O-COM

THE OPTIMA MAGAZINE

SYSTEM SOLUTIONS

FOR CELL AND GENE THERAPEUTICS

REGENERATIVE THERAPIES

A FINGER ON THE PULSE OF THE FUTURE

EN pharma - life science | November 2020

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NEW OPPORTUNITIES, NEW DYNAMICS

Hans Bühler
Managing Director / CEO
OPTIMA packaging group GmbH

Dear readers,

Behind us lies challenging weeks and months. The COVID-19 pandemic has changed all our lives.
But even a crisis holds opportunities. New dynamics emerge and established technologies gain importance.
It was and is especially important to us to support you with comprehensive service and quality. Solution-oriented and, as always, in partnership.

In this issue of the o-com, you can read how Optima masters the crisis together with you. Synergies within the Optima Group, inventive talent, creative power and a lot of flexibility were and are the ingredients to get through this time in the best possible way.
You can also expect exciting news, user reports and technical articles on our four top topics: Flexibility, Safety, Digitalization and Sustainability.

I wish you good health and strength for the challenges ahead.

Yours,

Hans Bühler

26 On the pulse of the future

Cell and gene therapeutics are considered to be the hope of medicine. Optima Pharma now offers a holistic system solution for the production and fill & finish of these novel drugs.

22 Equipped for the fight against COVID-19

Adimmune has joined forces with Optima Pharma in the fight against COVID-19. With a new turnkey high-speed syringe line, the Taiwanese pharmaceutical company is ideally prepared for filling a COVID-19 vaccine.

40 The three aspects of digitalization

In this article, we have summarized how you benefit from digitalization. It is about much more than collecting and networking data.

The huge commitment of all our staff has continued to speed up the completion of filling and closing lines for potential vaccines.

During the crisis, machine solutions like the OPTIMA ImmuFill® were in particularly high demand. This solution enables the filling of reagents for diagnostic test kits.

JOINING FORCES TO FIGHT COVID-19

The COVID-19 pandemic is presenting major challenges for companies worldwide, and Optima is no exception. But as we all know, every crisis brings its own opportunities. New solutions have been found for the challenges posed by these times, by adapting tried and tested technologies and creating new ones. Digital technologies are continuing to grow in importance.

When, in March 2020, the pandemic hit Germany with full force, we at Optima immediately took a number of measures to ensure that we were there, serving our customers, employees and partners to the best of our abilities. An internal task force was immediately formed to assess the latest developments on a daily basis and define the right measures to take. For example, an online information portal was set up for our workforce, and strict infection prevention measures were introduced. Many of our employees were and still are working from home. At the same time, we informed our customers about the measures we were taking and how we were maintaining business operations. Optima Materials Management, Assembly and all other departments worked on solutions to adjust to the situation in the best possible way and to avoid serious delays.

Global availability of goods assured

Having identified new ways of working in this challenging situation and launched the first crisis communication measures, we focused on supporting you, our customers and partners, in this unique situation: with our expertise, highly flexible machine solutions, virtual machine acceptance, and digital services.

The corona crisis is leading to strong shifts in demand. The need for specific consumer goods and hygiene products, pharmaceuticals, and medical technology has increased exponentially. We have responded rapidly to this development and are providing special machine solutions that can be flexibly adapted to meet changing market demands. We have assisted companies in the cosmetics industry to convert their manufacturing to produce disinfectants. Ventilators are also scarce. Our highly flexible OPTIMA MPS machine solution helps to counteract these current shortages and automates the manufacturing of air filters to be used in ventilators. Various diagnostic methods, including PCR test kits, are used to detect coronavirus. Optima provides suitable filling and closing equipment for all diagnostic test kits. The OPTIMA VFVM and OPTIMA SV / H filling and closing machines are used for filling prospective vaccines and medications for treatments.

Synergetic effects make new solutions possible

In a crisis, the motto is, "stick together". With Optima, this aspect was also particularly apparent, both in terms of evening out capacity between the individual business units and in designing manufacturing and packaging solutions for protective masks. Cooperation between all business units meant that Optima was able to offer fully automated manufacturing machines with different performance levels for FFP protective masks within a very short time. Tried and tested packaging systems with different performance ranges were able to be flexibly adapted to package disposable protective masks.

Digital is the trump card

The pandemic has strengthened Optima's resolve to continue to single-mindedly follow its chosen path towards becoming a digitalized company. The opening of the Optima Digital Innovation Center and the presentation of our new Smart Services (see o-com special issue for Interpack) are the foundations for this. In the same way as the Additive Innovation Center has been advancing 3D printing technology in the production of parts, the Digital Innovation Center will play a significant role within the

PCR tests, among other methods, can be used to detect SARS-CoV-2. Optima provides suitable filling and closing equipment for all diagnostic test kits.

IMPORTANT FOR YOU

- Optima has maintained the production and supply of spare parts during the Corona crisis and successfully carried out adjustments to capacity.
- In the run-up to the pandemic, the supply chain had already been made crisis-proof through strategic measures that had been put in place.
- Tried and tested technologies like virtual FATs, Smart Services, and new communication formats such as webinars have continued to grow in importance.
- During the pandemic, the synergy effects within the Optima Group were particularly beneficial.
- Specific machine solutions for urgently needed products were delivered very rapidly or adapted to meet the new requirements.

The Barrier Technology webinar was a great success and proved to be a valuable addition to trade shows.

The company is reaffirming its digital direction in opening the Optima Digital Innovation Center. Smart Services can be experienced at first hand there.

OPTIMA Total Care offers virtual Factory Acceptance Tests. Optima customers can decide the extent to which they want to make use of them.

Optima Group as a think tank and in further developing and presenting digital solutions. At the Digital Innovation Center, Optima will present its own Smart Services in addition to digital technologies and applications relating to augmented and virtual reality. The new showroom will make digitalization tangible for customers and visitors. Customer webinars, such as the Barrier Technology webinar, will also be an added feature in the future.

The issue of remote service is of major importance right now. Smart Services include the area of "Smart Assistance", as well as others. With our "Remote Assist" digital service, our experts are virtually on hand to assist you on any mobile device when there are format changes or process problems. This is how we ensure that you receive optimum service in these situations, too.

Virtual FATs ensure delivery on time

Virtual machine acceptance means that Optima can ensure that machines are delivered on time during the crisis. This is how the most complex virtual machine acceptance in the company's history was performed. Over 30 employees working for a customer in the USA tracked every step of the virtual factory acceptance test every day. This variation has additional advantages, besides prompt delivery.

"This means that additional customer experts who are not part of the acceptance team can be called in for certain areas," explains Heiko Kuehne, Vice President for Cosmetics & Chemicals at Optima Consumer. Key suppliers were also contacted by Optima to answer the customer's questions. This has generated an exchange of ideas across disciplines and strengthened the partnership. Moreover, operating staff who do not normally get to travel to the acceptance test are also able to gain an in-depth insight. This means short commissioning times and a rapid start to production. "This is the confirmation that we made the right decision some time ago when we added virtual FATs to the portfolio of our life cycle management program, OPTIMA Total Care," says Kuehne. Customers can choose the extent to which the acceptance process is accompanied virtually – either as a complement or in full.

The supply chain is assured

Many companies' supply chains have come under severe pressure as a result of the COVID-19 crisis. The new logistics center and special strategic measures have enabled us to safeguard the availability of our machine solutions and services.

For instance, the ongoing performance of risk analyses, even before the pandemic, in order to safeguard supply chains has really paid off. Parts that require a high level of expertise are purchased from within the Optima Group or produced by the extensive in-house manufacturing facility. Approximately 150 qualified employees and state-of-the-art machinery, including 3D printing technology, are available.

Setting the right direction even before the crisis hit

Long before the pandemic hit, the focus of procurement was already on Europe, which has now benefited Optima. Alternatives were developed for procuring single-source parts. We identified what are known as the 'long lead time parts'. This was carried out in a highly coordinated collaboration with colleagues in the technical departments of the business units within the Optima Group. "A specially appointed task force management team carries out daily monitoring and is constantly exchanging information with potential bottleneck suppliers," reports Heiko Funk, the Managing Director of OPTIMA materials management GmbH. The right stock level was put in place for critical articles. Purchasing department staff were largely mobile in order to guarantee operational effectiveness. The operational areas of logistics and quality assurance worked in separate shift teams in line with the appropriate hygiene guidelines.

Social responsibility

As a contribution to tackling the crisis, Optima has assisted the company Wrapping Solutions, based in Rosengarten, Schwaebisch Hall, with respect to manual folding devices for the production of protective masks to cover the mouth and nose, and is advising Wrapping Solutions and other companies on developing automation solutions. The great efforts made by all our staff have helped to accelerate the completion of machine solutions for urgently needed products, such as potential vaccines. This is due to the guiding principle to which Optima is committed: We care for people.

MORE ABOUT THIS TOPIC

www.optima-packaging.com/fightcovid19

NEWS

Sustainability as a key issue

Optima is expressing its new strategy by setting up the "Sustainable Solutions" department. The company is focusing specifically on the issues of Flexibility, Safety, Digitalization and Sustainability, because more and more consumers appreciate packaging that is as environmentally friendly as possible. This is no small task. First of all, not everything that looks environmentally friendly actually is. Secondly, packaging that is genuinely environmentally friendly often brings new technological challenges along with it. That is why Ulrich Burkart (left) and Dominik Broellochs attach particular importance to "honest packaging". They head up the newly created "Sustainable Solutions" department and are well connected both internally and externally, including with research institutes. First significant successes: A packaging line for toilet paper rolls for Fripa, which produces very high quality packaging made exclusively from uncoated paper. There is also a "GreenLution" capsule system for portion packs made of a single material that can be completely recycled. This was launched with the cooperating partners Wipf and Saentis Packaging.

Filling system for COVID-19 vaccine

Optima is supplying a high-speed vial filling system for a COVID-19 vaccine candidate. This will be shipped to the US-based company Catalent's Biologics site in Bloomington (IN). "We are very pleased to be able to contribute to overcoming the coronavirus pandemic and to support Catalent in increasing its production capacities," said Gerhard Breu, Chairman of the Optima Pharma Division.

A high-performance filling system like this one is currently being customized for Catalent.

1,9 million €

is the expected cost of the one-time treatment of spinal muscular atrophy (SMA) with the Zolgensma gene therapy, at least in the first year after its market launch. A price will then be negotiated between the manufacturer and the German National Association of Statutory Health Insurance Funds (GKV). The drug was developed by the Novartis subsidiary Avexis, and it received conditional EU approval in May 2020. Around 550 to 600 babies with this rare neuromuscular disease are born every year in Europe. It is caused by a missing gene. Under the terms of flexible pricing models, Avexis has proposed reimbursing health insurance companies for the cost of the treatment if it fails to work.

Jan Glass, the new CFO of the OPTIMA group

Jan Glass succeeded Dr. Juergen Kuske as Chief Financial Officer of the Optima Group on May 1, 2020. As a result, working in collaboration with Hans Buehler, the Managing Director / CEO, he is taking over the management of the central departments. The industrial engineer has worked for Optima in a variety of management positions since 2016. Most recently, Jan Glass has been in charge of OPTIMA life science GmbH, in order to devote himself to the new, more wide-ranging job.

