O-COM

THE OPTIMA MAGAZINE

ACHEMA 2022

CSPE 2.0, DIGITAL FEATURES, CLIMATE-FRIENDLY REFRIGERATION

SOLUTIONS FOR EFFICIENT PROCESSES

EN pharma | December 2022

LEGAL NOTICE

o-com is the current communications service
of OPTIMA packaging group GmbH

OPTIMA packaging group GmbH
Steinbeisweg 20 | 74523 Schwaebisch Hall | Germany

OPTIMA pharma GmbH
Otto-Hahn-Straße 1 I 74523 Schwaebisch Hall I Germany

Editorial Team
Jan Deininger, Felix Henning

Responsible for content according to German media law
Hans Bühler

ACHEMA 2022: A BRILLIANT NEW START

Gerhard Breu
Chairman,
Optima Pharma Division

Dear readers,

What does it take to ensure a successful trade show presence? New machines, efficient as well as climate-friendly technologies and innovations, an interested professional audience with many in-depth questions and highly motivated Optima employees. You could experience all of this as a whole at ACHEMA 2022 in Frankfurt am Main.

Couldn't make it this time? No problem! In this issue of Optima's o-com magazine, we've consolidated all of our current focus topics for you. Gain insight into the solutions we at Optima Pharma have found to address the current challenges of our time.

Alongside a review of ACHEMA, other highlights await you in this issue: Find out how we can make your production even safer and more efficient thanks to digital features. In addition, we have further expanded our turnkey success formula Comprehensive Scientific Process Engineering (CSPE) into CSPE 2.0. This full service package has also impressed our partners at Thermo Fisher Scientific VVS, for whom we have implemented an OPTIMA FillCell for viral vectors with an isolator. Read for yourself what made this project so exciting.

Enjoy reading!

Yours,
Gerhard Breu

14 Looking back at ACHEMA

ACHEMA again at last! In our cover article, we look back together on this successful event that finally took place again in person at the end of August 2022.

8 CSPE 2.0

More efficient, faster, more comprehensive – the CSPE approach from Optima Pharma is being further optimized under the name CSPE 2.0. Read this article to find out how we are extending the successful concept for turnkey projects.

18 Digitalization

What may still sound like a buzzword has long since become reality in pharmaceutical production. Digital features add real value when it comes to production data management, maintenance, operator guidance and knowledge transfer. Read how it can make your production safer and more efficient.

NEWS

Optima received the "CO_2-neutral company" label from the climate foundation Baden-Wuerttemberg. From left to right: Dr. Stefan König, Managing Director, Julia Kovar-Mühlhausen, Head of Climate Foundation Baden-Wuerttemberg, Dr. Patrick Rapp, Secretary of State for the Ministry of Economic Affairs, Labour and Housing Baden-Wuerttemberg, Hans Buehler, Managing Director/CEO, Dominik Broellochs, Business Development Manager Sustainability.

Environmental and climate strategy with measurable goals and successes

Optima complemented its existing sustainability strategy with a holistic environmental and climate strategy. This means new measurable steps, and milestones that already have been implemented, become transparent. With consistent use of renewable energies, Optima has been able to reduce greenhouse gas emissions by 40% to date. A comprehensive package of measures will reduce the climate footprint by an additional 25% by 2030. In addition, all German locations have been working net-climate-neutral since 2022. As a result, Optima also assumes responsibility for currently non-reducible and non-avoidable greenhouse gas emissions. Starting in 2023, Optima will be able to determine the individual climate footprint of customer projects, implement reduction measures in cooperation with customers and, through residual compensation, deliver net-climate-neutral machines and systems. Additional environmental measures will be implemented in the future.

More space for isolators and freeze drying

Additional space was created at the Optima Pharma location in Mornshausen for the growth of pharmaceutical freeze drying. More than 1,000 square meters of assembly area have been added, an increase of 50%. Now the Radolfzell site, the manufacturing site of the Metall+Plastic isolators and decontamination technology, will follow with an expansion. A new assembly hall with 1,800 square meters and a new administration wing with 600 square meters will supplement the existing building in the future.

New service location in the USA

Fast delivery of spare parts, remote support, on-site service calls, maintenance work and system qualification, as well as training training of operating personnel at customer sites are now among the tasks of the new Optima Pharma "Service Hub" in Raleigh (North Carolina). The new location is close to the manufacturing sites of many pharmaceutical companies and Optima customers, and perfectly complements the Optima subsidiary in Green Bay, Wisconsin. In addition, the number of service employees for North America is expected to triple by the end of the year.

100 YEARS of FUTURE

Photo: Ufuk Arslan

"100 Years of Future": Anniversary celebration and inauguration of the CSPE Center

The opening of the Optima Pharma CSPE Center II in May 2022 was celebrated together with Optima's 100th anniversary. The CSPE Center II is an important chapter in a remarkable and long success story. Millions were invested to provide customers with a new level of system integration in turnkey projects. For the first time, freeze dryers can also be assembled in the new hall. The Minister-Presidentof Baden-Wuerttemberg Winfried Kretschmann took part in the anniversary celebration "Years of Future" as a guest of honor. He congratulated with the words: "Companies like Optima are beacons. They accept every challenge, reinvent themselves again and again and still put their heart and soul into their work – and have been for 100 years. They took action in the transformation processes that profoundly shape our economy, in digitalization, and sustainability."

The assembly of glass syringes requires the highest level of precision.

New machine for glass syringe assembly

Optima Automation presents a new assembly machine for glass syringes. Maximum precision is an essential feature to process safe-to-use syringes. Product-friendly processes, individual dosing and curing technologies, as well as comprehensive quality and process controls are central features of the new OPTIMA GSM.

Review: ACHEMA 2022 in Frankfurt

"ACHEMA again at last" was the unofficial motto of the 2022 show. The Optima Pharma team was happy to be at the show in person again to discuss the latest technologies and innovations in fill & finish, freeze-drying and containment. From digitalization and flexibility, to turnkey competence, and cell and gene therapies – there was much to discover in the Optima Expert Zones.

GO INTO PRODUCTION EVEN FASTER WITH CSPE 2.0

Even more efficient, faster and more comprehensive – Optima Pharma's CSPE approach is undergoing further optimization under the name CSPE 2.0. With the valuable experience gained from numerous projects, we are continuing to expand the successful concept for our customers and are creating the right conditions for it. The new CSPE Center II now provides 4,300 square meters more space for assembly, commissioning and qualification testing of filling and closing equipment, isolators – and now freeze dryers too. Delivering fully tested turnkey systems saves time on site and means that production can be launched more quickly and reliably.

IMPORTANT FOR YOU

- CSPE: a comprehensive, scientific process bringing significantly faster, safer production start-up to turnkey lines
- With CSPE 2.0, the process is being enhanced even more.
- CSPE 2.0 largely encompasses installation and operational qualification as well as parts of performance qualification.
- Now it is also possible to integrate freeze-drying systems.
- An additional CSPE Center is now providing an additional 4,300 square meters of space for turnkey systems.
- Optima Pharma's service network is being expanded to provide worldwide coverage.

The CSPE (Comprehensive Scientific Process Engineering) approach is a comprehensive, science-based concept that reduces the time from system design to production start-up. Optima Pharma has developed the CSPE concept to do everything in its power to reduce the time-to-market for its customers' products while maintaining the highest possible quality at delivery. As a comprehensive system provider, Optima Pharma now handles further qualification measures in-house, including significant further parts of cycle development. This significantly reduces the time needed between installation and the start of production at the customer's site, thereby cutting the overall time for customers from product development to market launch.
As of this year, Optima Pharma has considerably more space to carry out this comprehensive work. The new CSPE Center II was opened in May 2022 at Optima Pharma's headquarters in Schwaebisch Hall, Germany, in conjunction with the Optima Group's 100th anniversary celebrations. This means that 4,300 more square meters of assembly space are now available. "The CSPE Center II sends out an important signal: Despite the pandemic and the challenges associated with it, we are investing in the future, creating jobs and even more efficient processes for our customers," says Gerhard Breu, Chairman of the Optima Pharma Division. A three-story office building complements the state-of-the-art assembly hall.

From left to right: Hans Buehler, Managing Director/CEO of the Optima Group, explains the operation of a pharmaceutical filling line to Winfried Kretschmann, Minister-President of Baden-Wuerttemberg, Jutta Niemann (Member of the State Parliament, Buendnis 90/Die Gruenen) and Harald Ebner (Member of the Federal Parliament, Buendnis 90/Die Gruenen). Numerous lines have been delivered to customers worldwide for the filling of COVID-19 vaccines with the highest priority at uncompromising quality.

High levels of integration for turnkey lines

"As part of CSPE 2.0, we are increasing the integration level of the systems even further. Work that had typically been carried out at the customer's construction site will now be carried out to an even greater extent at one of our CSPE centers," explains Breu. "More specifically, we are carrying out most of the Installation Qualification (IQ) and Operational Qualification (OQ), as well as part of the Performance Qualification (PQ) for all line components, i.e., filling line, isolator, and freeze dryer, on our site before shipment," adds Matthias Naser, Optima Pharma's Chief Operating Officer. In the CSPE Center II, which is 14 meters high, freeze dryers can now be assembled with the other system components and tested under real-life conditions as a complete functioning unit.

The opening of the new CSPE Center II (center) has increased Optima Pharma's production area in Schwaebisch Hall's Solpark business park by more than 4,000 square meters.

Provides space for freeze drying: In the new CSPE Center II, complete systems can be fully assembled and tested as a unit for the first time. This massively reduces the time-to-market for customers.

"Production-ready" in the fastest possible time at our customers' sites

The planning of the complex turnkey plants is assisted by simulation and digital engineering. As early as the system design stage, Optima Pharma optimizes the distribution of VHP (Vapor Hydrogen Peroxide) in the isolator. By using simulations, we can create the best initial conditions for developing the cycle. The right positions for the indicators in the cycle development can be accurately identified. In the final cycle verification and validation on site, which comes later as part of the performance qualification, the simulation result, confirmed by the cycle validation, can be used to prove that the decontamination process is safe. In many cases, there is no need to repeat tests on site, thereby saving valuable time before production kicks off. The time spent on installation and qualification at customer sites is reduced by several months. The systems are already much nearer to being "production-ready" when they leave the CSPE Center.

Media troughs running in the floor make it possible to supply the completed pharmaceutical filling line for the integrated Factory Acceptance Test (iFAT) with process heating and cooling, demineralized water and compressed air. The tests carried out in the CSPE Center ensure that both the later installation and the Site Acceptance Test (SAT) conducted on the customer's premises run much more smoothly and rapidly. Alongside simulations and cycle developments, the comprehensive iFATs also include interface and safety circuit tests, leak and smoke tests, automation and software application tests, as well as SCADA integration. Optima Pharma's range of services includes extensive qualification testing for the entire production line, including isolator and freeze dryer tests. In short, Optima Pharma's customers receive a turnkey line tested to the maximum for a significantly safer and faster production launch.

Optima Pharma's worldwide service personnel, which is being tripled in the USA, for example, from 2019 to the end of 2022, will also ensure "production readiness" 24/7. A new service hub is opening in Raleigh, North Carolina in 2022 (see the report on pages 12 to 13). Here, Optima Pharma will be offering comprehensive services, sales of systems and spare parts as well as training. The aim is to be able to provide better, more rapid support to customers in the Pharma sector. "The new service hub will bring us even closer to our customers and allows us to provide faster service along with enhanced spare parts availability," explains Ulrich Unterriker, Managing Director of Optima Machinery Corporation in Green Bay, Wisconsin.

Larger, more efficient and more convenient

Meanwhile, back in Schwaebisch Hall, Germany: For Optima Pharma, the new building means short distances, a pooling of strengths and efficient operating processes. The experience gained from operating CSPE Center I was incorporated into the design and led to further streamlining. It is designed to be 25% larger and provides even more space for the large turnkey lines. System modules are transported smoothly and quickly by cranes with an 8.5 meter hook height from incoming goods to the assembly hall. Along with the adjoining three-story office building, the new structure covers 7,000 square meters.

The media troughs running in the floor of the CSPE centers can be quickly connected to all line sections. This means that commissioning can take place under realistic production conditions.

Optima Pharma is now able to carry out even more comprehensive qualification measures in-house as part of the enhanced CSPE process. This further reduces the time between installation and the start of production at the customer's site.

Expansion in the Pharma business unit

Optima Pharma inaugurated the first CSPE Center in June 2019 at its headquarters in Schwaebisch Hall. Ever since, CSPE Center I has been operating at full capacity. At Optima Pharma's Gladenbach-Mornshausen site, the existing assembly hall for freeze drying systems has been extended by 50% in the past year. An expanded building with office and assembly space is being planned at Optima's subsidiary Metall+Plastic in Radolfzell on Lake Constance. If the strong growth continues, CSPE Center II can be expanded to the south to include another CSPE Center with access to the CSPE Center II loading yard.

Project experience has shown that CSPE is successful. The scientifically validated, comprehensive approach to engineering expedites the implementation of turnkey projects. In any case, customers who order complete systems benefit from fewer "friction losses", as any interface problems will have already been resolved on the supplier's premises. That's how CSPE delivers what it promises. The system is "production ready" in the fastest possible time.

