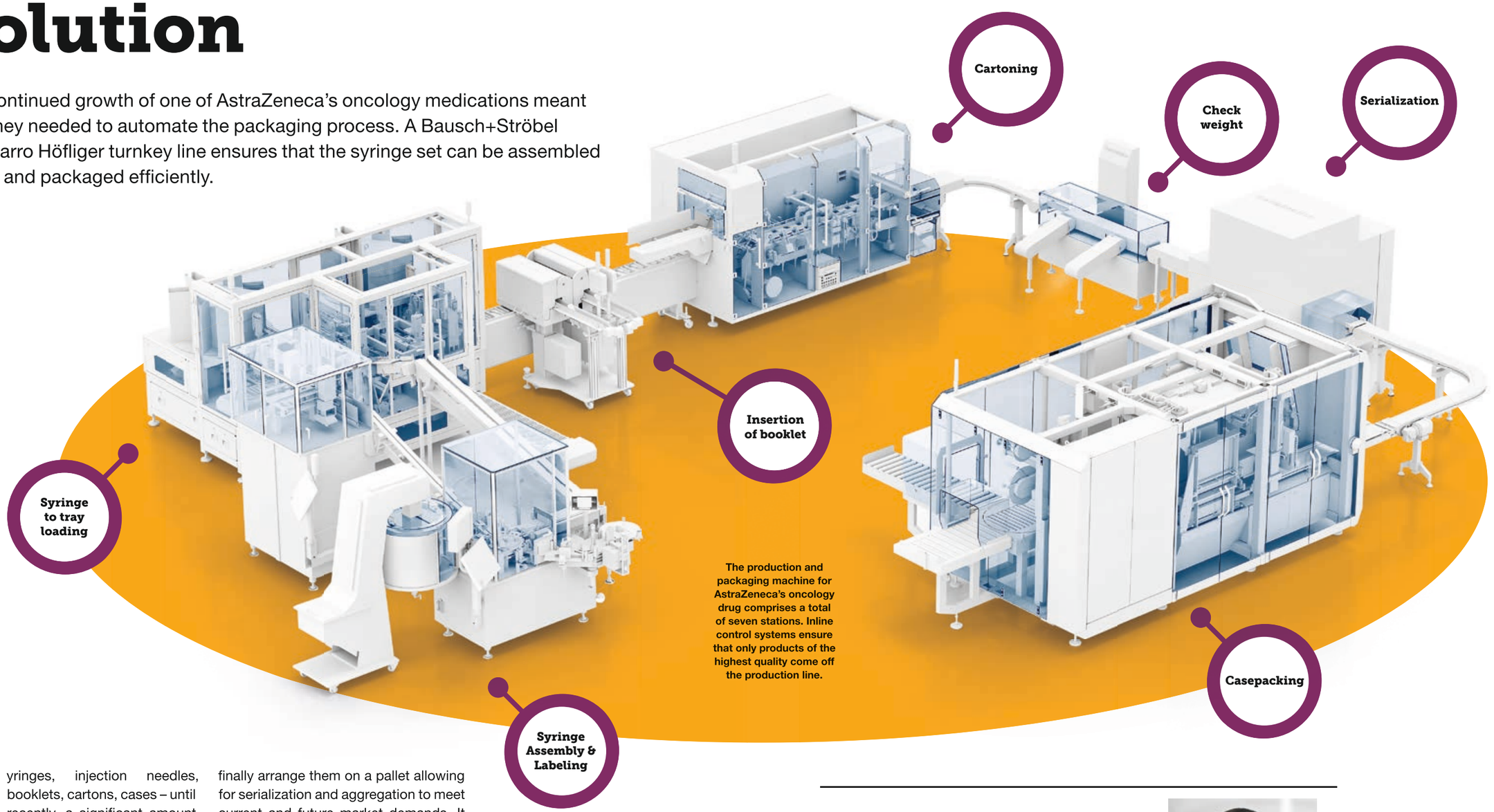
In which areas do you see the largest growth opportunities?
I see the largest potential in the production of dry powder inhalers. We offer DPI machines for the filling of blisters and the assembly of inhalers – as part of our portfolio for Medical & Pharmaceutical Device Assembly – as well as capsule filling machines. This sector is particularly supported by the government. I also see growth opportunities in the automation of suture production where many processes are still done by hand. But transdermal and oral delivery systems, wound care products and new drug delivery systems are also becoming increasingly important. My goal is to find a key customer who will successfully automate the manufacture of their products. Such a positive example will convince other companies.

Sales Manager Baykal Karadeniz sees the greatest potential for growth in the production of dry powder inhalers.

Janine Kvofsky, Harro Höfliger, shutterstock.com/OPIS Zagreb

A well-rounded solution

The continued growth of one of AstraZeneca's oncology medications meant that they needed to automate the packaging process. A Bausch+Ströbel and Harro Höfliger turnkey line ensures that the syringe set can be assembled safely and packaged efficiently.



The production and packaging machine for AstraZeneca's oncology drug comprises a total of seven stations. Inline control systems ensure that only products of the highest quality come off the production line.

Syringes, injection needles, booklets, cartons, cases – until recently, a significant amount of the packing process for this product by AstraZeneca was done by hand. Global increases in demand for the medication, however, made it necessary to automate the packaging process within the production line. For Harro Höfliger, that meant finding solutions to insert the syringes and injection needles into the plastic tray, package them into folding cartons and shipping cases, and finally arrange them on a pallet allowing for serialization and aggregation to meet current and future market demands. It also included systems that kept a close eye on quality control. Another requirement was that the machine processes needed to be adapted to the packaging material with its complex design as far as possible. This was achieved, among others, with a tailor-made solution for the intricate separation of the nested plastic trays and cover.