Vfa requests support and assistance from the political world

In a position paper, the German Association of Research-based Pharmaceutical Companies (vfa) has outlined the way in which it believes sustainable pharmaceutical research and production should be promoted in Germany. Among other things, it is calling for supply chains to remain robust and for administrative procedures to be simplified, as well as for research networks and digitalization to be encouraged. The association has also highlighted the economic and health-related consequences of a pandemic that is out of control. The cost of pandemic prevention is negligible in comparison. The position paper continues saying that the German state needs to "support the research and development of vaccines in a targeted way". What is indispensable are measures to increase vaccination rates, for instance smart reminder systems. The vfa also vehemently opposes restrictions on intellectual property rights (IP) and patent protection, which could lead to a decline in the global supply of medicines.

IMPORTANT FOR YOU

- Adimmune in Taiwan is researching a vaccine against COVID-19. The clinical phase is scheduled to start in August.
- A high-speed Optima system is designed for the processing of vaccines in pre-filled syringes. This features isolator technology from Metall+Plastic.
- Features such as a specific in-process control, an integrated syringe inspection machine, a glove leak tester as well as a CIP/SIP system are part of the project.
- By means of the technical and scientific CSPE approach, in which Digital Engineering methods among others are used, technical advantages have been achieved on the system. During lockdown, the process simplified the virtual FAT quite considerably.
- The company Adimmune is also a licensed manufacturer for global pharmaceutical groups and a leading national producer of vaccines.

In the CSPE Center of Optima Pharma the system was assembled with isolator and tested, followed by a virtual FAT.

Buffer area: If the in-process control detects deviations in the filling accuracy, the reject is reduced to a minimum.

EQUIPPED FOR TACKLING COVID-19

The pandemic calls for innovations and speed as well as safety and commitment at all levels. A new turnkey high-speed syringe line with isolator could possibly make a contribution. Optima installs this at Adimmune in Taiwan.

Adimmune is a leading licensed manufacturer in Asia of human vaccines of global pharmaceutical groups. Holding US and European certifications, the company produces to the highest quality standards. Adimmune is also very successful in the development of its own vaccines. Quite a few of them are undisputed market leaders in Taiwan and also gain substantial market shares beyond the country's borders. Heparin as well as research into cell culture-based vaccines are other core activities of the listed company, founded in 1965.

In the spring of 2020, an announcement by Adimmune that the clinical testing phase for a vaccine against COVID-19 would most likely begin in August 2020 garnered attention.

Beginning of a successful partnership

Some months before the outbreak of the pandemic, Adimmune decided to expand its existing capacities with an Optima turnkey system for syringes. This line is the first high-speed line for syringes in Taiwan to use isolator technology.

If the vaccine against COVID-19 receives approval, this will most likely be dispensed in pre-filled syringes with the new Optima system. The high-speed system is designed for the typical syringe formats for vaccines 1 ml long and 1-3 ml.

The fully automated manufacturing process of the system starts with the unpacking of the syringe tub: An OPTIMA DBA-S debagger removes the secondary packaging, an OPTIMA TRR robot removes the Tyvek protective film as well as the additional cover. After transferring a nest into the processing position of the ten-head OPTIMA H6-10 filling and closing machine, the product is dispensed row by row into the syringes. Rotary piston pumps handle this with great precision. Once this process is complete, the ten-head piston insertion takes place. The line output is up to 36,000 syringes per hour.

To achieve maximum flexibility in terms of processing very sensitive medicines, Optima has the option of incorporating a peristaltic filling system into the design, which can be integrated into the system via a trolley. A crucial feature in the long term, as Adimmune also conducts research in the area of sensitive biological agents. Adimmune also benefits from a specific in-process control to ensure the highest possible filling accuracy.

Adimmune is the largest vaccine manufacturer in Taiwan. With FDA and EMA certifications, the company also produces under license from global pharmaceutical companies.

Minimized product loss, maximized product safety

The entire filling and closing area is isolator-protected. This uses leading isolator technology from Metall+Plastic, Optima's subsidiary which specializes in this. The safety aspects in particular were a vital consideration for Adimmune in the decision for isolator technology. American and European authorities clearly favor isolator technology. As a licensed manufacturer for global pharmaceutical groups, this is another crucial factor for Adimmune. One advantage of Metall+Plastic isolator technology is also the special HVAC unit. Simplified installation and excellent accessibility for the service are impressive features.

HVAC stands for Heating, Ventilation, Air Conditioning and means the A/C unit of a pharmaceutical plant, which ensures optimal production conditions through accurate control of various parameters.

Fast and safe format and product change are further key criteria for Adimmune. The isolator cycle times determine this first and foremost. In particular, the special evaporation technology for the H_2O_2 as well as the catalytic ventilation, another specific development from Metall+Plastic, are responsible for the time advantage.

During construction, further important conditions have been created for highly efficient decontamination cycles. In the context of Digital Engineering (for example, computer simulations), that Optima and Metall+Plastic performed as part of the comprehensive technical and scientific approach CSPE (Comprehensive Scientific Process Engineering), the even distribution of vaporized H_2O_2 was calculated and visually displayed. The positions of the direct H_2O_2 injection nozzles, in particular, were therefore optimized.

The turnkey concept again plays an important role. Each isolator geometry is individual, and the many complex installations have significant influence on the H_2O_2 flow pattern. Initial flow simulations facilitate and display potential weaknesses even at an early stage.

Full commitment to comprehensive quality

It is worth noting that Adimmune has invested in format sets for every individual licensing partner. Every customer receives their pharmaceutical product produced with its "own" format set – whether the customer's formats overlap or not. An additional syringe inspection machine, which is installed inline, as well as the glove leak tester ordered, emphasize the high commitment to quality. From this perspective, the company has also opted for a Clean-in-Place/Sterilize-in-Place System (CIP/SIP), which cleans and sterilizes parts that come into contact with the product on site.

Throughout the project in which the Taiwanese Optima distributor E2Joy Corporation was involved, weekly meetings were held at the customer's site. During this time, a close cooperation of all those involved and a relationship of trust developed. When the pandemic began, this partnership and the team spirit were extremely valuable for continuing the project using digital communication tools fully without any restrictions.

Cameras and lighting form part of the extensive equipment required for a virtual FAT. A large team carried out the preparatory work in the background.

The CSPE approach should pay off again under pandemic conditions. In the new CSPE Center at the Optima headquarters in Schwaebisch Hall, there are spatial requirements for a joint acceptance of the filling and closing machine with built-on isolator. Extraordinary, and yet "business as usual" for customers who order a turnkey project from Optima. When the question was raised as to how a Factory Acceptance Test (FAT) can be implemented without the presence of the customer – to lose as little time as possible – on account of the pandemic lockdown, the path to the virtual FAT was considerably simplified with the CSPE Center.

With CSPE to the virtual FAT

An enormous amount of effort is involved in a virtual FAT: High-tech cameras, streaming technology, channels enabling data transfer at the appropriate speed, cutting and sound technology as well as an experienced media team, which together with the project team ensures that the customer can experience and understand all the relevant information live. All of this must be planned, organized in a virtual FAT, and achieved over a timeframe that is identical to that of a "normal" FAT. As this effort ideally should only be incurred once for the complete system and not repeatedly for individual system components, the CSPE Center simplified the decision for this considerably.

With the virtual FAT, the turnkey system has proven its efficiency under almost real production conditions. As a result, the system could be dismantled at the end of July 2020 at Optima in Schwaebisch Hall and shipped to its destination in Taiwan. Can it be used to tackle the pandemic? The technical requirements are in place and Adimmune is also on a more than promising path. According to the Taipei Times dated July 16, the clinical phase is scheduled to start in August.

After removing the Tyvek foil and the cover, the syringes are brought into the processing position.

High output of up to 36,000 pre-filled syringes per hour: Rotary piston pumps ensure dispensing with a ten-head concept. Additionally, Adimmune can put a peristaltic pump system into operation.

The new OPTIMA 4SSadvanced for four-sided sealed pouches: Higher levels of performance and greater flexibility come together.

IMPORTANT FOR YOU

- The OPTIMA 4SSadvanced new four-sided sealing pouch machine can package many different medical products such as wound dressings, post-operative wound dressings, advanced wound care products and dressings containing ointments.
- There is very high flexibility in terms of format, and the processing speed is very fast (up to 70 metres per minute). The machine's concept dispenses with the costs for format parts.
- Format changes are largely automated. Any residual manual activities are supported and made safe in a sensible manner.
- A new machine design with a vertical machine plate: Simplified flexible configuration of ancillary machine functions and optimized line integration with Optima Life Science web converting systems. Inline secondary packaging can also be carried out.

THE POUCH SYMBIOSIS

An innovation in four-sided sealed pouches: The new OPTIMA 4SSadvanced offers a host of improvements and radical innovations in the packaging of medical products.

Wound dressings, post-operative wound dressings, advanced wound care products and dressings containing ointments are the standard domain of the completely redesigned OPTIMA 4SS advanced. The packaging machine is the ideal add-on to the Optima Life Science web converting lines. It means that manufacturing and packaging can be combined in-line.

High performance or high levels of flexibility? Machine design often just addresses one of the two criteria. In the new OPTIMA 4SSadvanced, we have successfully combined both of these aspects and achieved a particularly high standard. The new longitudinal sealing tools now have a separate gear drive, which provides a high-speed processing speed of up to 70 meters per minute for foils and films. There are now three instead of two cross-sealing tools per transverse sealing station, which also makes a contribution to higher speeds.

Rapid, optimized format changes

Typically, machine users in the medical technology sector often carry out one or more format changes every day, so great importance has been attached to having the right features. With the OPTIMA 4SSadvanced, changeover times for formats have been optimized and the entire changeover process has been greatly simplified. Some of the format changeover work is done automatically. It is simply activated by "pressing a button" on the HMI. Functions that are carried out manually rather than automatically are systematically supported and safeguarded.

To do this, small screens have been installed in direct proximity to machine functions which require operator intervention during format changeover. These indicate new target values that are set by the HMI. The machine can only be restarted once all values on the system have been correctly set and the actions have been confirmed by the operator. For example, manual settings may include the distance between the sealing wheels for the bag width, stops for unwinding or even seal printer settings.

Another important aspect with frequent format changes is the cost of format parts. With the OPTIMA 4SSadvanced machine design, these are dispensed with. At the same time, the new concept means the format range is extendable. The track for packaging material has now been increased to a maximum width of 420 mm, which corresponds to a maximum seal width of 400 mm. This means that even post-operative dressings of 350 mm long can now be packed by this machine.

Any changes in parameters can be tracked at all times. Users simply log in to the system by entering their name or using an RFID chip or their company ID card. If necessary, detailed reports can be printed out, which can also include an audit trail.

The new design is remarkable when it is compared directly with the previous model. The machine functions are no longer installed on a horizontal machine plate; instead,

Sealing station: The four-sided sealed pouches are sealed in a continuous process.