IMPORTANT FOR YOU

- Tripling of Optima Pharma service personnel in the U.S.
- New service hub in Raleigh, North Carolina
- Customer proximity and fast availability of services and spare parts
- Availability of pharmaceutical lines is thus further improved

EVEN CLOSER TO OUR CUSTOMERS

The Optima Group's Pharma business unit is massively expanding its service presence in the USA. The number of service personnel in the U.S. will triple between 2019 and the end of 2022. Mid-2022, Optima will be opening a new service hub in Raleigh, North Carolina. The service hub will be offering comprehensive services, systems' sales and spare parts, along with training. Optima's goal is to expand capacity to meet the needs of pharma customers.

For Optima Group, the Pharma business unit serves as an important and growing market in North America. The pharmaceutical sector yields high demand for Optima machinery and systems, as well as its services, generating expansion opportunity for Optima. The service hub will be located in Raleigh, North Carolina. Raleigh is located in what is known as the Research Triangle, where many of Optima Pharma customers are located. Restrictions on travel has made direct customer contact more difficult for every company. "The COVID-19 pandemic has once again demonstrated how important local support is", says Gerhard Breu, Chairman of the Optima Pharma Division.

Rapid availability of services and components

"The new service hub will bring us even closer to our customers and allows us to provide faster service along with enhanced spare parts availability", adds Ulrich Unterriker, Managing Director of the Optima Machinery Corporation in Green Bay, Wisconsin. Experienced engineer, Doug Nash will be overseeing operations within the new service hub. Nash studied electrical engineering and has 20 years of experience as a maintenance engineer in filling and packaging companies within a variety of industries, including pharmaceuticals.

Calibration of pharmaceutical systems is just one of the many services offered at the new site.

Be it remotely or on-site, Optima's service experts will find solutions to customers' challenges around the clock.

The new service location in Raleigh, North Carolina aims to ensure optimum availability of machinery and systems.

Optimal pharma system availability

By expanding our service presence in the U.S., we are continuing to optimize the availability of our customers' machines and systems," says Holger Burgermeister, Director Service at Optima Pharma. Optima Pharma, working in cooperation with Optima's Green Bay office will provide both remote and on-site customer support from the new service hub. Optima Pharma sales experts will also be available to provide advice on new and existing machine projects. Comprehensive services offered will include maintenance, modifications, qualification of pharmaceutical systems, and the training of operating personnel. Spare parts will be stored at the site to ensure system availability at all times.

Service personnel numbers to triple between 2019 and 2022

Optima Pharma's presence in the American market has been consistently expanding in recent years. Service personnel is expected to increase by threefold near the end of 2022. Optima has had a subsidiary in Green Bay, Wisconsin for almost 40 years. In 2017, the site expanded by 1,200 square meters. In total, over 50 sales and service staff provide on-site support to Optima's American customers in the pharmaceutical sector.

OPTIMA PHARMA LOOKS BACK ON A SUCCESSFUL ACHEMA

Optima Pharma's Expert Zone proved to be a big draw for visitors at ACHEMA 2022. The technologies and innovations presented in the exclusive visitor area perfectly reflected the diverse requirements in fill & finish, isolator technology and freeze drying, many visitors agreed. Topics ranged from the premiere of a new machine to the CSPE approach (Comprehensive Scientific Process Engineering) and digitalization. New system concepts, climate-friendly refrigeration technology for freeze drying, and ultra-efficient decontamination systems were also in high demand.

ACHEMA

The modern Optima booth at ACHEMA 2022 in Frankfurt am Main turned out to be a big attraction.

Despite the vacation season, the Optima Group's Pharma business unit recorded heavy visitor traffic at the important pharmaceutical trade show, which was held for the first time in presence again in Frankfurt am Main from August 22 to 26. Gerhard Breu, Chairman of the Optima Pharma Division, was very pleased with how the trade show went. "Together with our partners, we have risen to the challenges of the pandemic, which has unleashed a wave of innovation. A massive amount of new products are entering the clinical phase. As a result, we are now much more than a machine builder. In fact, we are a strategic partner and solution provider with a holistic approach – from designing complete lines, to providing support in the qualification phase, right through to the start of production. Direct feedback from ACHEMA visitors helps us understand their individual requirements." Many visitors at the trade show focused on the new efficiency potential offered by digitalization, reports Breu. There are many approaches: The services range from systematic, automated evaluation of performance and sensor data from systems to augmented reality in service. Optima Engineering also actively uses digital technologies, for example, for the comprehensive simulation of complete systems.

Integration of pharmaceutical lines is further increased with CSPE 2.0

These simulations are also part of CSPE 2.0, which was presented at ACHEMA. "Comprehensive Scientific Process Engineering (CSPE) is a technical and scientific approach developed by Optima Pharma that massively accelerates processes from system design to production start-up," says Matthias Poslovski, Vice President Sales at Optima Pharma. Comprehensive simulations as well as integrated factory acceptance tests of complete systems are an integral part of this. The CSPE process particularly offers significant advantages for comprehensive turnkey projects. As part of CSPE 2.0, Optima Pharma is further increasing the degree of integration of the systems, which the trade show visitors found very interesting. For example, in the new

The Optima Pharma trade show team informed visitors about future-proof, sustainable and efficient solutions for the current challenges facing the pharmaceutical industry.

Many visitors to the trade show focused on the new efficiency potential offered by digitalization. Smart Production Assistance Services, which can make pharmaceutical production safer and more efficient, were presented here.

Intelligent Production Assistance Services also include high-speed cameras that monitor key process steps and ensure maximum product yield and machine availability.

With the CSPE (Comprehensive Scientific Process Engineering) approach, Optima Pharma is accelerating the processes from system design to the start of production. As part of CSPE 2.0, Optima Pharma is also increasing the degree of integration of the systems, which the trade show visitors found very interesting.

Visitors find out more about Optima Pharma's technologies.

Feedback during in-person meetings was very valuable – both for trade show visitors and Optima experts.

The Optima booth at ACHEMA 2022 in Frankfurt am Main was packed with visitors. Despite the vacation season, visitors seized the opportunity for an in-person exchange of ideas.

CSPE Center II, filling and closing lines with isolators – and for the first time also freeze-drying systems – will be fully assembled in the new hall. During integrated Factory Acceptance Tests (iFATs), the system is tested as a single optimally coordinated unit with all functions – all measures that massively shorten the time to production start-up, explains Poslovski.

Precision and top speed with the MultiUse system

The unveiling of the new high-speed version of the OPTIMA MultiUse system was another highlight at the Optima booth. With the up to ten-digit version, up to 24,000 objects can be processed per hour. A special feature is that all product saving functions and the extremely high filling accuracy are retained even at high output.

Flexibility is also part of the concept: Different container types and sizes can be achieved with virtually no format change parts; different product paths – including freeze-drying – are also easy to implement.

Future-proof, alternative refrigeration technologies

In the Expert Zone, future-proof alternatives in refrigeration technology were presented which do not use refrigerants that are harmful to the environment. The most important variants used by Optima Pharma range from cascade freeze-drying to liquid nitrogen cooling and air freeze-drying. The opportunity to try out an air cooling system at a production system, which Optima Pharma will offer at the beginning of 2023, attracted considerable interest.

Metall+Plastic's award-winning DECOpulse® bio-decontamination system also attracted considerable attention, since rapid cycle times and extremely homogeneous H_2O_2 distribution in isolators continue to be key production advantages. The potentials of a new complementary method of cycle development using enzyme indicators were also presented.

New system concepts for cell and gene therapies were another highlight in the Expert Zone. Optima has developed a holistic concept for producing and filling these particularly high-quality medicines. Visitors of the trade show got the chance to experience the automated, modular and highly flexible machine platform and the digital integration of innovative technologies. Special machine solutions, for example for highly active ingredients, and energy-saving machine technologies were additional focal points for trade visitors in the Expert Zone at Optima Pharma.

MORE ABOUT THIS TOPIC

Scan the QR code to see impressions from ACHEMA and interviews with Gerhard Breu and Matthias Poslovski in a short video.

IMPORTANT FOR YOU

- Optima Pharma offers digital solutions for every challenge in pharmaceutical production, including: Production data management, maintenance, operator guidance and knowledge transfer.
- All solutions are specifically tailored to and validated for the requirements of pharmaceutical companies.
- Augmented reality can be used for every kind of production support.
- Virtual reality assists with system design and training operating personnel.
- Digital Engineering methods will reduce time-to-market within the framework of the CSPE process.

Augmented reality is an important tool in pharmaceutical production. Machine operators are guided through processes step-by-step thereby reducing the risk of downtime, increasing machine availability, and lowering product loss to a minimum.

EFFICIENT AND SECURE PRODUCTION

Digitalization at Optima always meant creating added value for our customers. We have developed a broad portfolio of digital solutions with this goal in mind. These solutions are used successfully in the initial systems. Optima has also undergone a massive upgrade in terms of cybersecurity. The following article will show you how pharmaceutical production has become more secure and efficient in production data management, maintenance, operator guidance and knowledge transfer.

"Successful management of production-related data is a major field of application for digital solutions. These solutions support our customers by making their production more transparent and showing them where there is potential for improvement," reports Marcel Klimmer, Product Manager at Optima Pharma. Customized software solutions are available to intelligently bundle data so that Optima customers know at a glance how their production is doing – from data analysis and successful data management to monitoring of entire production lines regardless of the manufacturer.

Traceability down to single items

Efficient data management offers secure and pharmaceutically validated data collection, serialized traceability of individual products and identifying trends and advantages. Key data can be easily and quickly displayed on a personalized dashboard and accessed worldwide at any time on any device. Production managers will thus always have a perfect overview, even retrospectively. In addition, processes can be video-monitored and analyzed in detail during machine downtimes. This means you can track your

The right format part at the right place. Another advantage of the digital format change assistant: New employees can be trained faster.

production targets around the clock and optimize the overall efficiency of the system. System availability will increase, and downtimes can be significantly minimized. Traceability down to single objects allows all process and production data to be assigned to the single object. Rejects can be traced back to the affected objects in the batch.

Maximum security – maximum yield

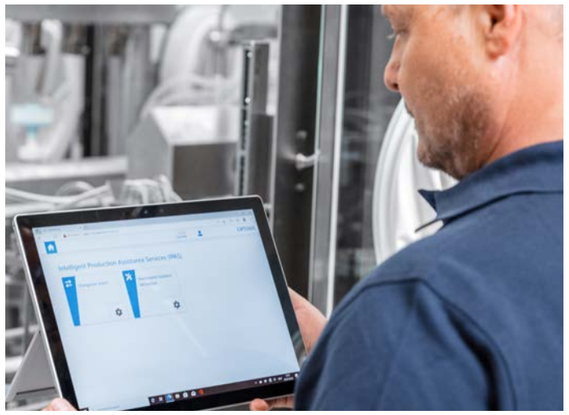
Both, data and moving images can be recorded and accessed worldwide. On request, cameras in the interior of the systems will continuously record live images that the customer's employees can view at their production location via their company's network, as well as showing alarms. It is also possible to use them in case of an alarm. If the machine control system detects a fault, it stores a certain sequence before and after the alarm is triggered and assigns a time stamp as well as other production data, such as the batch number. This means that alarms can be analyzed quickly and easily, faults can be remedied and product losses minimized.
Video material helps assess problems during production and recognize non-critical situations. This allows for transparency, easy access to data for public authorities, and reduce rejections due to uncertainties. Last but not least, the cameras improve the overview for operating personnel.

Planning maintenance at an early stage

"Digitally optimized maintenance also increases system availability," adds Tobias Dombrowski, Sales Support Manager at Optima Pharma. Preventive maintenance makes system operators aware of the onset of wear. This means individual parts can be monitored and replaced early if necessary. Maintenance strategy can therefore be optimized and machine downtimes reduced to a minimum.

Data overview: Smart tools support production managers in evaluating key figures and recognizing improvement potential.

Digital solutions, including augmented reality glasses also help with production preparation, format change or maintenance work, which increases process security.



Knowledge transfer: Information, including videos, stored on the Optima platform makes it easy to understand concepts.

› www.optima-packaging.com/cybersecurity

Top cybersecurity

Remote access to the system results in maximum security: Together with the cybersecurity specialists LANCOM Systems, Optima has developed an innovative VPN solution for machines and systems. This establishes an even more secure connection and offers the installation of remote maintenance systems at the customer's site. The only one of its kind on the market, the solution allows for monitoring VPN connections, protects the machine network at the customer's site with a firewall and is particularly user-friendly.
In addition, our service experts will assist you with virtual tools around the clock anywhere in the world in case of process-related problems – independent of the device and directly on the machine. You only need a mobile device such as a smartphone, tablet or augmented reality glasses. Your benefits: Travel expenses will be minimized, and you will receive direct, easy and fast assistance in real time. Whether with VPN remote maintenance support or an audiovisual consultation on the machine, together we will find a solution to your problem.

Achieve goals faster with augmented reality

Digital solutions effectively assist with troubleshooting as well as with production preparation, format change and maintenance work. For example, digital assistants can lead system operators at the HMI step by step through a format change. This can also be achieved with using augmented reality glasses. As an option, the customer's employees can use scanners to scan format parts that need to be changed. These can be verified with a DMC code to make sure the correct parts are being used. Correct installation has to be confirmed on the HMI. This effectively minimizes the risk of machine downtime due to installing the incorrect format

Always at the customer's side during troubleshooting: With augmented reality glasses, Optima service experts can see what the system operator sees and provid targeted assistance. Important information can be displayed in the range of vision.

Production stops due to operating errors are costly in the pharmaceutical industry. A remedy is a digital format change assistant from Optima Pharma. As an option, format parts to be changed can be scanned, which increases process security.

parts, and machine availability is increased. Machine crashes are therefore prevented, and product losses are also kept to a minimum.