"A collaborative approach throughout the project made it clear that in Harro Höfliger we had chosen the right partner for the turnkey line."

Paul Bradley, Project Manager at AstraZeneca

The high-performance MCP (Modular Case Packer) from Harro Höfliger scores with its optimum accessibility, fast format changeover and reproducible setting options.

Bausch+Ströbel, an Excellence United partner, was also involved, delivering the machines to assemble the pre-filled syringes with plungers, and to label them. Such close collaboration with the customer, Bausch+Ströbel and other technology suppliers resulted in a turnkey line that showcases the strengths of Harro Höfliger's MKT horizontal cartoning machine and MCP modular case packer.

"Reliable processes and seamless quality control were critical in order to meet the demand for our medication," says Paul Bradley, Project Manager at AstraZeneca. He admits that the task was an ambitious one: "A set of the medication can be supplied with either two pre-filled syringes with needles or with just a single syringe and needle. As a result, Harro Höfliger received specifications for two formats with no changeover."

Smooth handling

All in all, the production and packaging line is made up of seven stations, with several in-line control systems. They ensure that the delicate syringes do not break, splinter or are scratched, that the sterile components are not damaged, and that the patient only receives complete, flawlessly packaged products of the highest quality.

The process begins with the unloading, infeed, assembly and labeling of the pre-filled syringes. "Our combined expertise, along with precisely coordinated technology and project management processes, allowed us to quickly find solutions to seamlessly integrate our systems," says Martin Kern, Sales Group Manager at Bausch+Ströbel. The next step introduces the de-nested plastic trays into the process. Servo-driven transfers tilt the syringes at a predefined angle to be able to precisely place them into a one- or two-syringe tray.

The supply of blister-packed injection needles with a safety system continues to be executed manually. Operators insert them into the product mounts in strips of five. The special form of the mounts ensures that once the needles are automatically separated, they will be placed in the correct orientation, lying flat in the tray. This placement is crucial in ensuring that the plastic cover can be positioned and mounted optimally in a later step. Tactile quality control checks whether each product's cover is positioned 100 percent correctly, ensuring only perfectly closed trays will be brought to the cartoning machine. The feeder is specially adapted to the folding carton with its characteristically inclined folding closure.

Reliable cartoning

No set is packaged without patient information or booklets: supplements corresponding to market-specific guidelines are placed on the tray as it is being transferred to the cartoning machine. In the MKT machine products are inserted horizontally into the folding carton, 30 packs per minute for both required formats. The subsequent weight control determines whether each folding carton is correctly packed. If it detects a deviation, the package in question is automatically rejected. The application of tamper-evident labels or vignettes ensures the required protection against manipulation and meets specific market requirements. A control unit also checks the correct positioning here, along with the completeness and legibility of the printed variable information, which includes batch number, manufacturing date, expiration date and any requirements for serialization and aggregation as per market demands.

Efficiency with a new design

Harro Höfliger's modular case packer MCP rounds out the end of the line. Apart from its efficiency in automatically stacking, packaging and sealing products, it also scores with the new turnkey design. The machine protection allows a complete overview of the packaging process, even better accessibility and an ergonomic work area. 15 folding cartons are fed on a single track, automatically grouped and stacked, then carefully side-loaded into the shipping case. The stacked cartons are aggregated with the help of a camera system. The case is then sealed with tape, labeled, affixed with a serial number and identified with a corner wrap label. After a camera system checks the code one last time, the cartons are assembled on a pallet. ■

AstraZeneca's successful oncology drug may consist of two ready-to-use glass syringes with a hypodermic needle or even just one syringe with a needle. For this reason, the specifications for Harro Höfliger provided for two formats without format changeover.

About AstraZeneca

AstraZeneca is a global, science-led, biopharmaceutical business, their innovative medicines are used by millions of patients worldwide.

AstraZeneca

Helmar Lünig

Keeps them tight!

A completely new method for the contactless sealing of water-soluble multi-chamber pouches enables more compact sealing seams, better haptics and a more efficient production process. Initated by market demands, the “water sealing with inkjet printer” project was developed and realized by the creative minds and makers of Harro Höfliger’s Engineering & Innovation Services.

Harro Höfliger, Janine Kyofsky

Good is not good enough – this philosophy motivates people at Harro Höfliger and in particular the Engineering & Innovation Services team. When it comes to improving established solutions or developing promising technologies for the future, the 16 employees go beyond their daily routine, bring out their creativity and literally put processes to the test.

They also scrutinized the heat sealing of water-soluble multi-chamber polyvinyl alcohol (PVOH) formed packs filled with detergents or cleaning agents. The result: For the production of the pouches, Harro Höfliger now counts on an innovative water sealing process based on a modified inkjet printhead. With the help of this device, water is applied with utmost precision and control to the lid film which then begins to dissolve. A roller then accurately applies it to the thermoformed base film filled with powder or gel.

Contact of the films results in a very homogeneous, dense and extremely durable sealing seam, which is much narrower than with heat sealing. Not only does this increase the design variety of the multi-chamber products, it also allows a more compact shape. Consequently, more packs can be produced per cycle with the same film width. In addition, the contactless water application causes no contamination and thus reduces the cleaning and maintenance efforts and expenses for the system. For consumers, the improved pressure stability means even more safety in handling.