Sealing and cutting

There are also small monitors that display the setting values that have to be set up and confirmed manually. Prior selection is made on the HMI.

they are installed on a vertical backplate. Using the backplate design, customer requirements can be implemented much more easily than was previously the case. These could be functional extensions such as printers, cameras or web edge controls, which can now be positioned with minimal effort.

Backplate design – in the vertical plane

The operator side at the rear of the backplate is also highly accessible. The new structure also offers significant advantages for line integration with Optima Life Science's web converting systems. These are designed based on the same principle and with identical processing alignment, so that all parts of the line function in perfect harmony with each other. Valuable space has also been saved by integrating the control cabinet into the machine frame.
The first machines are already in operation on customers' premises. The new machine concept is being used successfully in New Zealand, Finland and Germany and is garnering excellent customer feedback.

MORE ABOUT THIS TOPIC

The OPTIMA 4SSadvanced is a four-sided sealing pouch machine that produces flat pouches from foil, film or paper. The maximum track width is 420 mm; the length can be varied. The medical products are integrated into an inline production and packaging process. In a manufacturing process in a continuous track, the medical products are initially manufactured and checked several times, then sealed directly in film, foil or paper. The pouches are then cut and separated. Secondary packaging, for example a cartoner, can also be integrated into the line.

The secondary packaging – here with cartoner – can be integrated into the inline process.

FLEXIBILITY

After the components have been manually inserted, the automated assembly process starts. The machine design can subsequently be adapted to be fully automated.

All processing stations are integrated on the rotary transfer machine. Here the knob of the dosing mechanism is turned back to the starting position.

The dosing mechanism of the pen is pressed in at this station.

Self-medication with pen injectors will continue to gain in importance. Demographic change ist considered a major reason for this.

PEN-GINEERING BY OPTIMA AUTOMATION

It is very flexible: The new OPTIMA FPA machine is designed to handle the assembly, bonding, and locking of medical pen injector components. The performance and the processes used to manufacture the pen injectors can also be modified.

The use of pen injectors for self-medication will continue to grow. A major reason for this is the changing demographic structure in many societies, with a higher population of aging people.
Pen injectors consist of several components, which the OPTIMA FPA can assemble either fully or semi-automatically. The semi-automatic machine version is adaptable in terms of both performance and functions. It is particularly suitable for entering into this market segment.

Versatile: Pen types, performance, and processes

A central, unique feature of this compact machine platform is the flexible mounting of pen components by gluing or clicking into place. Either of the functions is required, depending on the type of pen and the OPTIMA FPA is ready for both. The machine includes the appropriate processing stations and is versatile without having to change formats. The machine also offers a priming function. This means that the patient using the pen has the added security of automatically administering a correct dose of the active pharmaceutical ingredient from the first dose onwards and does not have to do any manual priming.
Another new feature of the OPTIMA FPA is the option of adding a printer combined with 360° labeling. This means that customer-specific printing and labeling can be incorporated and individually positioned. The printing and pharmacode is checked by a camera system using OCR software. Additional in-process controls such as force-displacement measurement and other sensor technology ensures that the entire process meets the highest safety and quality requirements (such as GAMP 5). The OPTIMA FPA complies with other important regulations, including FDA requirements 21 CFR Part 11, via user management with defined access levels and automated reports. The machine operator can define inspection criteria and tolerances on an individual basis.

The priming function compensates the measured distance between the stopper in the cartridge and the flange.

Comprehensive inspection systems for high product quality

The OPTIMA FPA is designed as a machine platform and is customizable for pen systems that are made by different manufacturers. These are constructed in a similar way, but still require individual adaptations to the machine and by its software.
Customer-specific requirements and functions are implemented using the machine platform. The machine operator has the freedom to expand what was initially a semi-automatic process into a fully automatic process. In semi-automatic production, the different components are inserted manually; subsequently the production is completely automatic. If an increased output becomes necessary, the financial investment required is significantly lower than for a completely new machine.

IMPORTANT FOR YOU

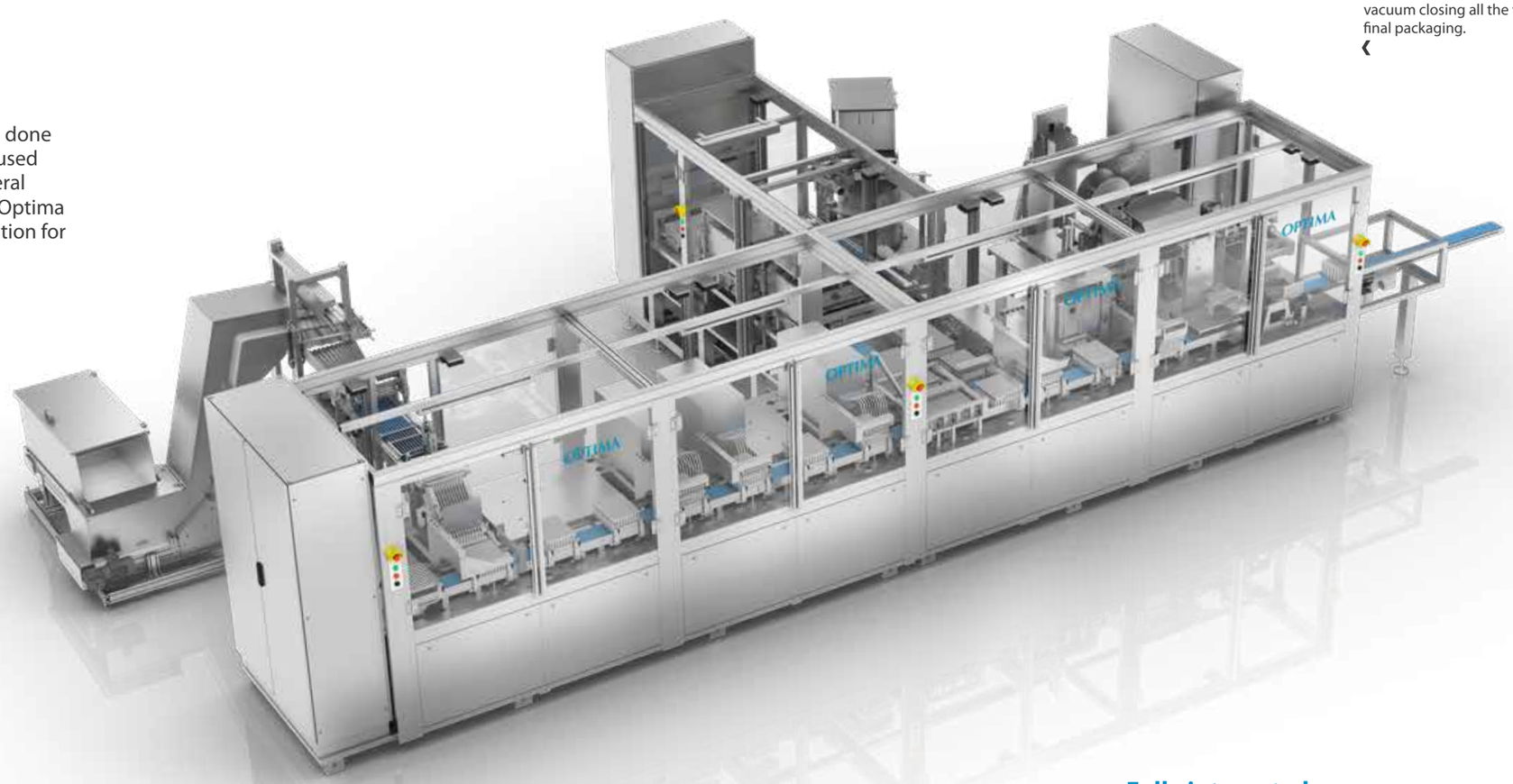
- The OPTIMA FPA for flexibly processing different pen-based injection systems
- A semi-automatic, entry-level machine with extension and upgrade options
- Completely safe: inspection systems for all processing steps, user authorizations, and reports
- Low space requirements due to the rotary transfer principle

A whole lot of functionality in a small footprint

The OPTIMA FPA is designed as a rotary transfer machine. This means that the individual assembly stages can be arranged to save space and have a minimal machine footprint. The machine is a perfect add-on to Optima Pharma's filling and closing machines, which are used to dispense liquid drugs into cartridges. The OPTIMA FPA can also be adapted for inline transfer to various secondary packaging systems.

THE COMPLETE SOLUTION

Diagnostics play a vital role in containing pandemics. If this is done based on blood antibodies, blood collection tubes are often used to collect the blood. Manufacturing these tubes requires several high precision steps in assembly, dispensing and packaging. Optima Automation provides an efficient assembly line as a total solution for this purpose.



The OPTIMA BCT-200 assembly line for blood collection tubes has many functions. These include cleaning, bacteria reduction, various dispensing stations for additives, drying and vacuum closing all the way up to the final packaging.

IMPORTANT FOR YOU

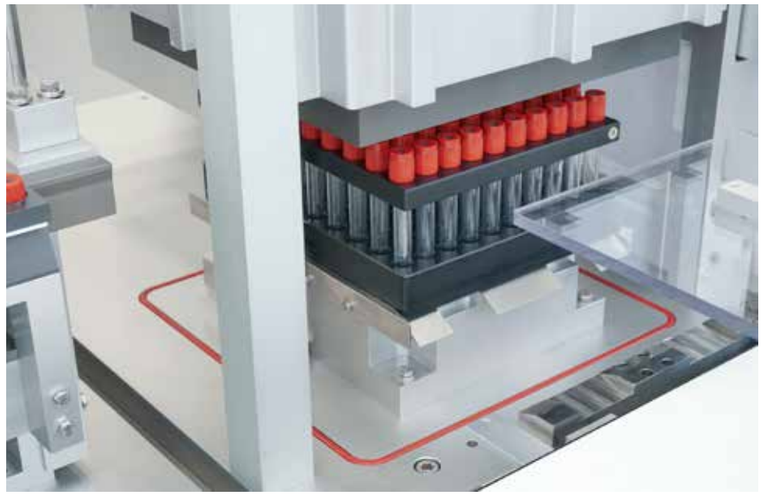
- A total solution covers all the processes involved in the assembly, additive dosing and packaging of blood collection tubes.
- An efficient, high-performance process: The best conditions for this are provided by specifically designed sorting pots and the combination with the OPTIMA BCA-200 assembly machine for the caps.
- The dosing technology is crucial to precise diagnostics – customer-specific solutions are developed in Optima Automation's dosing laboratory.
- The high quality of the blood collection tubes is assured by numerous process controls in the line.

Several steps in the manufacturing of blood collection tubes require specific expertise. The focus here: Firstly, the high, safe product quality of the blood collection tubes. Secondly, an efficient, reliable manufacturing process.

The OPTIMA BCT-200 assembly line features feeding systems and sorting pots that were developed and produced in-house, and that have been specifically designed for processing blood collection tubes. After being separated, the tubes are inserted into workpiece carriers. To remove any particles and prevent static charging, the tubes are first blasted with deionized air. Any bacteria that may potentially be present are then reduced by means of ultraviolet C-LED irradiation.