An additional tool assists with handling agar plates, which are used to proof a germ-free production. Previous, partially paper-based processes have been digitalized, and the system assists the operator with assigning sampling locations, monitoring exposure times and reporting. Errors and production stops can thus be avoided, a previously analog and error-prone procedure is digitalized and paper can be eliminated.

Knowledge transfer is another important application for Optima Pharma. Information stored on the platform, e.g. videos, support understanding. In addition, individual pieces of information can be stored at any time on each of the tools – for example, employees on the next shift can be made aware of certain issues. New employees should be able to familiarize themselves with your system functions as quickly as possible. Simulations and instructional videos make the first days on the machine easier, save time during training, enabling employees to operate the system quickly and intuitively. Above all, they provide a sense of achievement.

Using digital engineering to optimize system design

At Optima, knowledge transfer takes place both on the finished system, as well as at the design stage in the Digital Information Center. Digital Engineering is a standard component of our turnkey process CSPE (Comprehensive Scientific Process Engineering). Within the CSPE framework, Optima Pharma uses the full potential of Digital Engineering. Strength calculations, flow simulations or determining resonances of individual components assist the Optima developer during the design phase. Virtual machine models simulate important processes at an early stage. Early modifications minimize costs and time-to-market. Training can also take place on a preliminary virtual mock-up. Another benefit is that acceptance test can take place virtually and be documented, upon request.

In addition, using artificial intelligence will open up new future applications. Self-learning machines offer unprecedented potential for pharmaceutical production due to the vast amount of data, most of it unused.

"Digitally optimized maintenance increases system availability."

Tobias Dombrowski,
Sales Support Manager at Optima Pharma

Using a new digital solution from Optima Pharma, agar plates can be scanned and unequivocally assigned. In addition, timing functions are also integrated.

MORE ABOUT THIS TOPIC

www.optima-packaging.com/digital-features-greater-safety

NEW WAYS

FUTURE-PROOF REFRIGERATION SYSTEMS IN FREEZE DRYING

IMPORTANT FOR YOU

- The EU's F-Gas Regulation, other international regulations and climate protection in general require future-proof refrigeration technology.
- A wide variety of refrigeration technology solutions meet the most diverse requirements of pharmaceutical freeze drying.
- Future-proof solutions are: climate-neutral refrigerants in cascade systems, liquid nitrogen (LN2) directly or via heat exchangers, air refrigeration systems, as well as combinations of the systems mentioned.
- Synthetic cooling agents (R452A and R410A) are increasingly limited in the EU and are considered as a transitional solution to a limited extent.
- Tests with a Mirai air Cooling systems at a GT production plant (15 m^2): Coming soon at Optima Pharma!

Alternative coolants and correct cooling technology are booming because synthetic coolants are gradually disappearing from the European market and other regions of the world due to legal regulations. This raises the question, which alternatives are suitable for what application? The article also features a unique testing option at Optima.

The "new" coolants are proven in terms of their functionality; however, to date this has mostly occurred outside of pharmaceutical lyophilization. The properties of the synthetic coolants matched the specific requirements of pharmaceutical freeze-drying processes too well, so that the alternatives met with little approval. Now that climate protection has become increasingly important, the situation is changing with choices like the synthetic coolant R404A with a global warming potential of 3922 (expressed in the GWP value, see box on next page) and an alternative, natural coolant, such as R170 (ethane) that has a GWP value of just six.

Not only EU legislation is gradually restricting the sale of synthetic coolants with the F-Gas Regulation (fluorinated greenhouse gases). Similar regulations exist in places like Switzerland or the state of California in the United States. Industry experts are convinced that as availability decreases, the prices for these and the less harmful coolant blends such as R452A will continue to rise sharply. Anyone planning new freeze-drying systems today will therefore, rely on alternatives in cooling technology.

Different cooling objectives within the system

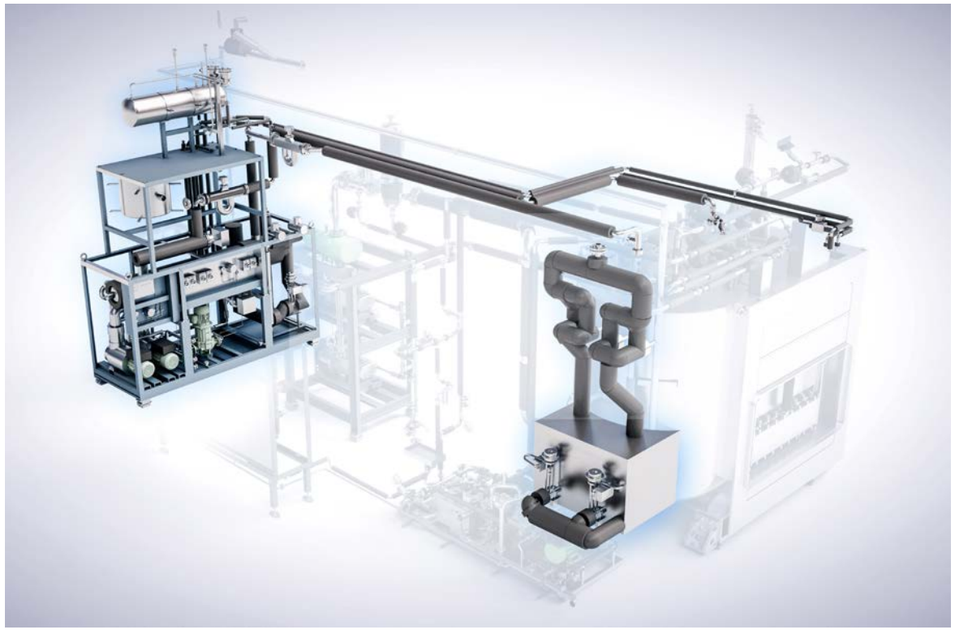
The freeze-drying process requires low temperatures in the freeze-drying chambers for its shelves and the ice condensers. Nevertheless, the requirements of the two components differ significantly in terms of cooling technology.

On the chamber side containing the shelves, the cooling technology meets several tons of stainless steel. As part of the batch preparation, the internal surfaces are cleaned and then steam sterilized at more than 120 °C. After external re-refrigerating and the loading process, temperatures as low as -65 °C are required on the shelves in order to freeze the pharmaceutical liquids.

This means the absolute temperature target is not extremely low. The temperature difference, the large mass to be cooled, and the time factor are the main challenges that cooling technology has to meet vigorously. Since the quality of a lyophilizate is particularly influenced by the freezing phase of the drug, the controllability of the cooling capacity is also important. A temperature curve should ideally be linear and not show any upward or downward deflections over time.

On the other hand, there is sufficient time to control the temperature of the ice condenser's cooling coils. The cooling target can reach as low as -80 °C. In contrast, a linear progression is not an essential requirement in this process.

In classic freeze-drying systems with synthetic coolants, a common cold source is sufficient to achieve these different cooling objectives.



Liquid nitrogen cooling system during assembly. Liquid nitrogen itself is a climate friendly and a proven medium for freeze drying processes. Liquid nitrogen will be produced with different methods – energy-intensive, as a side product from other processes or using regenerative energy.

When using alternative coolants instead of a second cooling source, a second cooling system may be used to meet the cooling targets in each case.
In general, further aspects must be taken into account in the system's design for a suitable "overall package". These are usually the specific requirements of the pharmaceuticals to be freeze-dried, the spatial requirements at the installation site, the existing technical infrastructure, and the importance placed on environmental protection.

Transitional period or uncompromising?

GWP values down to zero can now be achieved in cooling technology and are practical in pharmaceutical freeze-drying.

An overview of the currently leading, future-proof technical solutions:

1. Carbon-neutral coolants in the cascade system (flammable)
2. Liquid nitrogen (LN2) for direct cooling or for cooling via heat exchangers

Pioneering, but not yet established on an industrial scale in the pharmaceutical freeze-drying industry:

3. Air cooling systems (some with booster system)
4. The means and technologies mentioned above are combined in an overall system that implements the different cooling targets of the ice condenser and freeze-drying chamber, as well as customer-specific aspects.

As a transitional solution:

5. The synthetic coolant mixtures R452A and R410A in the classic design of freeze-drying systems are less future-proof (their availability is already limited due to legal requirements in the EU and will gradually be further restricted).

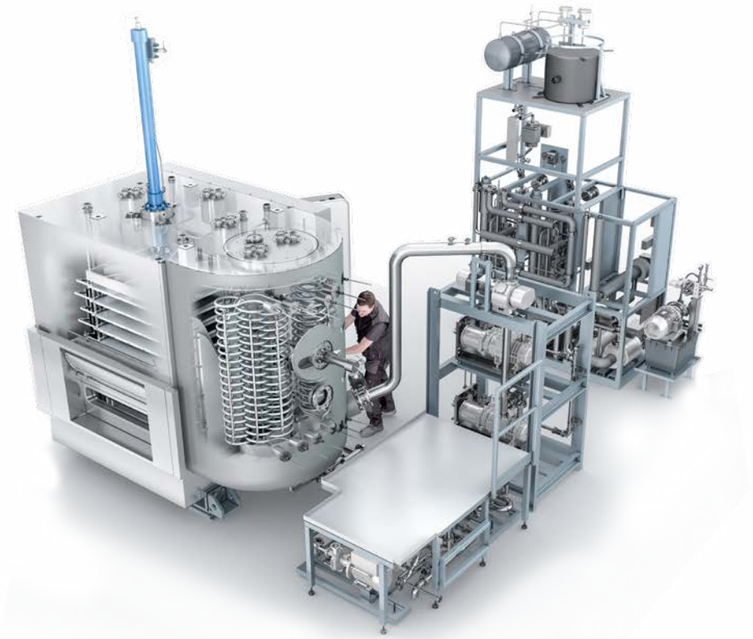
During a transition phase, synthetic coolant mixtures can be considered as an alternative with significant restrictions. Compared to conventional synthetic coolants, these mixtures are less harmful, but still unsafe for the environment. R452A and R410A have a GWP of 2140 and 2088 respectively. Although these coolants are available within the EU, the quantities are limited and they are gradually being phased out. Since the typical life cycle of freeze-drying systems is approximately 30 years, this alternative will only make sense for new systems in exceptional cases.

Background: GWP values and current EU regulations

The higher the GWP value, the more harmful the substance to the climate. A concrete example: The CO_2 equivalent of the organic coolant mixture R410a is 2,140 – always considered over a period of 100 years. This means that within the first 100 years after release, one kilogram of R410a contributes 2,140 times more to the greenhouse effect than one kilogram of CO_2. The release of 1 kg of R410a corresponds to the release of 2,140 kg of CO_2.

The European Parliament is now discussing additional F-Gas Regulation (EU) No. 517/2014. A reduction in emissions of 80-95% by 2050 is under discussion.

(Regulation (EU) No. 517/2014 of the European Parliament and Council dated April 16, 2014)



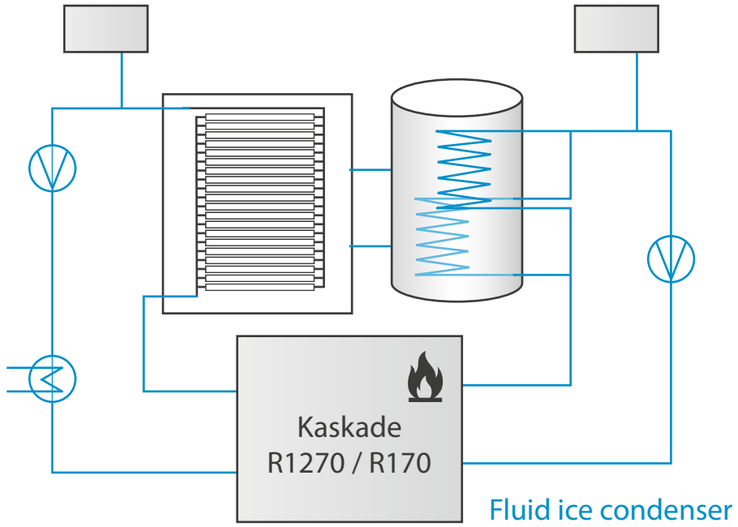
Coolants, harmful to the environment, are replaced by alternative solutions. Cascade system (cooling with liquid nitrogen), air refrigeration technologies and combinations of both are considered sustainable.

Better, sustainable

In order to create a sustainable freeze-drying system on the ice condenser side, a system with a separate cooling circuit often proves very practical. This means the ice condenser coils can be supplied with a heat transfer medium, regardless of the actual cold source. The system therefore, consists of cooling technology, a heat exchanger and a separate cooling cycle. This is in contrast to the direct evaporation of synthetic coolants, for example, which evaporate immediately in the ice condenser coils.
A fluid circulates in the separate cooling circuit as a heat transfer medium, at temperatures of as low as -80 °Celsius. The ice condenser coils and the cooling technology are connected via the heat exchanger. The type of cooling technology used remains variable. (The fluid on the side of the freeze-drying chamber has always circulated in the shelves according to the same principle.)
A second climate-friendly variant of ice condenser cooling is the evaporation of liquid nitrogen. Liquid nitrogen can escape into the atmosphere as a harmless gas. This solution has proven itself many times in the pharmaceutical freeze-drying industry. (The overall environmental balance of using liquid nitrogen in turn depends heavily on its production process.)
The individual variants of the environmentally friendly cooling systems and their possible uses will be examined more closely. The specific requirements for the chamber and of the ice condenser must be taken into consideration.