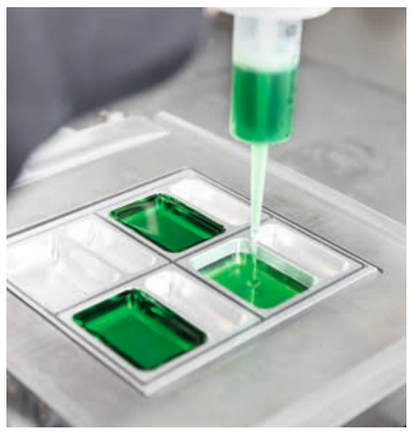
"Creativity is not something we do for ourselves. We always develop with a focus on applications to meet the needs of the market."

Achim Wolf,
Head of Engineering & Innovation Services

Creativity first, followed by process optimization

“And yet creativity is not something we do for ourselves. We always develop with a focus on applications to meet the needs of the market,” emphasizes Achim Wolf, Head of Engineering & Innovation Services. “The driving force behind this innovation project were our customers' new requirements for haptics and the design of multi-chamber products. We wanted to provide more attractive options for formed packs and make production even more efficient.” In accordance with the internal innovation management processes at Harro Höfliger, the team approached the water sealing project systematically in several phases.

“We start with proof of concept tests. Four different ideas were put forward for water sealing and we tested them all extensively. The printhead turned out to be ideal because every single drop of water can be precisely controlled and the contactless application offers many advantages,” explains Wolf.



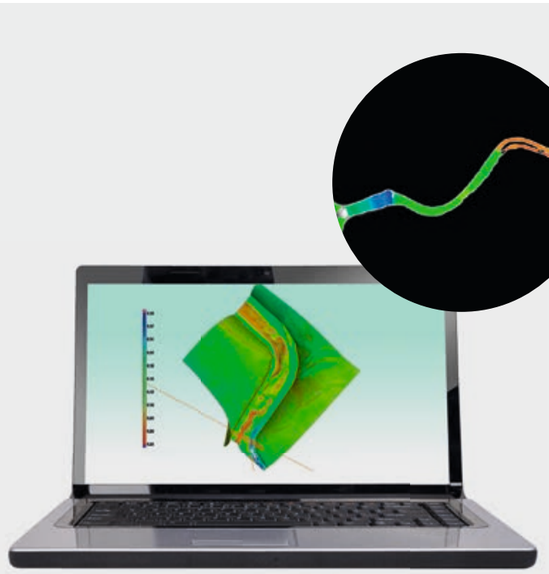
Left: The PVOH film is thermoformed to shape, then the chambers are cleanly filled with various media such as powder, gel or liquid.
Right: After water sealing of the top and bottom film, the multi-chamber packs are punched out or cut out.

In the next phase, testing the process capability on the prototype, his team focused on the need for 24/7 production at high speed right from the start. The Omni FS semi-automatic machine produced water-sealed samples that had to pass pressure, drop and dissolution tests. Only then was the system integrated into the customer's production line. “If necessary, my team is on site at the customer's premises until optimization is complete. Our in-house tests have resulted in complex knowledge that we are happy to pass on. We start with creativity, then we transition into process optimization,” explains Wolf.

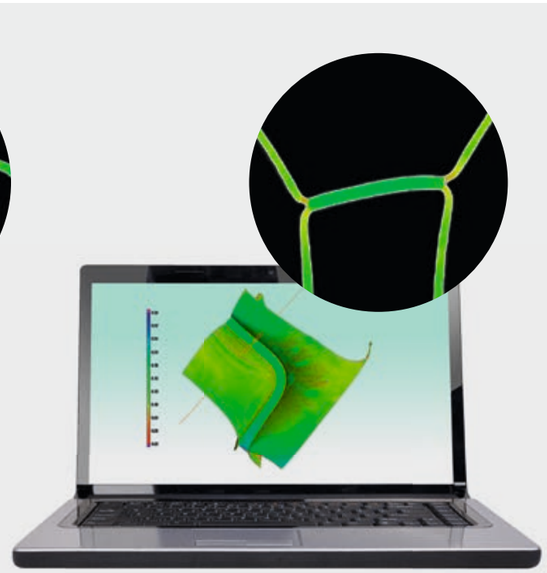
The new process enables a greater design variety of multi-chamber products as well as greater safety during handling by the consumer.

More accuracy, less material

However, water sealing is only one piece of the puzzle in the constant optimization of production processes for multi-chamber pouches. Achim Wolf’s team is also working on technical solutions and process parameters for the forming process, for example to reduce the material consumption of PVOH films. A new dosing process, enabling the filling of the powder formulation even more precisely and cleanly, has already been developed. In the next phase it will be adapted for customized application. Achim Wolf: “We are constantly revising the entire process and are always developing new products for our customers.”



The 3D computed tomography of the seal contour reveals: When heat-sealing water-soluble form packs, the seam shows minimal breaks.



Water sealing using a modified inkjet printer produces a homogeneous, durable and narrow seam.

Helmar Lünig, shutterstock.com/Haywiremedia, Harro Höfliger

Scale-up for increased reliability

With the expansion of cleanroom facilities and a state-of-the-art laboratory, Harro Höfliger is further increasing its testing capabilities for customers. New possibilities for product analysis and safety precautions help to minimize risks for customers, and employees as well. Four members of the team talk about the possibilities, benefits and opportunities this expansion offers.