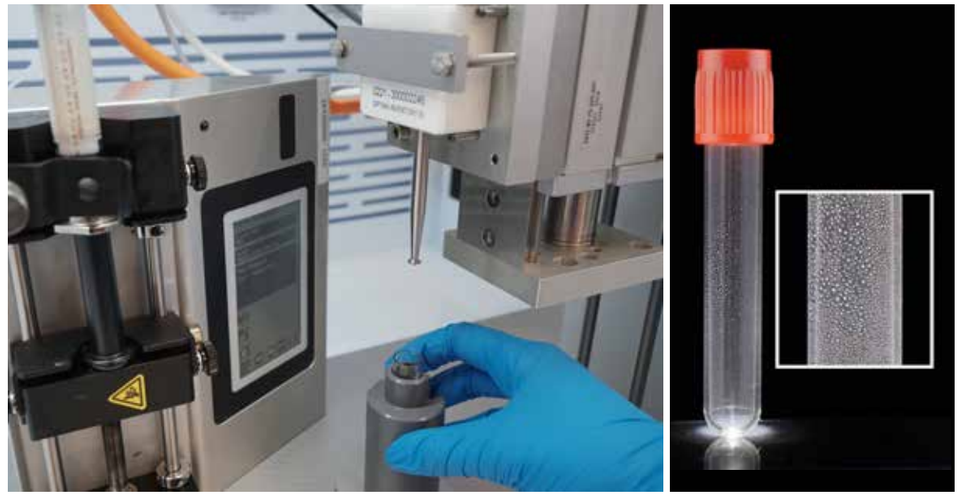
Fully integrated

Dosing stations for additives will follow in the OPTIMA BCT-200. These additives need to be added in specified amounts in accordance with the manufacturers' requirements or those of the diagnostic laboratory tests. It is typical for these additives to have very varying consistencies: A special system is available for polymer gels, which dispenses the gel with no bubbles and in a highly accurate way. For additives like silica particles, EDTA or lithium heparin, which are processed in liquid solution by a spraying process, a system with ultrasonic nozzles is required. Sedimentation is prevented here by an agitator in the tank. To achieve



The OPTIMA BCT-200 assembly line manufactures and packages blood collection tubes. Additives are dispensed into the tubes, which are then vacuum sealed.

Drying additives in blood collection tubes. Based on the OPTIMA BCT-200, Optima Automation is able to implement a wide range of customer-specific requirements for both assembly and manufacturing processes.



Uniform dosage following spray tests with additives. The conditions for the best outcomes are established in Optima Automation's dispensing laboratory.

optimal results, it is also possible to make fine adjustment to the dosing parameters. The OPTIMA BCT-200 also offers the right dosing systems for liquids like sodium citrate or additives in powder form. There is also the option of integrating additional dosing stations into the machine via free stations.

Depending on the additives used, the workpiece carriers are conveyed to a side-mounted drying station, or directly to the downstream stations. The drying stations consist of two downstream chambers, each with a capacity of four workpiece carriers. Throughout the drying phase, this system makes it possible to maintain the line output of up to 200 blood collection tubes per minute.

Once this process is complete, the blood collection tubes are then vacuum sealed. To this end, the caps that have been pre-assembled in the OPTIMA BCA-200, consisting of a plastic cap and rubber stopper, are fed out of a sorting pot and placed on top. The vacuum used here is also necessary for easily and accurately collecting blood from the patient later on, as well as conducting a reliable blood analysis.

The blood collection tubes classed as good are then labeled. Normally, information such as the expiration date and the batch number is printed on it. To provide protection for the blood collection tubes during transport, suction pads are used to remove them from the workpiece carriers and insert them into polystyrene trays. To ensure perfect protection during transit, the blood collection tubes are finally packed and sealed with shrink wrap.

Perfect interaction

For highly efficient processing, Optima Automation recommends combining the OPTIMA BCT-200 with the OPTIMA BCA-200, which mounts the caps ahead of time in a separate process. Control functions ensure that only those caps that have been checked are subsequently processed. This keeps production interruptions and defective parts to a minimum in all subsequent processes.

On the OPTIMA BCA-200 – as on the OPTIMA BCT-200 – the components are fed and assembled from special sorting pots made by Optima Automation. These caps can then be fed into the corresponding feed hopper on the OPTIMA BCT-200, and from there they are transported via a conveyor belt to the sorting pot.

This means that the OPTIMA BCT-200 and the OPTIMA BCA-200 represent a highly efficient duo of machines. This total solution from Optima Automation guarantees that the machines operate reliably and without any interruption.

MORE ABOUT THIS TOPIC

Dosing laboratory for additives – Diagnostic precision

Besides various process controls, the dosing systems are particularly critical for production to the highest quality standards. Additives can vary from manufacturer to manufacturer and from application to application, so Optima Automation has set up its own dispensing laboratory to provide customer-specific solutions. Here the original additives are tested and adapted to the OPTIMA BCT-200 specific dosing systems, and the dosing parameters for the assembly line are determined ahead of time.

Another outcome of these optimizations is extremely robust production processes. It is also guaranteed that the quantity of dosage intended for the additives is actually in the blood collection tube and that the correct mixing ratio with the blood is achieved during use. Even in the case of complex additive requirements, solutions for dosing additives in liquid, gel or powder form are determined in collaboration with the customer.

A FINGER ON THE PULSE OF THE FUTURE

The consultants Frost & Sullivan estimate that the market volume of cell therapeutics will have reached 13 billion euros by the year 2025.

IMPORTANT FOR YOU

Production

- Closed production platform using proven isolator technology
- Scale-out functionality due to standardized interfaces with external devices, for example, incubators and bioreactors
- Modular structure & process control with the option of creating your own process sequences
- High process reliability through automation

Fill & Finish

- Closed solutions for filling and closing using isolator technology
- High flexibility using robot technology
- Integrated "Product Saving Features" with 100 % in-process control
- High process reliability through automation

Regenerative therapies have ushered in a new era in medicine. Cell and gene therapies can now be used to effectively treat what were previously incurable diseases. However, producing them is a both complicated and protracted process. Optima Pharma offers a comprehensive system solution for safely processing cell therapeutics and viral vectors.

In medical circles, there are high hopes for cell and gene therapy, and they may revolutionize the treatment of serious diseases. A distinction is made here between in-vivo gene therapies, which can specifically repair genetic defects, for example viral vectors. There are also cell therapies such as CAR-T cells, which are genetically modified cells that are able to cure cancer. The first CAR-T cell products such as Kymriah® (Novartis) and Yescarta® (Kite / Gilead) and viral vector products such as Zolgensma® (AveXis / Novartis) and Luxturna® (Spark Therapeutics / Roche) have been approved, and the results are promising. There is an abundant pipeline for pharmaceutical and biotech companies, and current market research data is demonstrating that a new era in medicine has begun.

With in-vivo gene therapy, patients have one or more genes introduced into their tissue or organs to treat a hereditary disease.

In medical circles, there are high hopes for cell and gene therapy, and they may revolutionize the treatment of serious diseases.

Annual market growth of 33 percent

According to the Alliance for Regenerative Medicine, an international multi-stakeholder network with over 350 members, at the end of 2019 there were over 1,000 cell and gene therapies undergoing clinical trials, most of them at phase II stage. The US Food and Drug Administration (FDA) expects that between ten and 20 new regenerative therapies, including cell and gene therapies, will be approved every year over the next five years. This massive rise in new registrations will lead to an increase in the market share of cell therapeutics, from €1.3 billion in 2017 to around €13 billion by 2025 – with an annual growth rate of 33 percent [Frost & Sullivan]. This dramatic growth calls for innovative technologies that make it possible to produce small to medium batch sizes industrially and cost-efficiently – technologies that are not available at present

Flexible, economical and reliable production

At present, producing these valuable drugs is still very expensive and time-consuming, and is largely done on a laboratory-size scale. "We have received a growing number of inquiries for automated production and filling solutions," reports Dr. Andrea Traube, who since November 2018 has been Head of Market Development, focusing on system solutions for cell and gene therapeutics. Optima Pharma is an experienced solution provider for the most complex fill & finish challenges and is beneficially contributing this expertise to design production solutions for regenerative therapies.

Integrated System Solutions for Cell and Gene Therapies

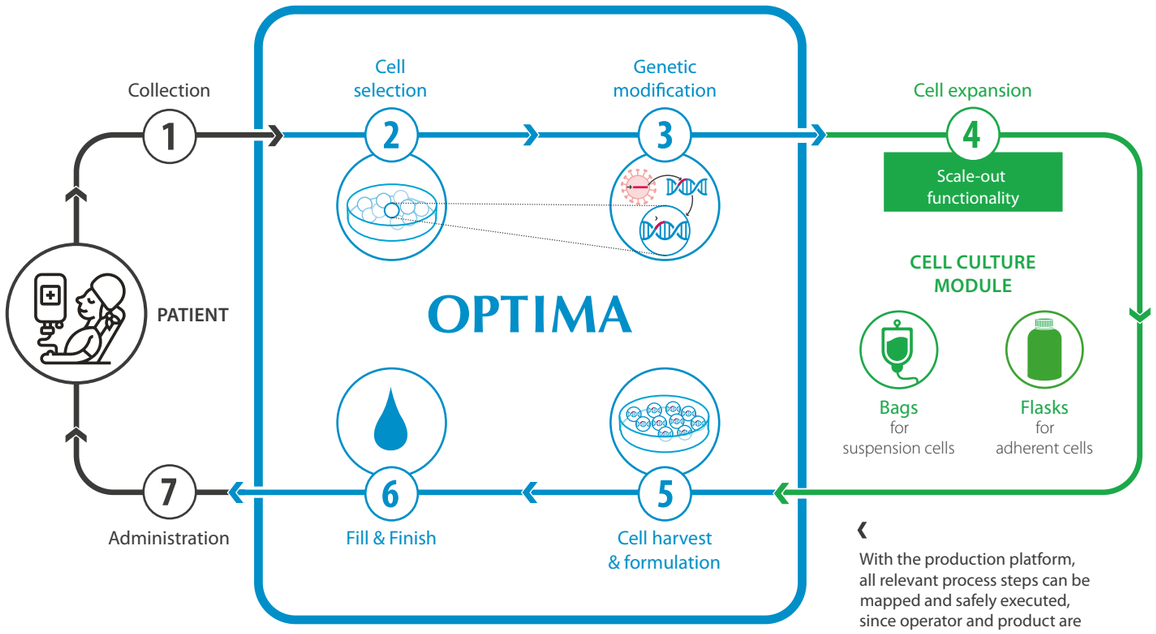
Optima Pharma is a partner for the entire life cycle of a product, from its clinical development to the commercial production and filling.

Currently the production and final filling of cell and gene therapeutics is mainly carried out manually, and in part on an individual basis for individual patients. It is ony possible to achieve the cost reductions needed while maintaining the same, reproducible quality in the manufacturing and use of these therapies by standardizing, digitizing and automating production processes. In close cooperation with pharmaceutical companies, our experienced expert has identified the requirements needed to make it possible to produce these therapeutics, which are very complex to produce on an industrial scale. "High-quality, sensitive products such as cell and gene therapies demand highly flexible machine solutions with a high level of operational reliability and a small footprint," explains Traube.