Natural, climate-neutral coolants in the cascade system

The gases R1270 (propene, GWP 3) and R170 (ethane, GWP 6) are usually used as coolants. These gases are in the cooling circuits and are not "consumables" - or operating materials. If these escape into the atmosphere, they are practically harmless to the environment.
For the required cooling capacity, natural coolants are pressurized in cooling circuits with compressors and released again. The resulting change in the aggregate states (gaseous and liquid) uses the cooling capacity (enthalpy) generated during evaporation. In the cascade system, this cooling capacity is "handed over" to a second circuit via a heat exchanger. This cycle works on the same principle and reaches an even lower temperature level. Depending on the size of the cooling system and the required redundancies, several cascades, each with two compressors, are used. With this cooling capacity, the adjustable shelves and/or the ice condenser coils are finally cooled with heat exchangers and circulating fluid.
Leaking natural coolants form a potentially explosive mixture in combination with air in closed rooms. Therefore, natural coolants should only circulate in an enclosed, controlled area – not beyond, neither through the shelves nor through the ice condenser coils. Still, in the enclosed area, heat exchangers transfer the coolants to the fluids. While gas detectors monitor the enclosed area, a slight vacuum is created through suction and evacuation. Optima Pharma has developed a particularly safe concept that detects potentially dangerous air/gas concentrations. If, for example, the explosion-proof fan should fail, in the event of a leak, there would be more time to react.



Fluid ice condenser

Schematic of a system with liquid nitrogen. The set of shelves is evenly cooled with heat exchangers. Direct evaporation of the liquid nitrogen takes place in the ice condenser.

Depending on the installation location, an exhaust air ventilation should be installed from the enclosed area to the outside of the building when installing a freeze-drying system with a cascade cooling system. Since people work near the equipment, these rooms must be classified accordingly. Country-specific regulations may need to be observed.

Liquid nitrogen as an alternative

Liquid nitrogen is often used for indirect cooling with heat exchangers, since it is largely climate-neutral. In this case, the production process determines environmental compatibility. In particular, when liquid nitrogen is obtained from regenerative energies, it offers the ideal conditions for use in cooling technology. The idea of sustainability can be extended even further if the evaporated liquid nitrogen is absorbed and accessible as purified nitrogen for use in other processes.
Liquid nitrogen is very suitable for cooling the shelves and, as shown, is used for cooling of the ice condenser. It requires a storage tank in the infrastructure, which many pharmaceutical companies already have on site. The technical implementation of the freeze-drying systems involves comparatively little effort. Liquid nitrogen greatly reduces the use of electricity and cooling water in the systems.

Air as a coolant

The principle of air-cooling is not new either, but was only available for mass production in recent years by the Mirai Company. The investment is currently higher than for other cooling systems, but the system works solely with air as a coolant and is particularly environmentally friendly.

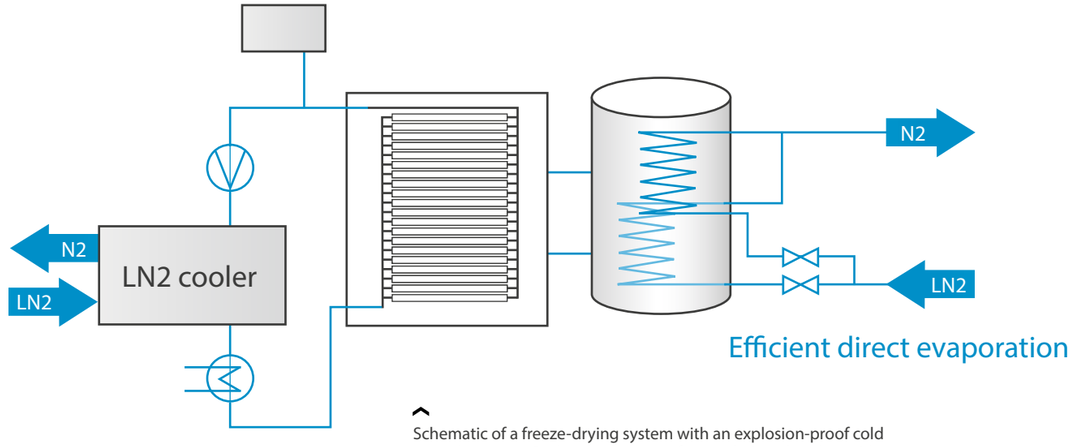
Air cooling systems have one special characteristic: they are an extremely efficient way to achieve very low temperatures with consistent performance. Therefore, their use in freeze-drying is preferred for cooling the ice condenser. The dynamics are less favorable when components need to be cooled as quickly as possible, as is the case with the shelves. This is still possible, though, by setting up an additional oil storage tank as a "booster". This tank can be cooled to -80 °Celsius over an extensive time period. If the shelves are then to be cooled in the freeze-drying process, the desired cooling capacity is available. In this setup, an air cooling system serves an entire freeze-drying system. In larger freeze dryers, two or three air cooling systems are required.

System mix with a second cold source

With the combination of different cooling systems, their respective strengths can be combined for optimal results. This requires a certain investment or the integration of existing infrastructure into the new freeze-drying project.
Very few pharmaceutical companies have had the chance to gain experience with air cooling technology or cascade cooling systems. Optima Pharma has invested in an air cooling system from Mirai to give interested parties and ur customers the opportunity to choose a different system. This system is combined with a production freeze-dryer with a footprint of 15m² and will be available for tests at the beginning of 2023.

Test Air-Refrigeration Technology!

Optima Pharma has also carried out extensive test series at its in-house production test facility with a cascade cooling system and alternative coolants. It was available for several weeks exclusively for this purpose.



Efficient direct evaporation

Schematic of a freeze-drying system with an explosion-proof cold cascade system. Both components – freeze-drying chamber with shelves and ice condenser – receive cold air from a central cooling system via heat exchangers and fluids in their own circuits.

Optima Pharma shared the latest findings with customers and interested parties. These findings are currently being incorporated into a major project at a Swiss location, where four large freeze-drying systems are being cooled using cascade cooling technology and natural coolants. This project is nearing completion. Jörg Rosenbaum is happy to talk more with you about cascade cooling technology – please reach out today!
Pharmaceutical companies will be able to make sustainable and safe decisions with expert advice from Optima.

Classic coolants and retrofit: Two FAQs

The question often arises as to why the use of climate-damaging gases have been and continues to be the norm, although there have been other options for a long time? The main reason is the specific coefficient of performance of a coolant. The performance of the synthetic, environmentally harmful coolants ideally correspond to the technical requirements of freeze drying systems. Climate-neutral coolants, on the other hand, are flammable, they have a narrower range of applications, and they require higher compression performance (i.e. a different compressor design). This is also an indication of why the subsequent change to another coolant only rarely makes economic sense.
A second frequently asked question revolves around the ice condenser coils: could a subsequent "system change" work? Until now, ice condenser coils have mostly been designed for the physical effect of the synthetic coolants that evaporate and then liquefie again in the circuit. This requires an exactly coordinated geometry of the ice condenser coils in interaction with the compressor performance. In new, environmentally friendly systems, fluid is now mostly used in the cooling coils of the ice condenser in a cooling cycle (without evaporation). In most cases, specific designs of the ice condenser coils prevent an economical retrofit. Subsequent conversion to the direct evaporation of liquid nitrogen in the ice condenser coils is only cost-effective in rare cases. The coolant (performance coefficiency), the geometry of the ice condenser coils and the performance of the compressors always form a coordinated overall system.

Optima Pharma will soon provide customers and interested parties with a Mirai air-cooling system in combination with a production system (15m² installation area) for tests.

MORE ABOUT THIS TOPIC

Tests with a Mirai air cooling system on production equipment?
At the beginning of 2023 at Optima Pharma in Mornshausen! Please contact Joerg Rosenbaum: joerg.rosenbaum@optima-packaging.com.

ARE ENZYME INDICATORS THE FUTURE?

During the last few years, a new indicator appeared on the market: Enzyme indicators (EI). Compared to the current biological indicators (BIs), these new types of indicators could offer advantages in the cycle development of bio-decontamination processes. A study by Optima and Metall+Plastic in cooperation with Protak Scientific provides exciting new findings and application processes.

BIs are tried and tested for isolator cycle developments intended for bio-decontamination processes. Nevertheless, BIs have certain restrictions, they are time and labor extensive during cycle development and have to be incubated for seven days before a final result can be seen. The result is either "growth" or "no growth" of live-spores of "Geobacillus Stearothermophilus" (used as a reference organism).
EIs on the other hand provide results within several minutes. After exposure, the indicators are evaluated with a luminometer. The RLU-value, in percentage, is determined from the measured luminescence via standardization (RLU – Relative Light Units). This achieves quantitative analysis more quickly. If the enzyme activity can be correlated with the killing of spores, it provides information on the decontamination process.

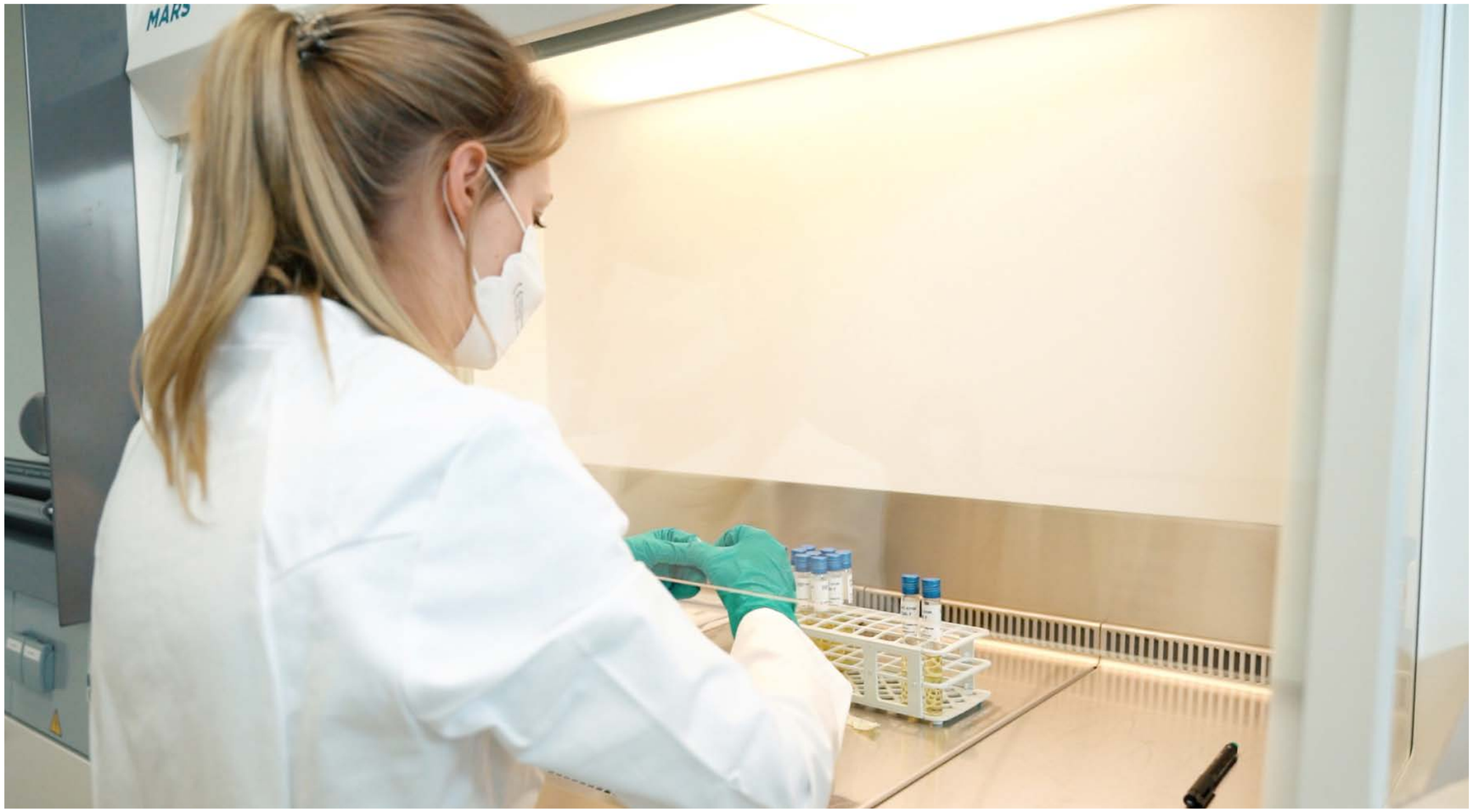
Data collection to understand EIs

To apply EIs correctly and avoid possible downfalls, it is necessary to understand strengths and weaknesses of the indicators.
In a first step it is determined how irregular or stable the EIs react to gassing with H_2O_2. This information will validate EI results. Significant findings indicate that variability (CV – Coefficient of Variability) is limited and a 30 % worst-case variability scenario is possible, provided no other value can be determined for the respective application. This is likely if only one EI per location is applied
It was also confirmed that an enzyme activity reduction can vary depending on local conditions. These discrepancies are based on different interactions with the H_2O_2 and

IMPORTANT FOR YOU

- Enzyme indicators (EIs) are new and provide benefits and application potential in cycle development for decontamination processes in isolators.
- EI results are available only a few minutes after a cycle. No incubation required.
- EI results provide quantitative information on the decontamination accomplishments and show only a small variability.
- Qualitative and quantitative correlations to biologic indicators were featured in several experiments. A larger data basis is necessary to verify and validate the results.
- A first application recommendation is provided for the complementary use of EIs in the cycle development of decontamination processes in isolators.
- EIs have the potential to be used as an additional control function for decontamination processes before production. Individual significant deviations and trends can therefore, be recognized

INNOVATION



In the CSPE Center laboratory at Optima: Biological indicators in a nutrient solution with a positive and negative specimen are prepared for incubation during cycle development. The complementary application of enzyme indicators for this process is rational. Metall+Plastic in cooperation with Protak Scientific researched application potentials.

the EIs, the characteristics of used decontamination systems or the orientation of the EIs. The evaluation was based on entire groups of indicators and the arithmetic means of the obtained RLU values, as well as standard deviations.