Nearly 20 years ago, when pharmacist Dr. Karlheinz Seyfang founded the Pharma Services department at Harro Höfliger and set up the first cleanrooms, he made the company a pioneer among machine manufacturers. Since then, this area has seen continuous growth and has become an integral part of the ALL YOU NEED service idea. When designing machines and developing processes, risk minimization is a top priority. With the range of services offered by the Process Services Division, Harro Höfliger guides customers every step of the way from the initial idea to production. The expansion of the cleanrooms and the new laboratory were imperative in order to further increase this service portfolio. The expansion is part of the ongoing commitment to improvements that motivates Harro Höfliger: Providing more service to our customers, the best possible protection for our employees and the environment, plus the opportunity to continuously optimize our machines.

We started to plan the expansion of our four cleanrooms three years ago. It was already clear at that time that we were reaching our limits with the available capacities. During factory acceptance tests (FAT), for example, a room may be occupied by a machine for up to several weeks. In addition, many of our customers wish to outsource trials because they do not have the necessary facilities in-house. Therefore, the decision to expand our capacities was made quickly. We now have a total of ten cleanrooms with a total area of more than 500 square meters, and an additional 60 square meters of laboratory space available. The largest room measures about 10 x 5 meters. Three of the cleanrooms are defined as High Potent areas. An additional air lock with an air shower makes it possible to work safely with highly potent active substances up to OEB 5. Four of the ten cleanrooms can be operated at a relative humidity of ten percent using additional dryers. A ring line supplies all cleanrooms with demineralized water. The air humidity, the air flow and the temperature can be controlled in every room as required. The measured values are shown on a display and saved for monitoring. In order to protect the environment, we not only filter the exhaust air, but also separate the wastewater: Contaminated water is channeled into a special tank for incineration by a disposal company. However, protecting our employees and customers was also very important to us: The air shower, descending door seals and a slight negative pressure in all rooms prevent contamination of the surrounding areas when processing active substances in the cleanrooms. Special air extraction systems at the laboratory workstations also ensure a more comfortable work environment.

"The expansion of our cleanroom capacities enables us to continue to meet the high demands of our customers."

Marcus Hild,
Project Leader Cleanroom Expansion

Dry

10 % r.h.

Additional adsorption dryers can provide a relative humidity of 10 percent in four rooms.

Pure

500 m

A 500 meter-long ring line supplies each cleanroom with demineralized water.

Secure

20,000 m³

... per hour. All cleanrooms are continuously supplied with fresh air.

Andreas Dalferth, Jan Seidl

Fume Hood

Air Shower / High Potent Lock

Power Supply

Overflow Grid

Additional Adsorption Dryer

Filter Fan Unit incl. Pipes

I – VII Cleanrooms

VIII – X High Potent Area

Most employees in Pharma Services come from the pharmaceutical industry. We know our customers, speak their language and understand what they need. These are important prerequisites for exchanging ideas in a true spirit of partnership. Our customers already benefit from the fact that we work with a wide range of products and formulations every day. Based on the experience of each individual employee, we have an eye for what will work and what might cause problems. This enables us to provide customers with concrete solutions, such as a specific dosing system for their products, while always keeping in mind a possible scale-up. The dialogue between Pharma Services, the Design Department and the customer is the recipe for success when it comes to machines that are optimally tailored to the product.

"We speak the language of our customers and exchange ideas in a true spirit of partnership."

Dr. Elke Sternberger-Rützel,
Head of Pharma Services

Thanks to the increased opportunities offered by the new cleanrooms and laboratory space, we can develop and verify filling processes in close cooperation with our colleagues in machine development. At a very early stage we can ensure a reliable, reproducible product quality across all scale-up steps. Thus, we can contribute, every now and then, to accelerating product approval together with the customer. By using the Design of Experiment (DoE) methodology, we perform experiments, for example, with different machine speeds and variable filter inserts, and identify a process window with parameters that work reliably.

The air shower provides a safe working environment when handling highly potent substances.

Extensive analytical tests can be carried out with the aid of classical and state-of-the-art measuring systems.

The largest cleanroom measures 10 x 5 meters and offers space for entire machines.

Andreas Dalferth, Harro Höfliger

"With the expansion of the laboratory, analytical methods have changed completely."

Karin Marek,
Laboratory Manager

Just two years ago, we restricted our approach to purely physical measurement methods. Now we can perform a much wider range of analytical tests. With the new particle measuring systems, ultra-fine particles can be measured, which could influence the later processing of a product. We now have new capabilities in the wet-chemical field. By using high-performance liquid chromatography (HPLC), we can determine if and to what extent active agent particles accumulate on machine surfaces. We aim to ensure, for example, that no uncontrolled loss of active ingredients occurs during filling processes. By measuring the uniformity of the mixture content, we test how a product behaves under different manufacturing conditions and whether this might influence the filling properties. For inhalation, we now have the New Generation Impactor (NGI), a kind of aerodynamic flow model of the lung. The NGI gives us the possibility to determine the fine particle fraction (FPF) or the fine particle dose (FPD). This analytical option is one of the most complex I know of. Now we have much better overall control of the filling process. We can analyze the CPP (Critical Process Parameters), the CMA (Critical Material Attributes) and other similar relevant information for our customers, or perform data queries directly via our extensive product database. All this offers the best prerequisites for providing our machine designers and developers with the solid data they need for the targeted, rapid and successful design of a machine or for improving existing ones. Now product analysis is actually fun!