Manufacturing in several process steps

The fabrication of cell and gene therapeutics involves numerous individual process steps. As well as the upstream processes like cell selection and enrichment or expansion, there are downstream steps like purification and final formulation. This also involves filling the product into specific vials that can be cryopreserved.
Two categories of products that are currently of major importance are cell therapeutics and viral vectors. Cell therapeutics, either genetically modified (such as CAR-T cells) or non-modified (such as mesenchymal stem cells), are produced in small scale batch runs. To this end, Optima Pharma supplies integrated system solutions that cover the entire production process chain, right through to final filling. In contrast, viral vector products are produced in larger batches. Optima Pharma is also well positioned in this area, with a wide range of filling and closing machines.

Cryopreservation is the preservation of cells or tissue by freezing them in liquid nitrogen.



With the production platform, all relevant process steps can be mapped and safely executed, since operator and product are always separated from each other.

Production isolators with individual process sequences

Closed production platforms for cell and gene therapeutics are based on proven isolator technology and have a modular design. This aspect is crucial. It ensures that there is maximum flexibility in terms of process sequence and integrating external devices like incubators. Here, the primary focus is on maintaining what is referred to as scale-out functionality, i.e. the multiplication of individual process steps, which makes it possible to simultaneously produce multiple batches, in particular for autologous cell therapies.

With autologous cell therapy, cells are harvested from a patient and then re-administered back to the same patient. With allogenic therapy, one or more patients receive cells taken from healthy people.

The production platform can be used to produce autologous and allogeneic therapeutics, suspension cells like CAR-T cells and adherent cells like mesenchymal stem cells. All the relevant process steps, from cell selection, cell activation, genetic modification, cell expansion, cell harvesting and formulation to filling into bags, can be mapped and safely performed, because the operator and the product always remain apart.

The customers can decide the level of automation they need. All variants are possible, from manual isolators with integrated centrifuge to fully automated expansion stages. As a result, the needs of clinics, research institutions, pharmaceutical contract manufacturers, laboratories, start-up companies and large pharmaceutical producers are met on an equal, personalized basis, and the processes are standardized, reliable, reproducible and efficient.

The manufacturing platform incorporates proven isolator technology, together with flexibility, modularity, high process reliability and scale-out functionalities.

Reliable filling with 100 % in-process control

Optima Pharma also provides a dedicated range of specific machine solutions for the Fill & Finish for therapeutics. As Traube explains, "The machine concept is primarily geared to meeting the needs of the customer's product to be processed." The product is what determines which vial or container will be processed. Here, particular care has been taken to meet the requirements for processing specific vials for cryopreservation. The products are very expensive, so it is very important to keep product loss to a minimum. A range of integrated technologies known as "product saving features" ensure high product yield and maximum cost efficiency. These include a variety of redosing, restoppering and recapping functions, as well as a 100 % in-process control. The use of robot technology allows for a high degree of flexibility, and users also benefit from an integrated glove testing system. The award-winning DECOpulse® decontamination system ensures fast and safe decontamination while saving H_2O_2.

The specific product portfolio of Optima Pharma and its comprehensive understanding of processes means that from now on, Optima Pharma is a partner in technology covering the entire process chain in the areas of production and filling of cell and gene therapeutics. "We are able to meet the challenge of providing our customers with support, by offering suitable machine solutions in a highly complex market environment that is undergoing dynamic development. Our highly flexible working methods mean that we are also able to perfectly adapt ourselves to our customers with regard to new developments and adaptations," says Traube.

Innovation: DECOpulse® now also ensures particularly consistent decontamination in the STISO sterility test isolator – with greatly reduced cycle times.

THE STISO WITH DECOPULSE®

Longer operating time and the highest level of pharmaceutical safety is what is on offer from the latest generation of sterility test isolators STISO. This is mainly due to DECOpulse®, the highly efficient, award-winning bio-decontamination system. STISO also scores high points for its ergonomic design and the "Plug & Test" principle.

Sterility testing is central to the aseptic processing of drugs, which must be carried out in strict accordance with regulatory requirements. Common practice is for sterile tests to be carried out under conditions that are as similar as possible to those encountered during production – for example, inside isolators or even with sterile workbenches in the laboratory. Where isolators are used in production, the use of sterility test isolators is advisable since, compared to sterile workbenches, these isolators offer considerably higher safety for avoiding false-positive tests.

The tests are mainly performed with gloves on the sterility test isolator, so ergonomic factors also need to be taken into account to ensure that the operator's processes are as simple as possible. The STISO sterility test isolator also satisfies these high requirements most effectively. The newly integrated DECOpulse® bio-decontamination system also provides the highest level of safety and efficiency.

So what exactly makes the DECOpulse® system stand out? This question can be answered by taking a look at the development of the new system.

From wish to reality: Development phase

A physical phenomenon provided the idea and basis for the realisation of DECOpulse®: H_2O_2 can evaporate at room temperature if the pressure in the liquid phase is high enough. Since the geometrical shape has an effect on internal pressure through surface tension, according to the Young Laplace equation, a micro-sized droplet or "sphere" of H_2O_2 would be suitable. In this case, the liquid H_2O_2 which is initially still visible as a spray mist (aerosol), would evaporate and thus no longer be visible to the human eye.

The question is how to achieve this small microdroplet diameter and, above all, what effects does it have in practice with pharmaceuticals? DECOpulse® works with several injection nozzles in the isolator. As was previously the case, these are mounted as direct injection nozzles in the plenum and above the CG diaphragm (membrane) for indirect injection. H_2O_2 is introduced into the isolator via two-substance nozzles, together with pharmaceutical compressed air as carrier gas. Here, the critical factors are the nozzle geometry, as well as numerous other

Background: The more the internal pressure in the ("micro") drop increases, the smaller its diameter is. According to the Young LaPlace equation, the microdroplet diameter d must be < 3 µm so that the internal pressure is greater than the atmospheric pressure (approx. 1 bar) and thus the desired evaporation can occur.

IMPORTANT FOR YOU

- New in STISO: DECOpulse® with "Atomization-driven Evaporation". In this process H_2O_2 evaporates at room temperature.
- H_2O_2 is particularly evenly distributed, especially in complex isolator geometries.
- Efficiency: Extremely effective and homogeneous decontamination for the highest levels of pharmaceutical security, with cycle times significantly reduced.
- There is no decomposition of the H_2O_2 by heat: Apart from the shorter cycle times (shortened injection, shortened aeration), the use of H_2O_2 is also reduced by approx. 40 percent, and the material loads are considerably lower.
- STISO based on ergonomic studies: Comfortable working positions and good accessibility of the isolator zones for 95 percent of the operators – without mock-ups.
- Other advantages are the modular design and "Plug & Test" with much easier installation. Integrated temperature control, yet temperature-neutral in the installation room and without affecting the pressure conditions in the installation room.
- Integrated Wi-Fi glove testing system and self-test function for test plates

SAFETY

Fig. 1: Percentage distribution by measured droplet size

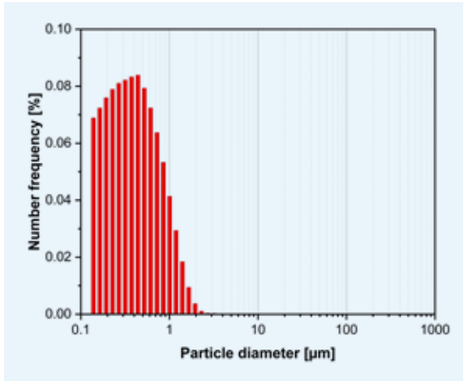


Fig. 2: Flash Evaporation (left): The chemical indicators here stay primarily magenta. In Atomization-driven Evaporation (DECOpulse®) magenta turns yellow – the chemical indicators change colour even in difficult locations. This confirms consistent wetting with H_2O_2. (Dotted boxes: Air return ducts. Comparable bio-decontamination cycles with 11- and 10-minute injection time of H_2O_2).

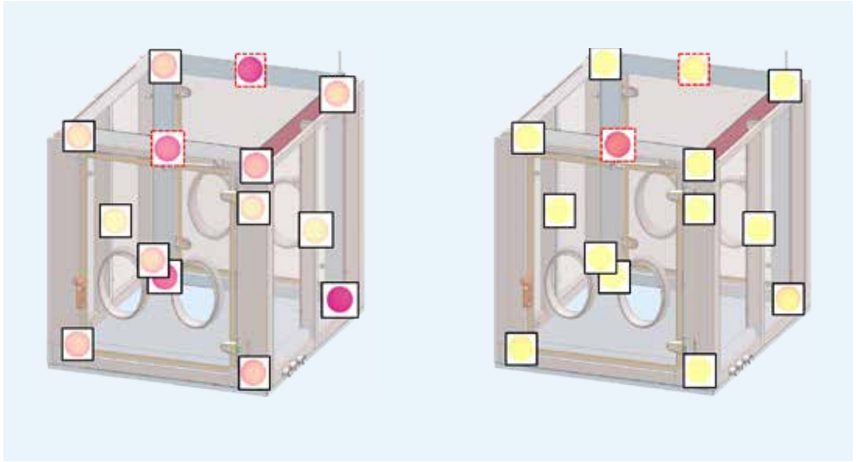
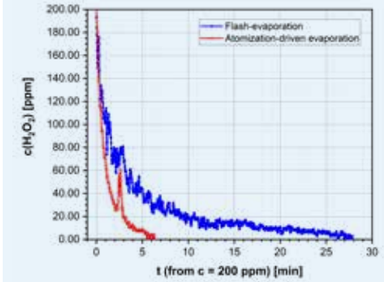


Fig. 3: The time advantage in ventilation: This effect is particularly visible at concentrations of 200 ppm and below. The curves of the Atomization-driven Evaporation and the Flash Evaporation (DECOjet®) move apart. (Remark: The peak in the progression of the red curve at approx. 2.5 min is the result of the process-related rinsing of the decontamination system with compressed air.)



parameters that need to be satisfied during injection to ensure the desired droplet sizes and turbulence for distribution in the plenum. A specific control system, for the valves, for example, and a "loop" through which the injection nozzles are supplied with the medium are further elements of DECOpulse®, which has a patent pending. One important aspect is that the H_2O_2 vaporizes and thus the general principles of gas phase decontamination systems take effect. Above all, the resulting processes of adsorption and desorption of the H_2O_2 molecules ensure an even distribution on the surfaces in the isolator room.

The size distributions of the droplets produced were determined during the development phase. This has ensured that with properly selected operating parameters, the achieved microdrop size is actually below the desired d < 3 µm. The diffraction of laser radiation at the microdroplets was measured to determine the corresponding size distribution. An example of the distribution is shown in Fig. 1. In this case 99.9 percent of the microdroplets in the final system have a diameter d < 3 µm! By taking measurements at different distances from the nozzle, the evaporation of the droplets can also be determined. By means of light scattering, the eye can perceive how the H_2O_2 spray mist moves away from the nozzle and gradually "disappears" as the microdroplets change into the gas phase. Thus the evaporation of H_2O_2 is achieved as desired with no active heating. Evaporation is achieved by atomizing the liquid, which is why Metall+Plastic calls this process "Atomization-driven Evaporation".