Worst-case location identified – independent of gassing time

The next step is to examine the qualitative correlation between EIs and BIs: will both indicator types lead to identical results if they are at identical locations and have identical decontamination cycles? D-values were the defined measurement for micro-biological killing per BIs location. EIs and BIs, both, correspondingly showed the best-case-locations. The worst-case locations for BIs and EIs were also identified. However, the latter would show additional potential worst-case locations in a risk-based approach. Therefore, a qualitative correlation was given.

To further examine the significance of EIs, the authors also tested what happens if the gassing time is continuously increased from 6 to 8 minutes and up to 11 minutes. A homogeneous result was achieved by examining 35 locations. The ranking of the measured RLU_{rem} values (RLU_{rem} : standardized relative light intensity as a measure for the remaining enzyme activity, rem = remaining) was the same during different gassing times. For example, locations with a high RLU_{rem} value showed a lower RLU_{rem} after a longer gassing time, but the "sequence" of decontamination success of the EI-locations was unchanged. The EIs were able to identify the best and worst-case locations independent from the total gassing time.

Can quantitative correlations between EIs and BI be determined?

The results, up to this point, only present information of the inactivity of the enzymes on the indicator. The question, however, is it possible to create a quantitative correlation between the enzyme activity reduction and the killing of spores? Further tests were conducted.

If several groups of BIs are placed in a fixed location in an isolator, the kill kinetics can be examined with the following process: Groups of BIs are placed into individual tubes with a culture medium, at a defined time therefore, interrupting the exposure. If the BIs are now incubated it will show "growth" or "no growth. For the BI groups with a short exposure time, growth (full growth) is expected, followed by an interval in which parts of a group show growth and the rest of the group shows no growth (fractional growth). After a certain point in time, all BIs of a group show no growth (total kill).

If this study is performed with a group of EIs, that are exposed at the same time to the cycle as the group of BIs, the observed growth can be correlated to the quantitative EI results (see picture on page 35). The obtained RLU_{rem} values for this time period, when the last full growth and the first complete kill is achieved, present threshold values that limit the range, where fractional growth of a group can be expected. This correlation will show if full growth, fractional growth or total kill can be expected, depending on each individual case and certain EI results (RLU_{rem} value).

Furthermore, an additional approach was discussed: from the experimental BI group results, SLR-values (Spore Log Reduction) can be calculated via the Halvorson-Ziegler equation, that then can be correlated with the EI results.

With EIs to BIs prognosis

The cited correlations were determined during an isolator test, where H_2O_2 easily reached the indicator locations on the work surface of the manipulation unit. The lessons learned were then applied to a hands-on decontamination application. The isolator was equipped with a typical load. Several indicator locations, in the isolator, were defined (e.g. different materials and difficult to reach geometrical locations) and investigated with two different decontamination systems.

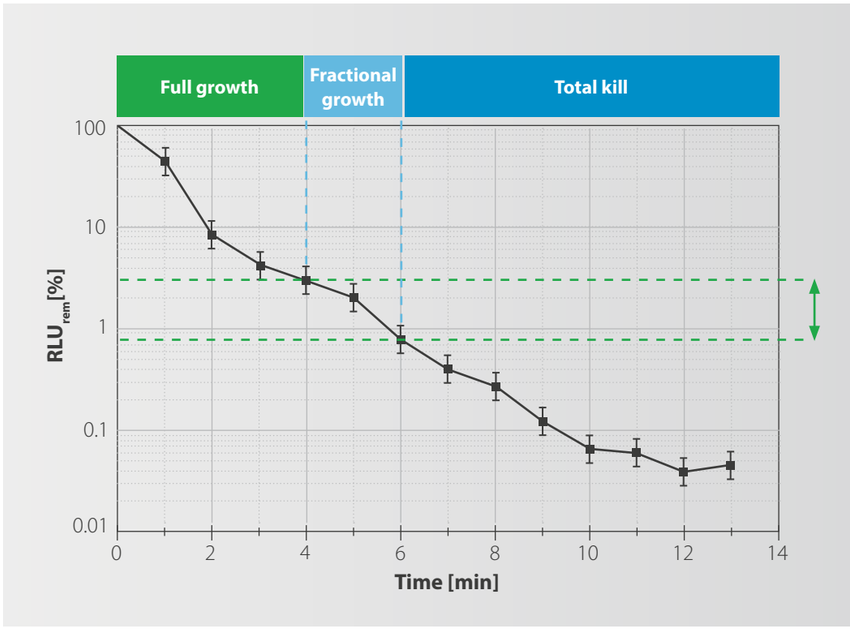
First, the correlation threshold values were defined. Based on these values and the measured RLU_{rem} per location, a prognosis for BI group results per location was established. These results were collated with experimental defined BI results according to location.

For each decontamination system 35 and 36 locations were evaluated. For the majority of locations the measured, results matched the expected prognosis. Five locations did not match, but were close to the values that would have fulfilled the criteria in accordance to the EI variability of 30%. The worst-case locations are most important for the hands-on cycle development. In this test, full growth of BIs was correctly predicted for all worst-case locations.

However, the authors would like to mention that in this context it is advised to perform additional studies and use a wider range of data to ensure the accuracy of the study. It is also recommended to examine additional data for locations with fractional growth.

Hands-on use of EIs

Upon the lessons learned, the authors present first recommendations of how to use EIs complementary to BIs during cycle development.



The H_2O_2 gassing of BIs groups: The graph shows the transfer from complete growth, and partial growth, as well as from partial growth to complete kill (green line). This threshold values can be brought into correlation with the RLU_{rem} values of the EIs (at identical locations and appropriate H_2O_2. gassing time).

Safe aseptic processes in isolators require a solid cycle development. Parameters for the decontamination process during cycle development are first defined, then qualified and validated on a regular basis. To date, only biological indicators are used. Recently Enzyme indicators were introduced that also react to H_2O_2 in a timely manner and are conditional to dosing volume and might have additional benefits.

First, threshold values for the used EIs and BIs have to be determined, beginning with the transfer from full to fractional growth and from fractional growth to total kill, according to the described process. To determine the current correlation of both indicator types, a minimum of three EIs and BIs per location, should be used in the same time intervals.

Either single or triple EIs should be used to examine locations in the isolator. Using triple EIs, the correct variability (CV),for each case, can be calculated. Alternatively, an EI variability of 30% can be assumed.

In accordance with local EI results (RLU_{rem} values) a prognosis for theoretical BI-group results can be prepared (full growth, fractional growth, total kill). In addition, this process identifies potential worst-case locations (these locations show the highest remaining enzyme activity, RLU_{rem}). In the next step, a D-value determination can be performed for these positions in a conventional way, using BIs at worst-case locations. It is recommended to perform verification cycles using BIs. Cycles for validation should also be performed with BIs.

The targeted determination of the D-value, of the worst-case location, reduces time and labor. It is significant that the indicators can be evaluated directly after the cycle and therefore, a quantitative result is available in a timely manner This also acts as an additional control function: BI results, based on EIs, should coincide with real defined BI results. If deviations arise, they have to be examined more closely.

EIs also provide another benefit. Since they are not based on living organisms, EIs can be placed in the isolator during decontamination, before production, to examine the decontamination success Significant deviations for each decontamination cycles and trends can so be detected.

MULTIUSE PORTFOLIO: FLEXIBLE AND HIGH PERFORMANCE

The latest generation of OPTIMA MultiUse equipment processes up to 24,000 containers per hour. The complete MultiUse portfolio covers applications from clinical studies to large batch sizes. The processes are transferrable on a one-to-one scale, up to the highest output, while maintaining precise dosing volumes, and maximizing the product yield and flexibility.

MultiUse line with process paths for liquids and freeze-drying.

IMPORTANT FOR YOU

- Continuous MultiUse portfolio from R&D to high performance applications with identical, transferable processes.
- New: High output up to 24,000 containers/hour, including complex fill & finish requirements.
- Flexibility to process different container types: Ready-to-use syringes, cartridges and vials (bulk or RTU in tubs or trays).
- Unique process varieties with turnkey options: Combination of different process paths in one system, including freeze-drying.
- Pharmaceutical optimized robotic and best in-process safety for minimized operator interference.
- Comprehensive functions for maximum product yield.
- Smart Production Assistance Services provide production and format change support.

When Optima began developing the MultiUse systems 10 years ago, the design team was literally looking at blank pages. Today, MultiUse machines are the safe and economical answer to complex dosing tasks for expensive pharmaceutical drugs and different active ingredients. They are well suited for a wide range of uses from clinical trials to high-speed commercial production processes. The MultiUse portfolio offers identical transferable processes, from one to 10 lanes.

The market demands higher outputs

Many biotech start-ups became notable companies or an interesting takeover candidate. The ratio of pharmaceutical produced drugs in Germany is more than a third. At the same time, specialized CDMOs (Contract Development and Manufacturing Organizations) for complex pharmaceutical drugs developed into larger enterprises.

INNOVATION

Nested containers are unpacked automatically. Bulk containers such as non-pre-sterilized vials can optionally be fed via a second product path.

Transfer of the containers into the highly flexible transport system. There is no glass-to-glass contact at any time in the MultiUse lines.

Highly precise dosing system, exact filling volume: If a fill volume is inaccurate, the container is immediately refilled instead of rejected – the so-called "re-dosing on request".

Freeze-dried or liquid? MultiUse: Both product paths can be processed at a common crimping station for vials.

New drugs receive additional approval for supplementary therapeutic applications and reach new markets. Conclusion: A dynamic and growing market demands MultiUse applications with a high-performance ratio.

The latest generation of MultiUse systems combines 10-laned processes and the specific characteristic concept of individual packaging. The output can reach up to 24,000 containers per hour. All features like 100% in-process control for vials, ready-to-use syringes and cartridges, as well as product savings are still available with a high output. The MultiUse portfolio includes all performance categories for small, medium and large batches.

Easy scale-up from the lab to high-performance filling

Optima Pharma places great emphasis on process transfer to all new systems and for all concepts. Scale-up is easier when processes can be "inherited" by the next generation of high-performance MultiUse systems. This includes guidelines for system adjustments in the millimeter range, homing function and more support processes. Validation of identical machine functions is possible and already validated processes are the basis for new systems.

Currently, Optima Pharma is designing a MultiUse machine complementary to the single-lane MultiUse machine for laboratories and for batches up to 2,000 containers, typically used for experimental purposes and stability tests. With this MultiUse version Optima offers identical functions that can be used within an isolator, but with a very small footprint. The processes can be transferred to the MultiUse production system later. Users benefit from the laboratory version by relieving the production machinery and using its potential to its fullest.

Turnkey: Many process paths – for maximum flexibility

The MultiUse portfolio provides the option to configure different processes within one machine. For example, a bulk path for non-sterile vials that are transported from the washing machine and sterilizing tunnel to the filling station. Parallel a RTU-path for pre-sterilized syringes, cartridges and nested vials or vials in trays can be integrated leading to the same filling station. A freeze dryer can follow and lead to a joint crimping station that processes both liquid and lyophilized vials.

The MultiUse portfolio adapted with the CSPE (Comprehensive Scientific Process Engineering) approach for different combined processes in one system is especially profitable. Machines are completely integrated and tested before the FATs (iFATs) with isolators and loading and unloading systems in the CSPE center. Subsequently, Optima Pharma performs a cycle development in-house, in order to save the customer time until production start.

Digital technologies and robots increase process safety

To comply with pharmaceutical requirements, Optima Pharma selected a different, innovative approach for automation. Depending on the assignment, a typical six-axle robot can be a disadvantage for pharmaceutical systems. Robotic arm movements, particularly, above open containers have to be avoided to maintain pharmaceutical integrity. In addition, the large space requirements of the robot, the possible disturbance of the laminar air flow, as well as lower speeds during the transport through the machine, call for specific robotic and pharmaceutical solutions.