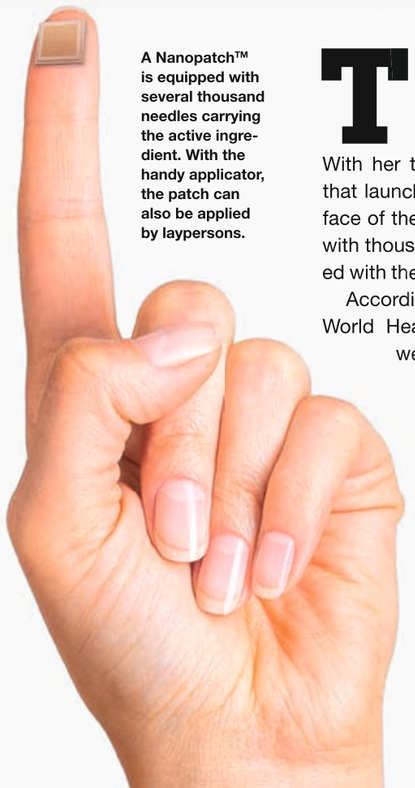
Our customers usually have certain ideas about the type of dosing system they want their product to be processed or filled with. With the help of the analytical facilities in our laboratory, we can determine at a very early stage whether these ideas indeed can be implemented or if we need to influence machine development with insights gained from previous research. Due to the regulatory requirements in the pharmaceutical industry, modifications to the machine or the product after approval are very costly and time-consuming. Therefore, certainty about the functionality of the process at an early stage is particularly valuable. As process managers, we work hand in hand with our laboratory team and the design department to meet the customer's specific product requirements. We never cease to welcome these insights as a part of our ongoing internal development. With the help of our new cleanrooms, we have the unique opportunity to recreate the product conditions found on the customer's premises, to better understand potential issues and to find suitable process solutions. By simulating real conditions, the complex test program for the qualification and validation of new machines can be scaled back. Tests for parameter setups or for special solutions can be transferred to Harro Höfliger. In this case, the customer preferably provides active pharmaceutical ingredients (API) or a placebo. Training and production support at the customer's site can also reduce the costly and time-consuming start-up phase of the machine.

"The expansion of the cleanrooms and analytical facilities gives us entirely new opportunities to identify and improve processes."

Michael Renz,
Process Engineer Engineering & Innovation Services

A micro revolution

Microneedle patches have the potential to significantly simplify vaccination campaigns. The Australian start-up VAXXAS and Harro Höfliger have taken the field with enthusiasm and expertise in search of an affordable, scalable solution.



A Nanopatch™ is equipped with several thousand needles carrying the active ingredient. With the handy applicator, the patch can also be applied by laypersons.

The young woman removes a round container from the packaging and places it carefully on her child's upper arm. With her thumb, she releases a boost that launches a tiny patch onto the surface of the skin. The patch is equipped with thousands of needles that are coated with the necessary vaccine.

According to information from the World Health Organization (WHO), as well as other NGOs, non-profits and private groups, conventional vaccination campaigns will be supplemented with such microneedle array patches (MAPs) in the future. They herald the end of syringes that can only be applied by qualified specialists. The end of liquid vaccines that require a continuous cooling chain. Especially in low and middle income countries, simple vaccination using a microneedle patch is a promising alternative. The Australian start-up VAXXAS and Harro Höfliger have been working to implement this technology, with a view to the cost aspect as well as the upscaling process.

An eye for the possible

The technology company, which came into being as an offshoot of the Australian Institute of Bioengineering & Nanotechnology of the University of Queensland, concentrates on novel vaccine delivery technologies. The Nanopatch™ that VAXXAS has developed is mainly designed for well-known vaccines. Right from the early stages, the interdisciplinary research team wanted to make sure that the ideas and processes from their laboratory studies would be reliably translated into high-volume series production. Mike Junger, Head of Medical Device and Process Engineering at VAXXAS, explains: "That's why we got in touch with Harro Höfliger, and we are really pleased that the experts were quickly ready to assist us in development of the device with a view to subsequent upscaling of the production process."

"It is a great technology which is going to simplify vaccination."

**Stefan Bernsau,
Director Needle Technology
at Harro Höfliger**

For Stefan Bernsau, Director of Needle Technology at Harro Höfliger, the collaboration has been a clear win-win solution: "A big part of our philosophy as a company is guiding our customers from the laboratory into production. That is why we often lend our expertise and resources to start-ups." The project with VAXXAS links several of Harro Höfliger's technology platforms: aseptic assembly, automation, and filling and dosing technology. Bernsau: "It is a highly demanding process development, since between the coating and sealing you have to include the drying process of the different active substances under aseptic conditions."

Harro Höfliger has been engaged in the topic of microneedle patches for quite some time and Stefan Bernsau regularly participates in conferences on this topic, including those of the WHO. He has built up a worldwide network that is working together to find practical solutions for this technology of the future. Bernsau: "It is a great technology with many challenges and it is going to simplify vaccination considerably. The consistent approach to new processes and developments together with VAXXAS, taking into account aseptic requirements, corresponds exactly to Harro Höfliger's philosophy."

Going skin deep

The Nanopatch™ from VAXXAS consists of a one-centimeter polymer square that contains several thousand micro projections, each just 0.25 millimeters high. These are coated with the vaccine, which they inject directly into the subcutaneous layers that are rich in immune cells. Thanks to the applicator, the Nanopatch™ can be applied quite easily, even by non-specialists. The special design ensures that the vaccine is consistently administered, regardless of age- and sex-related differences in skin structure. Cooling the active substance is not necessary, thanks to its solid physical form. "We have a 'do it yourself' corporate philosophy," says Mike Junger. "I trust my employees' abilities. They understand our product and they have the tools to do their job better than anyone

"In future, nanotechnology will be the norm in sterile manufacturing."