In addition, the R&D team of Metall+Plastic has researched the spatial distribution of H_2O_2 in a typical isolator geometry and the homogeneous surface wetting. As a comparison, bio-decontamination with DECOjet® and the flash evaporation system integrated here was used, which can be described as a hitherto market-leading system from Metall+Plastic which will continue to be installed upon request.

Hard facts

Chemical indicators that react by colour to H_2O_2 were placed at identical and in particularly hard-to-reach points in the isolator. Examples of these are corners or zones at and between glove openings (Fig. 2). The result are manifest in the truest sense of the word. The goal is to change the magenta colour of the indicators to yellow; which indicates complete wetting with H_2O_2. If one observes two cycles with a short comparable injection time, this is not completely successful in flash evaporation regardless of indicator placement. Multiple indicators retain their original color. In contrast, Atomization-driven Evaporation with DECOpulse® produces complete coverage: All the indicators are yellow, only one of them still shows a minimal presence of magenta. This convincingly demonstrates the very uniform wetting with H_2O_2 that can be achieved with the new system, even in complex geometries. This comparison is particularly meaningful where pharmaceutical safety is concerned. Furthermore, the D-values of the two systems were examined using biological indicators. In this case, the comparison yields a value of 0.86 min for Flash Evaporation, whereas Atomization-driven Evaporation with DECOpulse® takes only 0.47 minutes.

Another comparison: Aerosols and micro-aerosols, both of which are currently in use in today's bio-decontamination systems, have diameters (d) of about 100 µm to 1,000 µm and about 10 µm to 100 µm respectively and therefore do not directly vaporize at room temperature. The structure means that a more uneven distribution then takes place, especially in complex geometries. Thus there is a basic physical system difference and advantage for DECOpulse® compared to other aerosol-based systems.

It is also interesting to note that DECOpulse® (in comparison to DECOjet®) reduces the use of H_2O_2 by about 40 percent. This is particularly visible in the shorter aeration time as part of the decontamination cycle (Fig. 3). The curves in the diagram diverge significantly from each other from a concentration of 200 ppm. DECOpulse® demonstrates a time advantage of approx. 21 minutes for reduction to 1 ppm. A further 30 minutes are saved in the subsequent investigated range of reduction from 1.0 to 0.1 ppm. In practice, H_2O_2 concentrations ranging from 0.1 to 0.03 ppm are currently demanded. We expect that, even at these extremely low concentrations, the trend towards saving time will continue and even accelerate. (The times given are based on comparable bio-decontamination cycles with a 10-log reduction when the isolator is loaded). The reduced use of H_2O_2 also results in lower outgassing effects, which reduces the risk that H_2O_2 residues will affect the sterile testing process and also reduces material stress.

D-value: Sterility is taken to mean the absence of microorganisms. 100 percent sterility cannot be obtained in practice, so the decimal reduction time D (D-value) is a common standard. In pharmaceutical sterile processing, the minimum requirements are a 4-6 log reduction. In individual cases up to 12 log reductions are required.

Mission accomplished, award received

Pharmaceutical safety is significantly increased, cycle times are significantly reduced – thus STISO with DECOpulse® , has positioned itself as the benchmark system. By the way, the jury of the Interphex Exhibitor Awards has also recognized the advantages of DECOpulse® and has awarded the system the "Biotech Innovation Award 2019". But the STISO with DECOpulse® has even more advantages to offer.

A sterility test isolator is ultimately a workstation, so it is important to be able to work there comfortably and in safety for several hours.

While the STISO was still in the development phase, Metall+Plastic commissioned an ergonomic study. This has led to some important benefits: Today, about 95 percent of all potential operators reach all areas of the system using glove access. The STISO working positions can be adjusted for sitting and standing, and the angled front glass creates more distance to the glass, which also facilitates better ergonomic posture when working on the sterility test isolator.

Working as a team with the STISO

The STISO can be designed in a modular way with a flexible number of glove accesses, with or without material transfer chamber or, if required, with left or right wall connection. The greatly simplified ("Plug & Test") installation is facilitated by eliminating connections to the building services engineering. All it needs are power, compressed air and cold water connections. The STISO is unaffected by possible fluctuations in room temperature. The integrated heat exchanger system simultaneously ensures that no heat is released into the room and pressure conditions remain constant. The glove test plates are equipped with a Wi-Fi function for wireless testing. A self-test ensures that the glove tests are carried out correctly.

The first STISOs with DECOpulse® were delivered in late 2019. Right now, there are many more STISOs with DECOpulse® in the pipeline or under construction – as well as many production isolators with DECOpulse® as the new standard.

PUPSIT: TEST FILTER!

PUPSIT filter tests are a regulatory requirement in pharmaceutical production for European markets. Which options and strategies there are for this in systems engineering, what needs special attention in the design, and further background information will be presented below.

An explanation of EMA, why the agency considers PUPSIT to be mandatory, can be found at: https://bit.ly/3hJCflU

Extensive information on a PDA work group, which deals specifically with PUPSIT and the subject "Filter Flaw Masking", can be found at: https://bit.ly/2X0hJMg ❯

PUPSIT describes a process for filter tests, specifically and exclusively for product filters. "Pre-use post sterilize integrity testing" – indicates that the disposable filters will be tested for integrity after installation and sterilization, yet prior to use. This will ensure that the filter unit tested by the filter manufacturer (and possibly pre-sterilized) was not damaged during handling or installation, but especially not by the sterilization process in the system. A second filter test must be carried out at the end of a batch to reconfirm the correct condition.

PUPSIT has been and is still a controversial issue. The fact is that the European Medicines Agency (EMA) makes the implementation of PUPSIT filter tests for sterile medicinal products for the European market compulsory, while the American FDA does not stipulate this for its home market. Actually, even among experts of the PDA (Parenteral Drug Association) for example, further data evidence is requested to be able to better weigh the advantages and potential risks, which cannot be ruled out when conducting PUPSIT tests. One thing is certain: Anyone planning a system today must adhere to the regulations, which – as outlined – are clear.

Steam sterilization stresses the filter material

In the CIP/SIP applications (Clean-in-Place/Sterilize-in-Place) the sterilization process is compulsory, since the product filter is manually built into a non-sterile system at the designated place at this point in time. The SIP process ensures that the microbiological contamination (load) in the complete system, in filters and pipework, is reduced to the regulatorily intended sterile level. The steam sterilization applied at temperatures over 121 °C stresses the filter material and the pressure difference, which a filter withstands during steam sterilization, is clearly lower than at room temperature. Consequently, the test seems to be entirely appropriate at this point – just like a test that is carried out after production.

More on this in EU GMP Annex 1 Revision: Manufacture of Sterile Medicinal Products (Draft) under chapter 8.88: https://bit.ly/2EhArbt ❯

The filter integrity test works and proceeds as follows: It is crucial that a built-in filter is initially completely moistened. Only in this state will the filter material develop enough airtightness to prevent almost uninhibited air flow through the filter. This condition is used by increasing air pressure on the filter with a special test device. As a criterion for integrity, the airflow or the pressure drop is measured via the filter membrane.

The integrity of the filter can be verified on the basis of these two principles. During the bubble point test, the pressure limit is determined by the point at which an air bubble is formed through the gas (pressure drop) on the sterile side of the filter. The slightly gentler forward flow test measures the flow rate of the airflow exiting from the back. In both cases the specific measuring devices record this data, which is used in turn to clearly determine the filter integrity.

A silver bullet?

A key question for executing the PUPSIT is whether the filter should be moistened with Water for Injection (WFI) or with the product itself? Both variants demonstrate various features, which will be treated below.

First, the process with WFI: This comes with certain challenges for sterile handling. Because the WFI must be fed through the previously steam-sterilized product pipe, a previously closed sterile system. This system is "interrupted" again for the connection between WFI container and product pipe, to dock a container, which must be considered as a potential source of contamination.

There is also the issue of the aseptic level of the WFI used. Its quality is defined, but the low aseptic level of a steam sterilization is not reached via distillation or membrane technology, according to critics. Also, during the PUPSIT test method the WFI must have a temperature of 20 °C. If the WFI was generated using distillation, this must first

CIP/SIP cabinet with double product filtration. According to European regulations PUPSIT filter tests are mandatory.

IMPORTANT FOR YOU

- Product filter tests according to the PUPSIT principle are mandatory for all medicinal products, which are to be manufactured by Aseptic Processing and distributed on European markets.
- The PUPSIT tests can be conducted in the system with WFI or with the medicinal product. Both methods have advantages and disadvantages.
- One solution can consist of preparing systems for both methods. A subsequent change is unrealistic.
- Also, with regard to new systems potentially used for the sterile production for European markets, a decision about PUPSIT test options should be made during the design stage.
- Optima integrates special screens into the air inlet for the filter tests, in order to minimize the risk of filter damage at this point.
- The filter test devices can be integrated into the system control or have their own control and operating panel.

A safe pharmaceutical quality depends not least on disposable product filters in Aseptic Processing. After manual installation in the systems these are always steam-sterilized.

cool off again, which involves a certain waiting period and thus a certain risk of germination. At this connection point, another filter is therefore often installed for the WFI or also for the air introduced, to ensure pharmaceutical safety. In addition, it must be noted that WFI can still be found in the system after the test. A drying process ensures that during the filling process with pharmaceuticals, the undiluted quality of the medicinal product required is achieved as quickly as possible and only a minimum of product will be discarded.

The PUPSIT process with product creates its own challenges. Here the complexity increases in proportion, depending on how many different products are processed on one machine. Every product type has specific flow properties, meaning that the parameters which are recorded and provide information regarding the leak tightness of the filter, are dependent on the product and must be specifically defined for it. Particularly with the ever more specific medicinal products or machines, which are designed for a wide range of products, this can entail considerable effort. Increasingly more sensitive medicinal products are being processed that require cooling. This can make a filter test with product difficult, if not impossible, if this needs to be processed cooled, although the test, as mentioned, requires 20 °C. Another argument that can be used against tests with product is that in the case of a damaged filter the machine is already practically in production mode, this needs to be interrupted and the tests and preparations must be restarted. This also represents additional effort compared to tests with WFI.

Decision scenarios

Testing no type in particular can be viewed per se as the better option. The individual conditions under which a system is designed will decide on this. In fact, Optima is currently building predominantly systems which handle both test types. This is often advisable, if various application scenarios are conceivable over the time horizon of system use. Because one thing is certain: Subsequent conversion of an existing certified and validated piping system with SIP entails a very great effort, which should be avoided wherever possible. The same applies to the decision of companies considering a market entry into Europe. The decision should be made for or against the implementation of PUPSIT tests during the design phase. Any subsequent change to the system is hardly realistic.