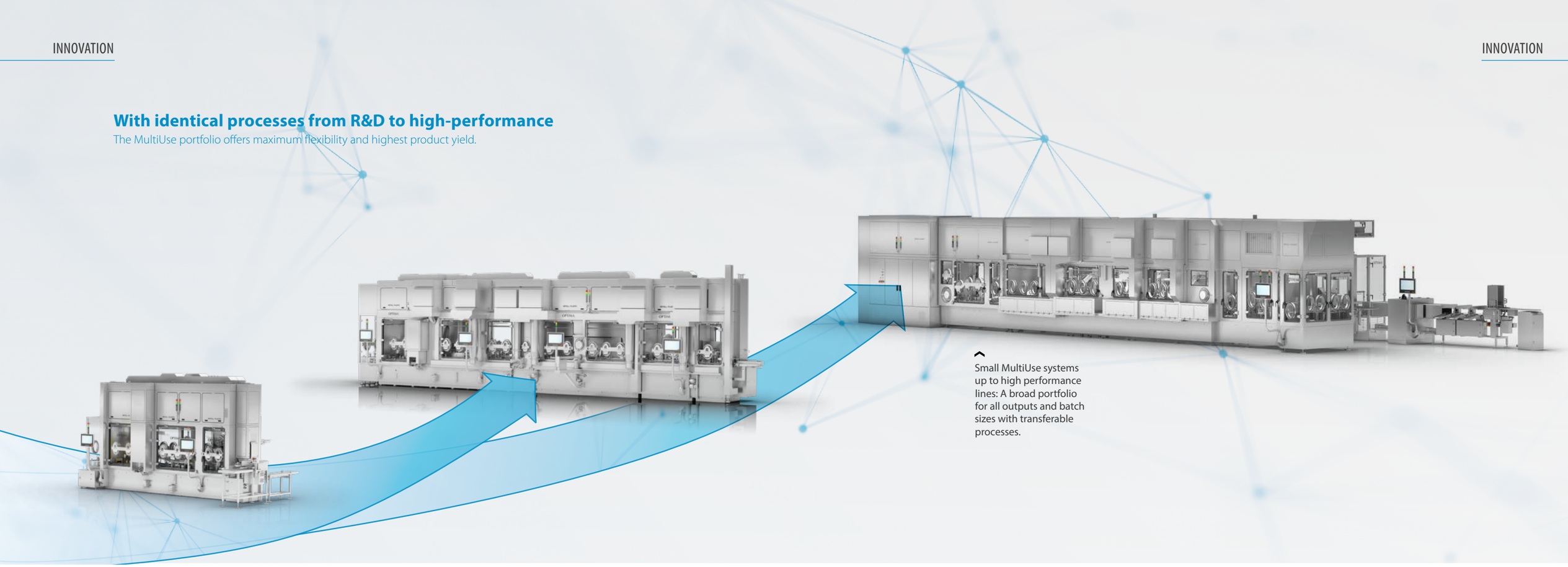
For these reasons, the MultiUse system contains different robotic types and kinematics and in part, newly designed robots. This highlights the fully automatic linear transport with a format-free design and ensures the gentle transport of containers throughout the entire machine: from de-nesting to re-nesting containers without any glass-to-glass contact.

Flexible robotic approach

Third-party robots can be used for de-nesting and feeding containers into the transport system. The free-programmable oval transport can also be reviewed as part of this process. Together with "conventional" robots, the oval transport offsets potential empty spaces in the nest and is part of the flexible re-nesting process. All robot functions reduce operator involvement to a minimum.

With identical processes from R&D to high-performance

The MultiUse portfolio offers maximum flexibility and highest product yield.



Small MultiUse systems up to high performance lines: A broad portfolio for all outputs and batch sizes with transferable processes.

An additional benefit: Optima Pharma programs all continuous core processes, including all transport systems in-house – this is more than "just" an integration of third-party components. Each MultiUse machine is controlled by central logistics. This full synchronization forgoes manufacturer specific software sub-systems and reduces the software's complexity enormously. This is especially vital if the standard process has to be changed. For example, if an individual stopper is added, all machine components stop and will be automatically married again to the process. A process that is easily controlled, specifically if coherent software controls the machine operation.

Weighing precision without compromises – up to high performance systems

Highly precise weighing systems are one of MultiUse system's most beneficial features. The transport system's impact on the weighing precision should not be underestimated. Optima's sophisticated transport and weighing technology achieves precise weighing results, avoiding potential errors due to oscillation.
Highly precise weighing results require a certain time to be completed. Optima succeeded in implementing these requirements into the new MultiUse high-performance machinery. In addition, individual weighing cells simplify the acquisition of spare parts.

Easy operation and increased innovation

Smart production assistance services from Optima have proven extremely useful for highly flexible systems. Digital technology supports systems during size part changes or the changeover to a new product. All tasks that need to be performed by an operator can be accessed with augmented reality glasses, a tablet or HMI and can be uploaded visually into the machine system, and information immediately implemented by the operator.

A re-printing function to maximize the product yield is a new feature. The vials or tubs can be reprinted, if they are classified as incorrectly labeled by the camera system. This assists bringing pharmaceutical production per batch even closer to the 100% mark. In addition, processing of pre-crimped individual cartridges was accomplished 100% air bubble-free using a multi-staged filling process in combination with vacuum stopper insertion. This means the stopper is always in the correct position, for the final pen application.
This machine design has an additional benefit. Different bio-pharmaceutical products require different handling. The individual handling of the object is the ideal requisite to fulfill individual requirements.

MultiUse – a model for success: Customers utilize its portfolio reliability

The bold decision to establish a new MultiUse machine system proved correct. Since the first customer bought a MultiUse in 2014 (they have since purchased a second MultiUse machine), the demand has continuously grown, especially since 2019. Today, MultiUse machines are very well established on the market. From laboratory to high-performance machines, the systems are in daily use in the pharmaceutical industry. Several customers, including international CDMOs and well-known companies, use the portfolio and operate MultiUse equipment with different outputs.

IMPORTANT FOR YOU

- Specific, highly flexible system design for viral vector products at CDMO Thermo Fisher Scientific VVS.
- With comprehensive product saving functions, fewer rejected vials lead to higher overall product yield.
- Isolator technology together with an air-sink concept for safe viral vector processing under Biosafety Level 2.
- Gentle handling and transportation – optimized for scratch-sensitive CZ vials.
- The turnkey concept known as CSPE at Optima Pharma was also a key factor in winning the contract.

System for viral vectors: Lars Waldmann of Thermo Fisher Scientific VVS reports that it takes several weeks in the production area before a gene therapy drug, which is extremly expensive, can be finally filled.

MAXIMUM VIRAL VECTOR YIELD FOR THERMO FISHER SCIENTIFIC VVS

For the first time, Thermo Fisher Scientific VVS (formerly Brammer Bio) is relying on an OPTIMA VFVM isolated filling and closing machine for fill/finish of viral vector products. This provides the Thermo Fisher Scientific group's Viral Vector Contract Development and Manufacturing Organization (CDMO) with a safe turnkey solution and minimal product loss per batch, as well as other benefits.

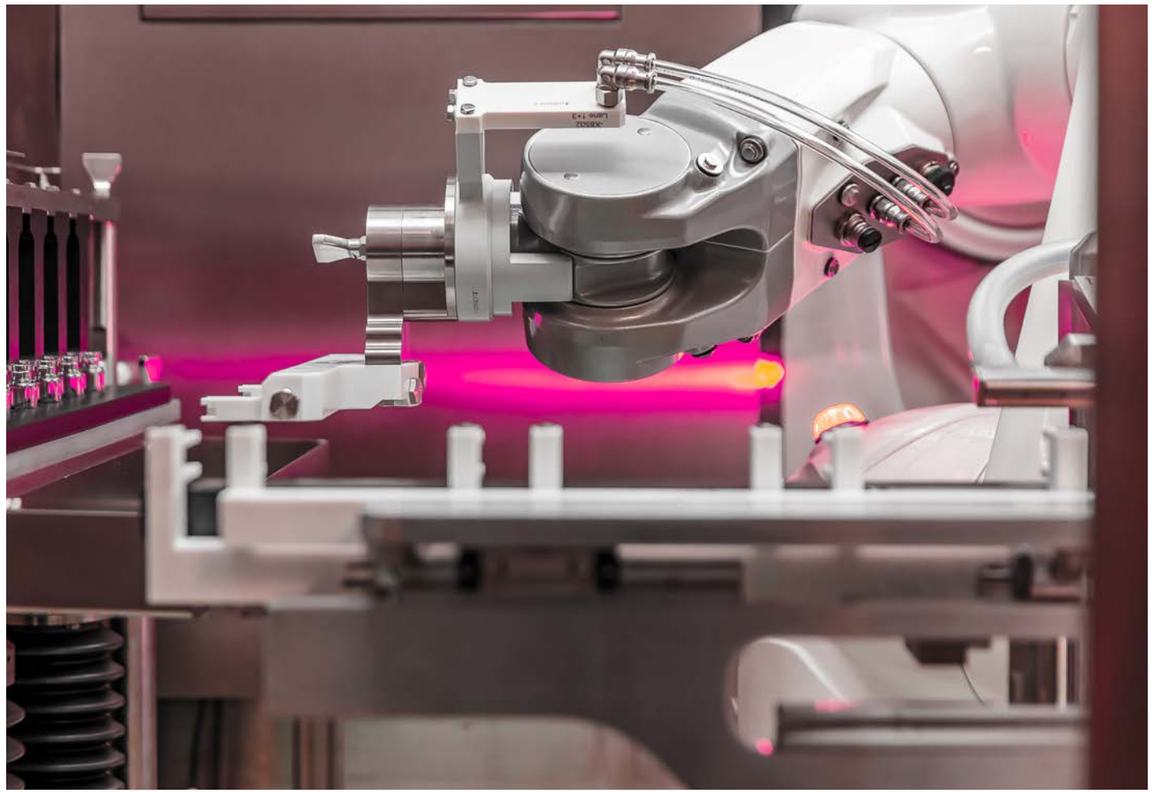
As a CDMO, Thermo Fisher Scientific VVS has already processed over 60 different viral vector products. In this relatively new field of gene therapeutics, this particular wealth of experience has been incorporated into the project with Optima.

Viral vector products are very expensive. Hence, the new filling system with integrated product saving features ensures the highest number of filled vials per batch, explains Dena Flamm (Business Development Manager at Optima Pharma). At the project start, Thermo Fisher Scientific VVS provided her with a list of these and other technical requirements. Optima, in turn, brought its experience from other viral vector projects to influence the design.

Gentle on plastics, flexible operation

Due to the need to freeze viral vector products for storage, Crystal Zenith® plastic vials (CZ vials) from West are a preferred vial type of Thermo Fisher Scientific VVS's clients, which Optima took into consideration during the design of the machine:

Both, CZ vials and glass vials, which can also be processed on the line, are ready-to-use components, pre-sterilized and shrink-wrapped in a vacuum. It is not easy to remove the vacuum sealed packaging material, but it is easily manageable at the ergonomically well-designed de-



Flexible, safe, and gentle handling during the transition to the transportation system as well as in the transportation system itself.

traying station even when using isolator gloves. If glass vials, such as from the Stevanato Group, are being processed, a Tyvek removal station is also activated. For all vial types, this is followed by an automatic de-trayer.
In a typical line design, an infeed (rotary) table would be used to align vials at the infeed lock. CZ vials have a high tendency to tip over and then block the infeed path, requiring multiple repeat interventions by operators to provide a steady incoming supply of vials. A specific linear infeed, which completely prevents vials from falling over, takes over here instead and transports even scratch-sensitive CZ vials in a very gentle manner to the infeed. At the end of the infeed system, vials are transferred into linear processing. This is accomplished with a robot that uses vacuum suction to transfer vials into the linear transportation system, a rake with grippers.

Same product quantity, more vials

Thermo Fisher Scientific VVS decided to utilize all available product-saving functions into the system. A peristaltic dosing pump, using single-use flow path components, is able to dose with extreme precision. At the start of the batch run, the priming function fills the first vials directly on the weighing cell up to their target weight. Because the weighing cell provide instant feedback on the fill solution volume dispensed, it eliminates the generation of rejected vials due to incorrect fill volumes which typically occur during priming of the fill system. During the filling process, 100% fill weight check and re-dosing functions can be activated to minimize rejected vials due to incorrect fill weights. The re-dosing function allows the filling system to add the exact amount of product solution to meet the required fill volume.

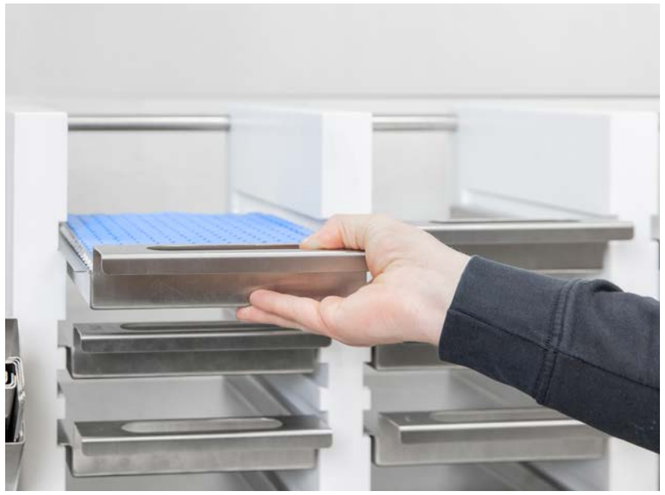
Material transfer chamber for components. In addition, the OPTIMA VFVM can process vials up to a size of 100R.

Vial trays are automatically removed with a robot before being moved into a linear infeed system.

Likewise, the closing process is designed for maximum efficiency and to minimize rejected vials. After the stopper is placed, sensors are used to check that it is actually positioned correctly. If the system detects that a stopper is missing, it can re-stopper the affected vial. Before aluminum caps move into the pick up location, they are checked for deformation. Deformed caps are dropped into a bin. This ensures that only round caps are applied to the vial. If, however, the system detected the absence of a cap, the process will be repeated. Besides minimizing or eliminating rejected vials during the fill process, another advantage of these process safeguards is that, in line with GMP, operator interventions are reduced to an absolute minimum.

Specific differential pressure cascade concept

Once the vials are closed, they leave the isolator-protected area and are automatically reloaded into trays.
Due to Biosafety Level 2 requirements Optima has integrated a differential pressure cascade concept into the isolator that is adapted to meet these requirements. Differential pressures between the processing zones are designed to direct the air flow specifically to the tray-loading area, which has the lowest differential pressure (air sink), thus avoiding operator contact with air from the product processing isolator zones. Within the isolator plenum, air returned from the processing zone is recirculated and then purified by HEPA filters. As an additional safety measure, "neutralized" return air from the isolator – about 10 percent of the total air volume – is vented outside the building and not supplied back into the cleanroom HVAC system.