**Mike Junger,
Head of Medical Device and Process
Engineering bei VAXXAS**

shutterstock.com/Cheers Group, Janine Kyofsky, Harro Höfliger

About VAXXAS

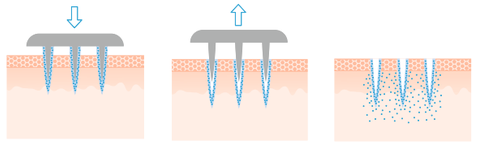
VAXXAS is a technology start-up founded in 2011 based on research at the Australian Institute of Bioengineering & Nanotechnology at the University of Queensland and is engaged in improving the performance of vaccines by delivery into the skin by the Nanopatch.

vaxxas

Many paths lead to the summit

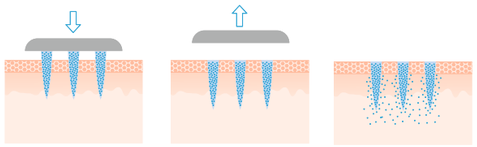
Microneedles are attractive for a number of markets: vaccination campaigns in developing countries are one area, but another is for more upmarket products such as migraine remedies. A diverse array of microneedle technology development teams and researchers are following different strategies in terms of choice of material as well as the application and delivery of the active substance.

Coated microneedles



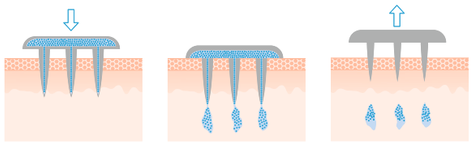
The microneedles made of metal or plastic are coated with a liquid active substance that dissolves later in the skin. To this end, they are either immersed in an active ingredient solution or imprinted and then dried.

Self-absorbing microneedles



The microneedles are formed from a suitable polymer (PVP, PVOH) and the active ingredient to be administered. When manufactured with a pressure process, the needles are already a component of the support patch, while in other manufacturing processes they are glued on in a later step. The needles dissolve completely once they penetrate the skin, giving off their active ingredient.

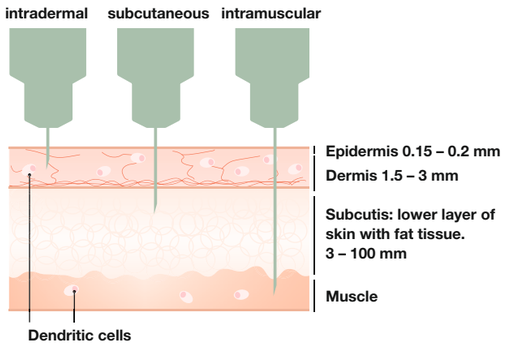
Hollow microneedles



Hollow microneedles (HM) are intended for the administration of higher doses of active substances. Channels are drilled into the stainless steel needles, for example with a laser. The active ingredient solution stored in a reservoir on the carrier film passes through the hollow needles into the skin.

Targeted protection

Recent studies have shown that intradermal vaccination may have advantages over the previously customary administration of vaccines into the subcutis or muscle. In contrast to the subcutis and the muscle, where only a few defense cells of the immune system are located, defense cells of the dendritic type are very common in the upper skin layer (dermis). These cells are responsible for initiating the immune defense. If the vaccine active ingredient is administered here, it ensures a stronger immune response and thus improved vaccine protection. Microneedle patches also follow this approach. VAXXAS aims to achieve a more targeted administration of lower vaccine doses in order to optimize their effectiveness.



else. We therefore didn't expect Harro Höfliger to solve all the problems on their own. It was important for us to develop our ideas further by collaborating with the machine building specialists with all of their experience, which guaranteed practical implementation in the end."

The hard facts

VAXXAS has now had their vaccine coating process for the microneedles patented. The next challenging task is to build a system on which the VAXXAS technology can be automatically and cost-effectively realized in large-scale production.

The largest challenges are the highly precise coating of the needles with vaccine, the subsequent drying process and the sealing, all of which have to be carried out under aseptic conditions. According to Bernsau, "in order to apply a large enough amount of active substance, the needles need to be coated multiple times. To do this, we need a non-contact, highly precise, automated and camera-monitored dosing system that works in a sterile environment."

This work is in progress. The VAXXAS brain trust and the specialists at Harro Höfliger are in constant contact to resolve issues as they arise. Junger explains: "We believe that in the future, micro- and nanotechnology will be the norm in sterile manufacture. But we still need to convince the regulatory authorities and the industry so that guidelines and standards can be adapted. Our Nanopatch™ is an important contribution to the process."

Harro Höfliger

When developing an upscalable process for future series production of the device, VAXXAS relies on the know-how of Harro Höfliger's mechanical engineering specialists.

World Health Organization

A powerful alternative

The World Health Organization (WHO) sees microneedle patches as an opportunity for vaccine delivery in low and middle income countries.

There is an urgent need for new tools and approaches to reach the 20 million infants that are not fully immunized each year.[1] The majority of the 1.5 million deaths that result from vaccine preventable diseases occur in just a handful of countries, with the weakest healthcare infrastructure, and where it is an enormous challenge to reach remote or conflict areas. Vaccine delivery in these countries is hampered by the requirement for most vaccines to be refrigerated from the point of production to the point of administration, the need to correctly prepare the vaccine by a trained healthcare worker, and the fact that many caregivers and children don't like needles or the pain associated with them.[2] Most vaccines are manufactured as multi-dose vials to reduce cost, but this presentation means there is reluctance to open the vaccine if there are not multiple children at the facility at the moment of vaccination. Microarray patches (MAPs) are designed to address these issues and revolutionise vaccine delivery in low and middle income countries.