The question regarding what the options are for companies that manufacture on their machines for European markets as well as the US market is also interesting. It is certain that the technical requirements for carrying out PUPSIT filter tests on such systems must be met, and that these must be verifiably performed during production for European markets. Which strategies these companies apply, if producing on the same systems for the US market, is open and remains an individual decision for each company.

On the system side, there is ultimately another design option which produces no difference in terms of function. The control of the filter tester, which measures and evaluates parameters, can be integrated into the system and operated via the HMI. This dispenses with individual manual work steps, which are required for connecting the tester. The control, however, also can remain attached to the testing device itself and brought with it to the point of use. This decision has no effect on the actual test and the test procedure.

Finally, it is worth noting that the system manufacturer should ensure the blow-drying of filter cartridges after a test with WFI is as gentle as possible. There is also the risk of damaging the filters, which in this case, however – unlike with steam sterilization – would only be detected after completion of a batch. Optima thus equips the air inlet with special screens, to optimize pharmaceutical safety.

New headquarters of the European Medicines Agency (EMA) in Amsterdam, which opened at the end of 2019. The EMA is responsible for the regulation of European pharmaceuticals markets.

THREE ASPECTS OF DIGITALIZATION

Digitalization involves a lot more than just the collection and networking of data. It means that many tools can be used to help pharmaceutical manufacturers achieve their goals. The focus is on maximizing plant availability and high production reliability. To achieve this, Optima Pharma is pursuing three principal strategies.

One good reason to use digitalization methods is that products are becoming more and more customized. The impact is even more marked with high-priced products manufactured using complex machines or systems. This means that numerous pharmaceutical companies are now showing great interest in the optimization possibilities that can be opened up by digitalizing production.

The automation experts at Optima Pharma have been developing the tools to do this for some time, consistently focusing on the customer benefits. Heiko Ellwanger, Director Automation Technology, stresses: "We are interested in concrete use cases which create a commensurately major advantage for our customers." In particular, advances in system availability could be achieved using digitalization tools. In the past, an important goal has been maximum yield (minimum waste) with high output, and this is now achievable even more than before with the help of certain digitalization products. Further requirements arise from customized medicine.

There are three aspects of digitalization that are generating sustainable benefits in pharmaceutical production: firstly, what is known as "Manufacturing Intelligence". It involves the comprehensive generation and management of the data that is produced in the course of production. Aspect number two is the support provided during the production process to minimize operator risks. The third aspect relates to improvements in maintenance. Here digitalization has a particularly positive effect on maintenance planning, and also brings with it economic and ecological advantages.

Digital aspect 1: The added bonus in terms of product and process safety

More than in any other industry, manufacturers in the pharmaceutical sector have an obligation to ensure product safety and to provide proof of it. Pharmaceutical companies ensure that this is true for every syringe, cartridge, ampoule or vial by recording and storing all the relevant production data. The shift towards more personalized medicine makes this even more important. Especially in critical process steps, the traceability of process data means that the transparency needed for product quality can be ensured. The basic purpose of digitalization is to make data available, to store it appropriately and to be able to reproduce it in an orderly, contextualized way. This means that the historical data for each individual product can be traced right from the raw materials, through production and filling right up to delivery. This is a bonus in terms of safety, not just for patients, but also for the manufacturer.

› Manufacturing Intelligence: Successful management of production data massively increases product and process safety for manufacturers and patients.

Digital aspect 2: Reduction in operator risks

A variety of digitalization tools are designed to make life as easy as possible for system operators and technicians. Support that leads to fewer mistakes or helps them to carry out their tasks faster and more reliably has several positive effects. The process of machine changeover between individual production batches or cycles can be relatively prone to errors. Especially when isolators are being used, a defect that is only discovered during the decontamination cycle is very time consuming. This does not just torpedo production planning, particularly with products that have to be filled within a specific time frame. Reduced plant availability also significantly reduces output and hence profits in highly priced products.

With the need for numerous interventions by the operator during production, format changes, line clearance, etc., it is therefore necessary to "lead the operator by the hand" using a range of digital tools. The level of support can be adapted to the operator's level of training and knowledge. This can be done by simply showing them the SOP (Standard Operating Procedure) on the machine HMI or even by showing them what to do step by step with the aid of augmented reality glasses in their field of vision. This dramatically minimizes potential errors. Digital instruments can also be used to record the activities actually being performed. This is particularly helpful when questions about the precise procedure arise in the post-production phase.

Digital aspect 3: Predictive, sustainable maintenance

Quite a lot of the data which is generated anyway in the course of production or that can be additionally collected as required can be used in the long term for maintenance. The relevant operators or modules of the machine are monitored with special sensor technology on the basis of a weak-point analysis. Presenting the trend development of certain parameters, when combined with expert knowledge, makes it easier to predict when a component will reach the end of its life cycle – and take action before it happens. Predictive maintenance and servicing do not just involve identifying the optimum time to make replacements. It means that the maintenance schedule can be planned in a targeted manner. Furthermore, components are no longer changed unnecessarily or too early, and that is to be encouraged in the interests of sustainability. But above all, predictive maintenance is an effective way of preventing unplanned plant shutdowns and machine failures.

IMPORTANT FOR YOU

How to make effective use of digitalization in pharmaceutical production

- Use Manufacturing Intelligence to make production data available and assess it in the right context. This creates added value for product and process safety.
- Simplify the work of plant operators and technicians by providing them with instructions, video tutorials and documents etc. in digital formats. This keeps operator errors to a minimum and in doing so increases plant availability.
- Benefit from digital maintenance tools which, together with generating the appropriate data, provide insights into condition-based component monitoring. This makes predictive maintenance possible.
- Digitalization allows you to benefit from greater process transparency and security over the complete life cycle of the system.

DIGITALIZATION

Remote Support: Optima experts support operators via video and audio transmission for troubleshooting, format changes and maintenance work.

Smart format changes: Scanning format parts ensures that the correct parts are used.

Cameras allow observation of the machine interior, fast intervention and analysis.

Advancing digitalization

The potential of digitalization is by no means limited to these three aspects. However, over the past two years, there are use cases that have already been rolled out in several Optima Pharma projects. Above all, the pharmaceutical industry's desire is to make processes as transparent as possible. Due to broad data acquisition and structured storage, it is possible, for example, to get to the bottom of errors afterwards in order for them to be eradicated in the future. For example, where a product in the quality laboratory does not meet the required specifications. When all factors affecting quality are available as a data collection, a successful analysis is possible, and any errors can be corrected. This idea is not a radically new one, but it can only be implemented if there is enough computing power.

Software and hardware, IT and OT (Operation Technology) play a twin role. Data acquisition is just as important as graphic representation. In the near future, artificial intelligence (AI) will also play a key role. Heiko Ellwanger explains: "A specialist is frequently able to interpret new trends. With AI that has been properly trained, a machine operator is also able to do this." For example, a torque curve of an engine can be used to predict a component failure. Or even more importantly, in the pharmaceutical sector: Using trend graphs showing specific process values such as temperatures and pressures, it is possible to identify the critical status of the entire process, which could otherwise lead to out-of-spec products. The specialist, or alternatively the AI, can initiate timely countermeasures.

Digitalization plays an increasingly important role in changeover and line clearance. For example, product paths are exchanged or emptied and packaging materials are removed. Finally, the system is cleaned and sterilized before the next cycle can be performed. Marcel Biedermann, Project Engineering Manager at Optima Pharma, says: "There are massive risks here that can severely affect the production process. So we also support the operator here using digital technology." With the aid of virtual techniques, they can identify critical points more quickly, for instance. The most important thing is to guide them digitally through the SOP as specified by the customer.

Cameras: An extra pair of eyes for the production manager

Cameras also have a role to play. When they are placed within the system, they allow the machine interior to be observed. This means that the production manager can always keep an eye on the process from their office. If necessary, they can quickly intervene. High-speed cameras also provide clarity when looking back at recordings. With camera support, critical processes can be precisely analyzed during machine setup or in the event of a malfunction.

All the services that offer digital production support will be successively enhanced. An important part of this is Operation Support, which supports operators with video tutorials. For instance, the tools for error analysis, for example with the aid of cameras, are grouped together under Data Management. Changeover Support encompasses the services for a more secure format changeover, and with "Digital Documentation", Optima Pharma provides support for technicians and operators with comprehensive technical information including circuit diagrams, P&ID schematics, operating instructions, etc.

Time to Market: CSPE to accelerate the process

The customer is not the only one who benefits from digitalization. Even Optima Pharma itself benefits. "The CSPE package is essential for our engineering," says Ellwanger. CSPE stands for Comprehensive Scientific Process Engineering, and it covers a wide range of tools that act as catalysts from the concept phase and integrated FAT to the operation and modernization phases. As well as digital engineering and simulation, the engineers are also using virtual reality to build up a picture of the plant at an early planning stage. Some customers have already benefited from the digital mockup, which has proven to be particularly useful in the COVID-19 pandemic. Finally, what takes place in the CSPE Center is not digital and virtual at all: an integrated FAT (iFAT) that merits its name – thanks to the provision of process heat, demineralized water and compressed air. In the wake of the COVID-19 pandemic with its strict travel restrictions, iFATs have already been provided with virtual technology that has enabled customers to be "live" at every step without the need to travel.

All CSPE instruments are designed to achieve the shortest possible time to market. Depending on the project, they can speed them up by up to six months. "First and foremost, the customers benefit from this, and so of course the patients do too," says Biedermann. After all, if a newly approved drug comes onto the market earlier every week, that's worth a lot to everyone involved. The knowledge gained by Optima Pharma's planners and engineers with every CSPE cycle cannot be underestimated. Biedermann reports: "We are becoming increasingly successful in optimizing processes and speeding up commissioning."

Digitalization: Not an end in itself, but rather added value

This in turn creates added value for the customer. Just like digital instruments for production provided by Optima Pharma. "For us, digitalization is not an end in itself, it's not just some playground where we want to sound out the limits," emphasizes Ellwanger. "All the digital tools always need to deliver a benefit to the customer. Once we recognize this, we will be able to implement the possibilities of digitalization quickly and convincingly."

REFRIGERANTS: NEW WAYS TO REACH THE GOAL

How can we slow down and halt climate change? This question only rarely makes it as far as pharmaceutical manufacturing. However, "classic" refrigerants used in freeze-drying systems are harmful to the environment. What is known as the F-gas Regulation set the course for the European Union as early as 2014, and is still impacting the design of freeze-drying plants today. Optima provides solutions.