The amount of valuable pharmaceutical product that is available per batch is optimally utilized using Optima technologies to achieve maximum product yield. This includes dosing on the weighing cell for priming and re-dosing.

At the end of the filling and closing process, the vials are collected in special trays.

The Metall+Plastic isolator works with the award-winning DECOpulse®system. As a result, Thermo Fisher Scientific VVS benefits from fast cycle times coupled with highly uniform vaporized hydrogen peroxide (VHP) concentrations inside the isolator. This specific characteristic is created by generating extremely small microdroplets that evaporate even at room temperature in a stream of compressed air. Targeted turbulence and injection nozzles that have been optimally positioned based on flow simulations ensure that the vaporized H_2O_2 is distributed extremely evenly. This ensures reliable decontamination, combined with short cycle times, especially since there is no need to heat up the vaporization system as required for tradition thermal vaporization processes.

CDMO, that means flexibility

Typically, viral vector products are manufactured in smaller batch sizes compared to other types of treatment. Thermo Fisher Scientific VVS anticipated a maximum batch size of 5,000 vials during the design process with Optima. Being a CDMO means that product and format changes are carried out frequently. Peristaltic pumps used with single-use components ensure fast, safe product changeovers. This is complemented by a central HMI for the filling machine and isolator, which generally simplifies operation. The configurations for upcoming product and format changes can be done on the HMI. Particularly noteworthy is the fully automatic, linear transport system, which requires no size-specific change parts. The OPTIMA VFVM can handle vial formats up to 100R.

Apart from the innovative product-saving features, the comprehensive turnkey approach – the CSPE process (Comprehensive Scientific Process Engineering) – was another reason for Thermo Fisher Scientific VVS choosing Optima (see the interview on page 47). When the final installation of the OPTIMA VFVM with isolator is carried out in the new building at Thermo Fisher Scientific VVS's site in Plainville (Massachusetts, USA), all that will remain to be done is to reconnect electrical connections and interfaces, which have already been tested, and finalize the connections to building utilities. Because the system is very compact and only few connections needed to be disconnected for shipment, the installation process is very fast. After successful installation, the fill line with isolator will undergo Qualification, followed by decontamination cycle development.

INTERVIEW

Hands-on experience of the CDMO service provider

Lars Waldmann
Staff Engineer, Global Engineering, Thermo Fisher Scientific Viral Vector Services

What are your investment objectives for the new filling and closing system?

We as a CDMO service provider are currently setting up a new production facility in Plainville (Massachusetts, USA) for gene therapy treatments. The extra capacity will enable us to serve more customers on a larger scale in this fast-growing market. In our existing production facilities, we use filling systems with isolators and have identified potential room for improvement. Optima Pharma's bespoke isolator filling system allows us to do this as required.

For Thermo Fisher Scientific VVS, what were the decisive factors in awarding the contract to Optima Pharma?

Optima filling systems are already in use at several sites of our Pharma Services Group worldwide. This means that we have gained extensive experience in a wide range of applications. The cost of producing gene therapy products also makes it important to use technologies that can fully utilize the amount of fill solution available. Optima Pharma has implemented product-saving technologies in the design. These include what is known as priming the filling system, re-dosing if necessary, re-closing if necessary, and checking the crimp caps for deformation. Optima Pharma also has one of the best isolator manufacturers in the industry through its subsidiary Metall+Plastic. By evaporating hydrogen peroxide at room temperature, the operation and installation of the isolator have been greatly simplified in comparison to other isolators.

One key argument that Optima lays claim to is its comprehensive turnkey approach, the CSPE process. Can you see benefits in real-world operation?

Sourcing the filling system and the isolator from the same manufacturer makes the project much easier to manage. If two or more manufactures would be involved in a project, we as the client would become responsible for all of the project coordination and signal exchange - and these issues can become very difficult. The Optima philosophy includes performing comprehensive internal commissioning prior to the Factory Acceptance Test (FAT) and Site Acceptance Test (SAT). This provides high levels of assurance that no major problems will be detected while running FATs and SATs. The equipment is fully tested before the handover to the customer; this significantly increases a successful, smooth start-up.

The system has not yet gone into commercial production, but maybe you have already gained some first impressions, for example from the series of FATs.

The filling system FAT was completed in November 2021, and the product-saving technologies worked flawlessly during the test runs. Over the course of a three-hour test run with 0.5 mL Crystal Zenith® vials, not a single vial tipped over, which is an impressive performance. Not a single vial was rejected due to a system error during the test runs. We look forward to installing the system in the coming months.

IMPRESSIVE PERFOMANCE: THE STISO

IMPORTANT FOR YOU

- Three sterility test isolators were delivered and installed in a short time.
- The modular design of the STISO saved time and money: less design expenditure, no mock-up required, easy integration according to room configuration.
- Largest work chamber on the market: instead of five STISOs only three systems were installed and covered the requirements of the customer.
- High availability and therefore more production time: The Metall+Plastic DecoPulse® system reduces decontamination time.
- Four glove port testing covers per sterility testing isolator provide independent operation.

Three sterility test isolators cover the function of the originally planned five STISOs. Two STISOs (left) are located in the middle of the room and the third STISO is installed on the right side of the room and flush to the ceiling.

An experienced sound engineer is an important part of a band during a "gig". New locations, different acoustics and usually little time to fine-tune. Like parameters, which are a big part of the sterility process for a sterility test isolator (STISO). Lead-time for this process is not just a few hours, but several months. Timing was a critical factor during a project for a well-known global pharmaceutical company, for their new "gig".

New sterility test capacities were needed for a new production facility and time was of the essence, since the installation was delayed due to reasons beyond the company's control.

While finalizing the project was imminent, the timetable was getting tighter. A most precious criterion was the delivery time, remembers Kenan Kanmaz, who received an inquiry while he was on vacation in August 2019. Two days after his return he met with experts from the customer and a specification was sent immediately to Metall+Plastic in Radolfzell. Including a very tight timeline for the required sterility test isolators. The first sterility test isolator for this customer was required to deliver in May 2020. In addition, all quotations and pre-order provisions had to be completed within two weeks.

Is it feasible?

Gerhard Breu, Chief Representative (Optima Pharma) and the former Managing Director Thomas Bertsche (Metall+Plastic) needed to decide if Metall+Plastic was going to accept this challenge. After several discussions, they decided to take the project on. Besides the timeline, quality machinery, process safety and fast decontamination were the customer's key requirements.

Originally, five sterility test isolators were expected to be required for the new facility. However, after reviewing the specifications for the loading capacities more closely it was evident that the customer would only need three Metall+Plastic STISOs.

In terms of the short delivery times specified by the customer, Metall+Plastic was depending on their special technical STISO designs. A crucial element was the modular design that adapts easily to individual environmental conditions. For example, the capacity and number of glove ports, as required in this project, can be maximized. The customer decided to purchase four glove ports, the largest alternative.

Ergonomics is an important part of a STISO in order for employees to reach all areas and work without fatigue. The STISO's ergonomic design creates a comfortable work environment for operators of any height. In addition, it does not require a mock-up, which decreases delivery time and overall cost compared to customized STISOs. Three modular STISOs rather than the five originally planned sterility test isolators were a convincing package – and Metall+Plastic was able to reduce the project timeline using three identical systems.

Tests in sync with requirements

The STISO is designed to fit in different room configurations and is suitable to sit flush with the ceiling, sideways flush in a corner, or back to back in the middle of a room. The latter two alternatives were implemented for this project. Only a few connections were required to connect the STISOs to the existing building structure, with compressed air, cooling water and power. Therefore, the STISOs will operate independently from environment temperature

The ergonomics of the STISO were developed together with experts.

The proper functioning of the glove testing unit can be tested and checked directly at the STISO.

due to an integrated cooling coil that compensates high room temperature and lowers the temperature to levels according to defined process parameters and tolerances. The process temperature can be lowered to 18 °Celsius. At the same time, the cooling unit ensures that no heat is released into the room. Like the modular design, this is a unique feature to help meet customer requirements.

The customer also had particular requirements to process internally defined error messages. Specific identical error codes alert operators and technicians about malfunctions; Metall+Plastic adjusted its software accordingly. Consequently, detailed documentation was created according to customer standards.

Metall+Plastic offers a very high standard for process quality and utilized components, including controls. In correlation with specific design features like service-friendly door sealing systems, work chambers and MTC's in 316L stainless steel, sterile design, air filtration systems and comprehensive sensors with different alarm functions, very high process safety is ensured using the sterility test isolator.

On time production – despite Coronavirus challenges

With the start of the Coronavirus, an unexpected obstacle emerged. Specifically concerning the cycle development. Many projects were delayed due to the first hard lockdown. Customers, understandably, did not want and could not have external personnel in-house. Once it was feasible to visit customers again, a long list of projects had to be managed. Even so, Metall+Plastic was able to keep the timeline for the FATs and SATs, as well as the start-ups.

The first STISO during the pandemic was installed in May 2020, as scheduled. The FAT for the second STISO took place in June and the FAT of the third STISO in September 2020. Due to reasons mentioned earlier, the cycle development was slightly delayed, but on time for production start. After the Process Qualification (PQ) of the first STISO in December 2020, the two remaining sterility test isolators were placed into the laboratory area only a short time later.

Four glove ports are adequate to reach all areas in the STISO's work chamber easily.

A loaded STISO: the decontamination process of the inside surfaces will start shortly, to test the sterility of pharmaceutical drugs.

Well-coordinated – Cycle times reduced to a minimum

The pharmaceutical company selected the DecoPulse® biodecontamination system from Metall+Plastic. One of the system's features is the homogeneous distribution of H_2O_2 into the isolator and onto the surface of the loading station, while reducing H_2O_2 at the same time. This means less H_2O_2 has to be removed from the isolator. Due to the small micro droplets, the H_2O_2 becomes an atomization driven evaporation system using our patented DecoPulse® technology. The catalytic ventilation system from Metall+Plastic is an important feature to minimize the remaining H_2O_2 very quickly.

In summary: The sterility test isolator from Metall+Plastic will give you more production time. To put it in numbers: 49.0-gram H_2O_2 is injected during the entire decontamination process and it takes ten minutes to achieve a 10-log germ reduction. Subsequently, it only takes 35 minutes of ventilation time to reduce the H_2O_2 to a remaining 0.5 ppm concentration and only an additional 25 minutes for safety ventilation.

Due to the short cycle times and gained production time, the customer waived the loading port – saving space, as well as acquisition and maintenance costs. To maximize production time even more, four glove port tester covers, for the four glove ports, were ordered for each of the sterility test isolators. The GTS-WL is connected with the system's HMI via WLAN and integrated in the machine's design. The integrity testing time for all four glove ports per isolator is therefore reduced to 15 minutes. In addition, the systems can be operated independently.

Conclusion: Reaching your objective with the correct technology.

FREEZE-DRYING: PEPTIDES IN STABLE FORM

Biopharmaceuticals are often unstable liquids and therefore have poor shelf life. This includes the raw materials, such as peptides and olionucleides, which are necessary for the production of important biopharmaceutical drugs. Freeze-drying is one way to bring these sensitive molecules into a stable form. OPTIMA pharma GmbH in Gladenbach, Germany develops and produces these special systems suitable for these active pharmaceutical ingredients.

Different packaging materials like vials, microtiter plates and trays are used in freeze-drying equipment.

IMPORTANT FOR YOU

- mRNA-based pharmaceuticals are versatile therapeutics with a growing number of application prospects and become more interesting and gain in popularity.
- Peptide and oligonucleotides are less stable in liquid-form than freeze-dried.
- The freeze-drying process requires considerable expertise and the systems have to be designed according to peptide and oligonucleotide requirements.
- Our expertise: Modular freeze-dryer design that is configured to customer process specifications – from laboratory to commercial production.

Frozen, pressurized, heated: This sounds like torture. While in fact, they are actually a daily routine in the manufacturing process for biopharmaceuticals and many other drugs, providing a gentle method to remove excess water. The result is the required active ingredient in form of a fine powdery substance.

Freeze-drying, known also as lyophilization, is preferred by the pharmaceutical industry to convert antibiotics, hormones, antibodies, RNA-based vaccines, and many other pharmaceutical drugs into a storable, solid powder form.

"Most patients receive these drugs in liquid form rather than tablets; since the sensitive molecules are not particularly stable in liquid form. They can change in structure and thus lose their effectiveness," explains Stephan Reuter, Managing Director of Optima Pharma GmbH, Gladenbach, Hesse. The company specializes in the development and production of freeze-drying systems.

Gentle evaporation of frozen water

What makes freeze-drying a gentle process? A key aspect is the frozen water that evaporates under vacuum (sublimation) while the temperature is gently increased again. Ideally, only the required product remains, in the form of a fine powder. Another way of extracting a dissolved substance from water is familiar to anyone who cooks: boiling water until it has evaporated. However, this latter approach is anything but gentle. The problem here is that the product will be irreversibly damaged by sustained high temperatures. In addition, not only water will disappear but the required product might change to a gaseous state and is thus lost. "Freeze-drying, on the other hand, is a safe method and proven for converting even sensitive biopharmaceuticals into a stable and storable product," Reuter says.

Biopharmaceuticals: freeze-drying is preferred

Due to factors like the Coronavirus pandemic, as well as the growing number of biological pharmaceuticals and their transport, demand for freeze-drying continues to increase. Optima Pharma has doubled its production area in Gladenbach, where the freeze-drying equipment is manufactured, and the number of employees has almost doubled since 2014. The company's export share is more than 85%. With an average growth rate of 7-10%, the company can look optimistically to the future.