1. UNICEF. WUENIC Analytics. (2019).
2. Arya, J. & Prausnitz, M. R. Microneedle patches for vaccination in developing countries. J.Control Release (2016).doi:10.1016/j.jconrel.2015.11.019

7 arguments for microneedle patches

- Single dose delivery without vaccacine preparation
- Easy to apply
- No cold chain necessary
- Delivery by minimal trained personnel possible
- Reduction of vaccine dose by targeting immune cells directly
- Reduction of costs
- If vaccine shortages occur, the number of doses at hand can be increased because less vaccine is needed per micro patch in comparison to injections.

Read the complete article by WHO online: **www.harro-magazine.com**

Excellent service for small series

Since the beginning of 2019, the newly founded 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 looking for an experienced partner and a high level of personalized service.

The state-of-the-art Experic location in Cranbury, New Jersey also serves as a high-tech showroom, where customers can experience technology by Harro Höfliger and Uhlmann.

Experic

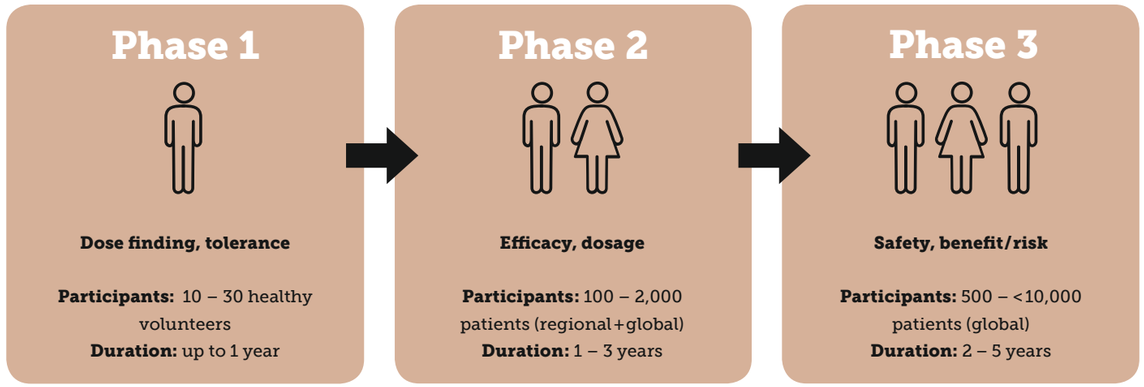
The production of clinical trial materials can present a real challenge, especially for small pharmaceutical companies, niche providers and start-ups: Small batch sizes must be produced under strict GMP guidelines (depending on the trial phase, between 10 and 10,000+ patients participate in the studies). Having the right equipment technology is another key component when it comes to successfully producing clinical trial supplies. However, investment in the appropriate equipment at the clinical trial phase can be cost prohibitive for many small pharmaceutical companies. A potential solution is to find a contract service provider who can offer the right equipment technology, understands the importance of a scalable process, and can cater to the needs of small and specialty pharmaceutical clients. Unfortunately, given the number of mergers and acquisitions in this field over the past few years there are fewer alternatives to choose from and it has become more challenging for this segment of pharmaceutical companies to find the right partner.

Experic, a US based company started to address this problem in early 2019. As a partner for smaller companies, Experic manufactures and packages clinical trial materials and specialty commercial supplies on the customer's behalf. Equipped with state-of-the-art dosing machines from Harro Höfliger and a blister machine from Uhlmann, Experic covers the entire spectrum of capsule and blister filling. "The Harro Höfliger principle is based on comprehensive manufacturing processes from the laboratory to production scale," explains Dr. Justin Lacombe, Director Pharmaceutical Development at Experic. "Following positive clinical results using drug products made on pilot-scale equipment, product and manufacturing process know-how can be seamlessly transferred to Harro Höfliger production systems with the same underlying technologies. The combination of a consistent single source and critical technology reduces the risk of having to modify the process at a later stage, saving time and, of course, money."

"The Harro Höfliger principle is based on comprehensive manufacturing processes from the laboratory to production scale."

Dr. Justin Lacombe, Director Pharmaceutical Development at Experic

Plans for the formation of Experic date back to 2015. During this early phase, Harro Höfliger was already involved in the project and later became an investor. "With Experic, we see a huge potential for our US customers," says Peter Brun, Team Leader Pharma Services at Harro Höfliger. "The facility closes an important gap in the production and the primary and secondary packaging of small series of pharmaceuticals in the US. Moreover, it serves as a high-tech showroom where customers can experience our technology live." The comprehensive service offering not only includes production, but also a GMP warehouse, DEA vault and worldwide distribution of clinical trial materials. "With Experic, startups and smaller pharmaceutical enterprises gain an experienced partner who can guide them with professional expertise during clinical studies all the way to product approval," explains Thomas Weller, CEO at Harro Höfliger.



Iconovo relies on the perfect combination of form and function right from the development stage.

Design made in Sweden

Iconovo specializes in the product development of customized DPI devices – and utilizes an integrated approach.

Cross-border networking as a recipe for success – the Danish-Swedish Medicon Valley is a prime example. Countless pharmaceutical, medical technology and biotech companies established themselves on both sides of the Öresund and benefit from their geographic proximity and close cooperation. One of them is Iconovo, a start-up with headquarters in Lund specializing in dry powder inhalers (DPI). The company is committed to providing customers with the optimum combination of inhalation device and formulation, and to paving the way for the market launch of their product with a variety of service offerings.

"An effectively inhaled drug therapy requires a well-designed inhaler and an appropriate powder formulation. The design of the device must be coordinated with the formulation of the drug," explains Dr. Orest Lastow, co-founder, CEO and Head of Research & Development at Iconovo. "Our customers, which include many generic drug manufacturers, often do not have the necessary resources to carry out the lengthy, cost-intensive and risky development work in-house. This is where our long-standing experience in inhalation, in some instances spanning several decades, comes into play."