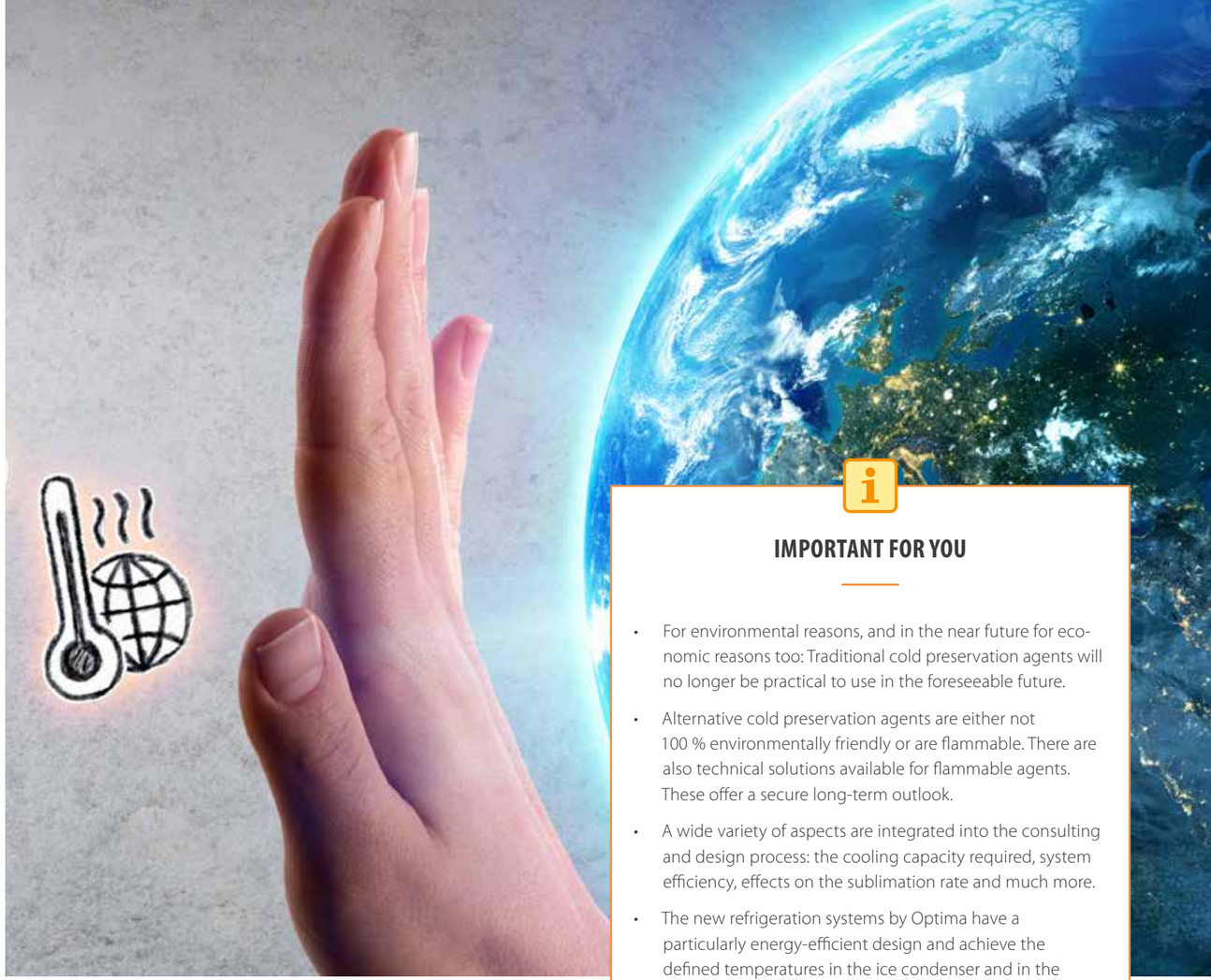
It is known that refrigerants such as R404A are damaging to the climate. The "Global Warming Potential", or GWP for short, provides information on this. For instance, R404A has been widely used for years, and has a high GWP value of 3922.

A generalized ban from 2020 on refilling refrigerants with a GWP in excess of 2,500 recently had additions by way of exceptions that apply to freeze-drying systems, among other things (Annex III dated 1 January 2020). Nonetheless, experts anticipate that their output will be reduced, and resources such as R404A will become massively more expensive, because the ban will remain in place for the majority of applications. Aside from considerations regarding climate protection, it will no longer be possible to use these refrigerants in a viable way in the medium to long term, even from an economic point of view.

The alternatives

The chemical industry is carrying out extensive research into finding alternatives to using refrigerants that damage the climate, and it is creating innovations. However, up to now all of these have all had one major drawback: they are flammable. By way of comparison: Here the GWP values range from 6 (R170) to 146 (R455A), which means they do indeed meet climate-friendly requirements. However, freeze-drying systems need to be specifically designed in order to safely use these refrigerants. In this case, the solution is a secondary circuit for the ice condenser (see diagram on page 45).

Furthermore, there are non-flammable refrigerants that comply with EU regulations and have a GWP value of less than 2,500. These include R410A which has a GWP of 2088. In all likelihood this will remain available in the medium term, at least for another ten years or so. R448A, which is also non-flammable and is also likely to be available in the longer term, has a GWP value of 1387.



IMPORTANT FOR YOU

- For environmental reasons, and in the near future for economic reasons too: Traditional cold preservation agents will no longer be practical to use in the foreseeable future.
- Alternative cold preservation agents are either not 100 % environmentally friendly or are flammable. There are also technical solutions available for flammable agents. These offer a secure long-term outlook.
- A wide variety of aspects are integrated into the consulting and design process: the cooling capacity required, system efficiency, effects on the sublimation rate and much more.
- The new refrigeration systems by Optima have a particularly energy-efficient design and achieve the defined temperatures in the ice condenser and in the installation surfaces with extreme precision.

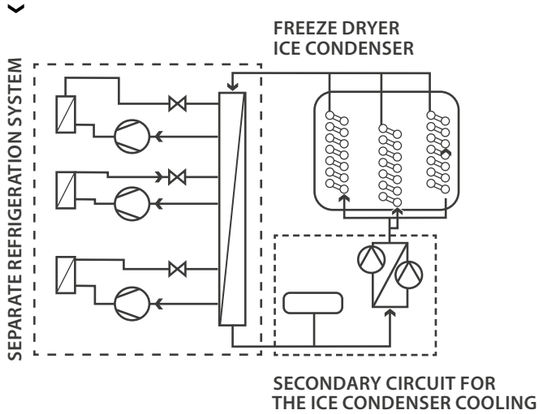
These refrigerants represent progress in terms of climate protection, compared to their "predecessors", but they are not a solution, so if you are fully committed to climate protection, there will be no alternative to flammable refrigerants in the foreseeable future.

Advice and planning

In the meantime, there are a number of different ways to provide plant operators with an individually customized solution. Depending on life expectancy and other criteria, it may even make sense to consider retrofitting existing freeze-drying systems. The following overview provides an introduction to the different approaches:

- **LN2 refrigerants:** This technically proven solution has been known for years and is future-proof in terms of the F-gas Regulation. The investment costs in relation to the refrigeration system are lower here compared to the following solutions, but the consumption costs increase the

Indirect ice condenser cooling: Flammable refrigerants are located in the refrigeration system. The refrigeration system cools the silicone oil that flows through the ice condenser's cooling coils. The cooling coils in the ice condenser have to be adapted for this.



New solutions for alternative refrigerants: If these are flammable, specific refrigeration systems are required for freeze-drying. Refrigeration systems from Optima are also particularly energy efficient. ❯

❮ The F-gas Regulation calls for a rethink in designing freeze-drying systems.

more often the system is used. This means that freeze-drying plants with LN2 refrigerants must be adapted to meet the operator's operating scenario. This solution is suitable for new projects. However, with minimal effort, existing plants for climate-damaging refrigerants could also be converted to an LN2 system.

- For the use of **refrigerants** which are expected to be available in the medium term, such as R410A, and refrigerants available in the longer term, such as R448A: Both are **non-flammable, but neither is completely environmentally friendly:**

There are two variations that can be considered; direct and indirect cooling of the ice condenser. From a technical point of view, the indirect cooling of the ice condenser makes the system future-proof. Here the refrigeration system is designed to provide indirect cooling of the ice condenser. Flammable refrigerants can also be used at a later date by replacing the refrigeration system.

It is not yet possible to say whether the classic design where the ice condenser is cooled directly will require future design changes to the ice condenser in order to comply in the long term with the F-gas Regulation. First and foremost, with this solution the investment costs are lower than with the solution referred to above. However, retrofitting could be technically complex or even technically impossible. Should a retrofit of the ice condenser be deemed necessary and technically possible, the total investment will be greater than for indirect cooling of the ice condenser, which will be implemented immediately. The operating costs for both variants are higher (approx. +10 to +30 percent compared to conventional freeze-drying systems.

- **Solutions for flammable, environmentally friendly refrigerants:** It is still possible that the chemical industry will be able to find the silver bullet, which in this case means refrigerants that are both non-flammable and completely environmentally friendly. For those who do not want to rely on this and who already prefer a comprehensive, future-proof, environmentally friendly variant today, they could design their refrigeration system as a cascade system, for example. In addition, the indirect cooling of the ice condenser must also be carried out here via a second circuit. Investment costs are higher than those for classic freeze-drying plants (up to +40 percent higher). Operating costs are also higher by around 30 percent.

Lower energy consumption: new refrigeration system

In the design of refrigeration systems, there are variations that can satisfy specific user needs in the most effective way, including the latest innovations. For the first time, Optima is offering refrigeration systems that have been developed in-house and that are specially designed for use with flammable, climate-friendly refrigerants as cascade systems. Another new variant is the Mirai system, which uses air as the "refrigerant".

There are differences in performance and efficiency depending on the system. The cooling capacity for the installation areas and the ice condenser in the air system, for example, is up to 50 kW per module. The Optima refrigeration system Module 4 delivers up to 37 kW; the Optima Module 5 up to 74 kW per module; both are for flammable refrigerants. The effectiveness of cold generation for primary drying (the proportion of cooling capacity to the power required) also needs to be taken into consideration. Here, compared with other systems, the two Optima modules demonstrate very good results. The investment costs are a significant factor, to say the least.

It is also clear that the new Optima systems' energy consumption, as well as the energy consumed by the air chillers, has been massively reduced by the use of frequency converters. Only the energy that is actually required is consumed here, and this varies significantly depending on the phase of the freeze-drying process. The precision of the temperature reached has also been substantially improved. This is less than ±1 K in the range of the setting plate temperature.

The right technology and good advice are essential

There are other important factors: The refrigerants have an effect on the cooling capacity of the particular technology. Compared to the traditional refrigerant R404A (100 percent), the alternative refrigerants reach values of 64 to 149 percent (both using a reciprocating compressor). For companies who do not shy away from making financial investments, the use of air chillers is an additional option to achieve the required cooling capacity.

Under the F-gas Regulation, new framework conditions apply to the design of freeze-drying systems. Optima addresses this situation with a variety of system concepts. There is no one perfect solution, but with the variants mentioned above, Optima is well prepared for any new situations. Optimal solutions are created by working in close cooperation and in strong consultation with the user.

THE FUTURE MARKET OF CELL AND GENE THERAPIES IN NUMBERS

> 1,000

regenerative therapies are in clinical trials at the end of 2019.

10–20

approvals for regenerative therapies annually for the next five years.

13

billion euros, the market share of cell and gene therapeutics will be 2025.

33

percent annual market growth for cell therapeutics from 2017 to 2025.

Sources: Alliance for Regenerative Medicine/FDA/Frost & Sullivan

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