Reuter is confident that this positive trend will continue. "Already, about one-fifth of the top 100 pharmaceuticals are freeze-dried, and for biologics it's already almost half," Reuter says. As an engineer, Reuter has two decades of professional and management experience in the

pharmaceutical industry, which provides many insights. He foresees methods for continuous product development. "The demand for freeze drying has also increased the requirements for the lyophilization process itself. As a result, we develop innovative, sustainable and visionary solutions for these needs."

Peptides are promising pharmaceutical drug candidates

The freeze-drying of peptides, in particular, requires complex production processes and special expertise. Peptides are small proteins, i.e. protein molecules. They consist of several amino acids linked by peptide bonds. Peptides have numerous functions – some act as messenger substances in plants, and others as hormones in the human body. Due to their properties, there are numerous potential applications for these small proteins in molecular biology, immunology and (bio) medicine. Peptides offer a new opportunity for cancer patients, the chance for future individualized vaccines– and thus a promising strategy for an effective therapy. "Peptides are highly effective, and they exhibit high selectivity and specificity with regard to their biological targets," Reuter explains. "Peptides thus offer a promising prospect for novel drug designs and are of great value."

The fine art of freeze-drying

Due to their great versatility, freeze-drying equipment must be designed to meet the needs of peptide production, the final stage that involves solid-liquid separation. "The freeze-dried product they call freeze-drying "cake", is obtained at our customer's facility in containers that resemble baking trays," Reuter says. TThe final stable peptides are then available in milligrams to kilograms as a fine powder and used as active ingredients for the production of various pharmaceuticals.

"There is no off-the-shelf freeze-dryer that completes all requirements. We have to adapt the equipment to the particular pharmaceutical product, according to customer's requirements and on-site conditions. This is our expertise as a special equipment manufacturer," Reuter says.

The company is also involved in a promising new area of development: controlled nucleation. The focus is the freezing process that is difficult to control, especially for highly purified products. An irregular freezing process has a corresponding effect on the ice structure. However, controlled nucleation is a process that solves this problem: Additional pressure is created in the system and released quickly, resulting in forming very homogeneous ice crystals, while at the same time, accelerating the drying process.

Energy-saving

Shorter process times reduce the material consumption – and, above all save energy.

"Despite the benefits offered by freeze-drying, it is, unfortunately, also a very energy-intensive process, and correspondingly costly," explains Reuter. "After all, the stainless steel systems, which can weigh up to 30 tons, must first be sterilized with steam up to 130 °Celsius, cooled to freezing temperatures down to minus 70 °Celsius, placed under vacuum and then reheated to 130 °Celsius again, to start the process. This is the only way to achieve the desired temperatures inside," Reuter adds. "As a result, drug manufacturers are often reluctant to consider this technology for their products."

❮
Freeze-drying converts unstable macromolecules into a stable state.

"We have to adapt the equipment to the particular pharmaceutical product, the customer's requirements and on site conditions. This is our expertise as a special equipment manufacturer."

Stephan Reuter,
Managing Director of OPTIMA pharma GmbH

However, refrigeration technology and new high-performance cooling agents, yield significant savings: Using a dedicated refrigeration system lowers energy consumption. In addition, new innovative cooling agents also save 10 to 20% in energy. Considering the savings from shorter process times, freeze-drying systems today consume up 25% less energy than before these measures were implemented.

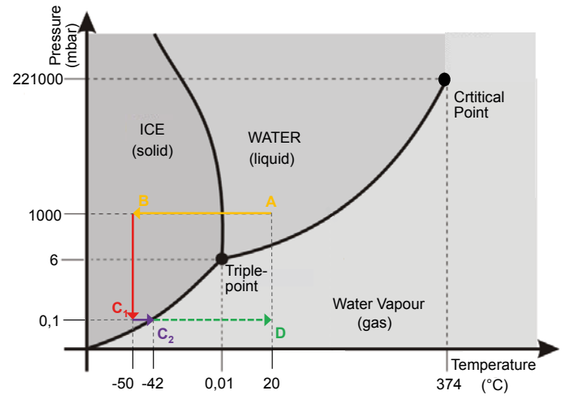
Focus on medical trends

Optima Pharma is also working to establish alternative cooling agents and to create more sustainable and environmentally friendly technologies (see article on pages 24 to 29). New trends in the pharmaceutical industry are an additional reason for new developments. For example, personalized medicine, mRNA and cell and gene technologies.

"These changes influence the production facilities of drug manufacturers, which require fewer large systems, but rather produce marginal and with smaller equipment," Reuter says. "Analogous to batch sizes, biopharmaceutical drug companies tend to install smaller freeze-dryers, and often multiple freeze-dryers at the same time. Even hospital pharmacies are interested in our systems." As a result, the footprint per freeze-dryer or the number of units is a key factor.

Today's freeze-drying process has become much more energy-efficient and more diverse than it was just a few years ago. Optima Pharma has made it a priority to keep an eye on evolving industry trends and to develop new process technologies accordingly – thus making an important contribution to innovative, high-quality pharmaceuticals.

Phase Diagram



A - B
Cooling the product and further freezing it until -50 °C at 1000 mbar

B - C_1
Pressure reduction to 0.1 mbar

C_1 - C_2
Increase in the temperature to -42 °C (at the phase-boundary line) leads to sublimation.

C_2 – D
Desorption of the surface bound water at higher temperature

❮
Phase diagram with transitions of the aggregate states using water as an example: Representation of the sublimation and melting process.

IMPORTANT FOR YOU

- High performance with 100% in-process control, high filling accuracy, and flexibility specifically for ophthalmic drugs processed by CDMO Jubilant Pharma.
- Peristaltic pumps and rotary piston pumps are installed for highest flexibility, allowing you to process even viscous products with high precision.
- The system handles conventional containers with droppers and caps, as well as the preservative free OSD technology for ophthalmic drug products.
- The preservative free OSD technology is processed by dedicated format sets without the need for system conversions.
- Flexible and space-saving design for limited spaces.
- Processing under sterile conditions.

EYES OPEN TO SPECIAL CDMO REQUIREMENTS

When purchasing machines specifically designed to process eye drops, Jubilant Pharma had two requirements: Flexibility and compact design. As a CDMO, Jubilant impresses customers with high efficiency and precise weighing results because ultimately, this leads to higher yields per batch.

For this project, a four-headed OPTIMA VFVM 10000 was used to implement the specific customer requirements. Jubilant, a CDMO in the ophthalmology industry pays great attention to high performance, high dosing accuracy, and flexibility in terms of varying viscosities and container types. The VFVM10000 offers Jubilant the opportunity to process eye drop bottles in combination with a variety of closure types including preservative free technology.

Jubilant has opted for two filling systems that are permanently installed in the machine. A disposable product path with peristaltic pumps is used as standard. The vertical arrangement of the four peristaltic pumps saves a considerable amount of space.

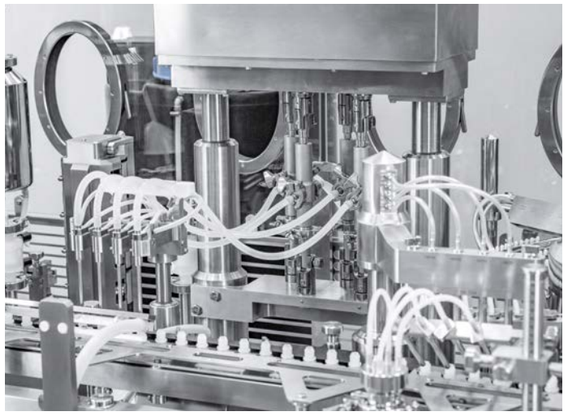
Since ophthalmic drugs are sometimes viscous, rotary pumps can also be used for dosing viscous products with high precision. Both pump types operate in four-digit versions. The OPTIMA VFVM achieves an output of up to 12,000 containers per hour.

Flexibility, performance, and control

Jubilant uses containers that are consistent in weight. The format-related weights are stored in the checkweigher control system; the gross tare weighing provides efficient 100% fill weight control with no loss of performance. Containers with gross weights outside the defined tolerances are rejected. The metering parameters are continuously adjusted based on the fill weights registered and analyzed by the control system. This ensures consistently high precision filling performance, giving CDMOs like Jubilant "weighty" arguments in its favor.

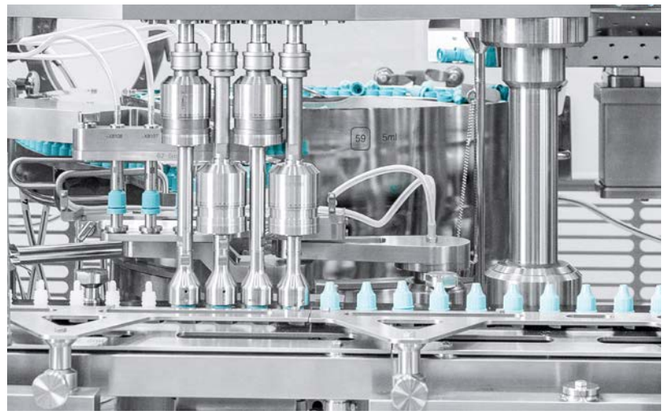
The production process with the OPTIMA VFVM10000 starts with the sorting of the containers and feeding them into the machine with a centrifuge. The correctly oriented bottles are transferred to the filling and closing station via a star wheel and segment wheel configuration to the linear walking beam transport system.

Dropper placement during nitrogen gassing. This extends the shelf life of opthalmic drugs significantly. If preservative free OSD containers are processed, they will be sealed once the special caps with integrated droppers are pressed in.



Four headed filling sytems: Concealed on the left are the stacked peristaltic pumps. Also installed – rotary piston pumps to process viscous products.

The line is operated with an Active Open RABS and under numerous laminar flow units in cleanroom class B.



A two-headed closing station ensures the caps are applied correctly, with the correct amount of torque for easy opening.

The sorting devices ensure the correct alignment and feeding of closures. The preservative free OSD technology is easily processed with dedicated change parts

After the filling process is completed the containers are transferred to the closing station with its specifically designed closing technology, depending on container type. Conventional plastic bottles are fitted with a dropper for dispensing the eye drops. The droppers are transported in a four-lane configuration and inserted into the container with pick & place technology. Optional available: Nitrogen gassing to minimize oxygen in the container.

Twist closure caps are placed via a pre-capping station followed by a final cap torque station.This ensures that always the correct torque force is used and therefore containers are always easy to open. The final torque station also measures removal torque as requested or on a sampling basis.

Once the closing inspection is completed, the finished containers are transferred to a double tray loading configuration at the discharge of the machine. Containers that do not meet the inspection criteria are rejected. The trays, containing only "good" vials, are removed at the end of the line.

Processing of Preservative Free Ophthalmic Squeeze Dispenser (OSD) technology

During the implementation phase, Jubilant chose also to process specific types of preservative free OSD technology. The technology consists of flexible bottles and pre-assembled, multi-part closures with integrated droppers and caps. For easy use, OSD caps are opened by tearing off a plastic tab on the cap.

Additional processing of the preservative free OSD technology was made possible and optimized by making design changes to the OPTIMA VFVM. Now, Jubilant Pharma has the flexibility to easily switch between preservative free OSD or conventional screw closures with dedicated change parts – like a typical format change. For instance, the format parts are located in the bottle feeding centrifuge and the conveyor for the screw caps, erecting the bottles. Sorting, feeding, and pushing the specific OSD closures into the flexible bottles are also carried out by simply using format parts, without time-consuming conversions. A special holder has been developed for pressing in the caps. This ensures stability when pressing the closures into the vials.

Key point: On-site service

In addition to being compact and flexible, high filling accuracy was very important for Jubilant. This was demonstrated in the FAT/SAT with an OEE (Overall Equipment Efficiency) exceeding 90% efficiency. Direct service from a North American subsidiary was another key deciding factor for Jubilant Pharma when awarding the contract. Optima Machinery Corporation has now two locations in the U.S. and the Jubilant account will be handled by Optima Machinery Corporation, Green Bay (WI).

One additional challenge was the limited space available at Jubilant's facility. The VFVM's compact design with stacked peristaltic pump dosing system resolves this issue. The system also had to be dismantled and reassembled on site in order to bring it into the production room. At Jubilant, the OPTIMA VFVM is operated in a Grade B cleanroom environment, therefore the system features Active Open RABS with integrated laminar flow unit above the filling area and additional laminar flow units outside the machine guarding, extending from the door opening zone to the room walls. In total, nine laminar flow modules are operating in the room.

Off to Canada

Over the course of the project, the Jubilant Pharma project team had the opportunity to be on site at Optima in Schwäbisch Hall, Germany, for the key milestones such as the mock-up study, the design review, and the machine factory acceptance test (FAT), despite the restrictions during the Covid-19 pandemic. By October 2021, the system passed the customer's site acceptance test (SAT) at Jubilant in Canada. After qualification, it was commissioned for commercial manufacturing projects for pharmaceutical companies in the ophthalmology sector.

100 YEARS of FUTURE

OPTIMA

1
Turnkey-Partner
for fill & finish, containment und freeze drying

> 18,000
Square meters assembly area
in Schwaebisch Hall
since 2022 (≈ three soccer fields)

> 2,800
Employees
worldwide

1
New service hub
in Raleigh (NC), USA

Raleigh

20
Locations
worldwide
Headquarters
in Schwaebisch Hall (D)

> 400
Service experts
worldwide

11848547/EN