Four platforms

Lastow and his 14 employees have developed ultra-modern DPI devices that are precisely tailored to the formulation to be administered and then licensed to customers. The product portfolio currently comprises four platforms, mainly focusing on drugs for the treatment of respiratory diseases: ICOcap (capsule based), ICOpre (disc based) and ICOone (for single use).

The flagship however is ICOres, a reservoir-based device for multiple applications. "Not only can we provide customers with device and formulation, but with a total package that includes analytical testing, documentation and, together with proven partners, the entire supply chain," he explains.

Harro Höfliger is also a part of the company's network. When Iconovo was looking for a laboratory device for manual, exact dosing of free-flowing powders into reservoirs, they did not have to search long. "Several of my colleagues and I have a long history with Harro Höfliger, and many of our customers have selected them as their supplier of equipment. Harro Höfliger is the first choice in the inhalation industry and a guarantee for high quality," says Lastow. When developing the dosing principle, inspiration had already struck his team to use a filling technique similar to loading a rifle with gunpowder. Harro Höfliger continued to develop this idea, as always with a view to a potential scale-up. The result is a table-top unit with a special micrometer screw.

Well equipped for the future

ICOres has two reservoirs, which can be filled with up to two different active ingredient formulations. A counter accurately indicates the remaining number of inhalation doses. With ICOres, Iconovo feels well positioned for future products (NCE). "Today, it is usually two drugs in one inhaler that you inhale at the same time. In the future, there will be three, or maybe four," says Lastow.

Does he see himself more as a CEO or a scientist? The answer comes promptly: "I have worked in the inhalation field for over 25 years and I think I see myself primarily as a product developer. I'm a problem solver, constantly trying to find better solutions."

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"An open discussion"

Marco Laackmann, Director Inhalation Technology at Harro Höfliger, in conversation with Orest Lastow.

Why did you specialize in the field of inhalation?
Personally I started with inhalation by accident. I did my PhD in aerosol technology and inhalation is an important application of that. Iconovo was founded to be an inhalation company since myself and many of my colleagues have worked with the development of inhalation product for a long time.

You are a member of MVIC (Medicon Valley Inhalation Consortium). How is it supporting Iconovo?
I was actually the founder of MVIC and used to be CEO for two years. MVIC is a fantastic network of 70 experts and companies specialized in inhalation and a partner in many of our customer projects.

What is the role of Harro Höfliger?
We have a long history and a very good cooperation. We have an open discussion about all aspects of manufacturing inhalation products and about technical solutions. Harro Höfliger is very generous with their experience and advice.

Inhalation experts: Marco Laackmann and Dr. Orest Lastow (right).

State of the art

A unique feature of ICOres is that it has two reservoirs which can be filled with the same dry powder formulations or with different formulations. This allows for the simultaneous delivery of up to four different active ingredients.

Ultra thin & high precision

The manufacture of pharmaceutical products requires the highest accuracy. The need for precision is clearly reflected in the coating process, the precise application of an active ingredient containing matrix onto a carrier material. Together with specialized technology partners, Harro Höfliger manages to integrate innovative coating processes into the production sequence – always with a focus on product properties.

The basic principle of coating is simple – applying active substances to web material. This process step is important, for example, in the manufacture of patch products such as TTS/TDS (Transdermal Therapeutic Systems), which enable the gentle absorption of active ingredients through the patient's skin. Coating is also used in the production of orally ingested films with a polymer matrix containing active ingredients. This applies to the wafer-thin, rapidly disintegrating ODF (Orally Disintegrating/Dissolvable Film) as well as to the slower soluble MBF (Mucoadhesive Buccal Films).

Superior quality

It is precisely this expertise that Harro Höfliger provides to its customers together with the necessary process support. This is mainly based on decades of experience in the processing of web material; but the precision needed is also achieved by fine-tuning the process to the customer's individual product requirements. For example, different coating processes are available depending on viscosity properties. This makes it possible to apply layers ranging from relatively thick to wafer-thin, or to process very cohesive masses. The ideal drying method required after coating can also be selected. Of course, quality assurance must always be a top priority when manufacturing pharmaceutical products. The coating processes therefore comply with GMP and GAMP5 standards. In addition, it is possible to integrate optical systems and sensors for quality control throughout the entire process. For example, a measuring device can move along the web and continuously determine the thickness of the coating layer. In other process areas, consideration is also given to the special requirements and documentation regulations of the pharmaceutical industry. All relevant data can be recorded automatically.

Janine Kyofsky

Flexibility through modularity

The production of the matrix precedes the coating process. Even at this early stage, Harro Höfliger provides customers with the necessary resources. To begin, the individual components can be weighed and mixed. The entire post-coating processes are also covered – from cutting and packaging to cartoning. System extensions are possible at any time due to the modular design concept. "On request, we can offer our customers a turnkey system where all components harmonize," says Hartmut Thier, Director Web Converting Technology at Harro Höfliger. "But regardless of whether the goal is the production of small batches or large quantities, we support our customers throughout all process steps, right from the initial idea."

The recently expanded cleanrooms at the Allmersbach site play an important role in terms of process reliability. "Even the smallest quantities of a new product can be tested there for their process capability – so that subsequent coating and all other steps can be precisely adapted," explains Hartmut Thier. "Naturally, extension and scale-up options are a given at Harro Höfliger."

Further information on the topic can be found online at:
www.harro-magazine.com

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