O-COM

THE OPTIMA MAGAZINE

GOING INTO PRODUCTION QUICKLY

FILLING LINES FOR COVID-19 VACCINES IN RECORD TIME

A RACE AGAINST TIME

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TAKING THE LEAD WITH TECHNOLOGY

Gerhard Breu
Chairman,
Optima Pharma Division

Dear readers,

The past months have shown that anything can be achieved with close and reliable partnerships. We have completed filling systems for the leading COVID-19 vaccines for our customers all over the world in record time, and we have commissioned them as quickly as possible. This has only been possible with close cooperation and your trust. Thank you!

In this issue of o-com, you can read about how Optima gives you a head start in the market. Our CSPE process and a whole host of turnkey skills enable us to get complex pharmaceutical systems into production as quickly as possible. Our successful CSPE concept has proven itself. With the valuable insights gained, we are already developing CSPE 2.0 with interested customers. At the Schwaebisch Hall site, we are also building a second CSPE Center.

Only those who use leading technology can take the lead. In our success stories, we present a new innovation project that develops production solutions for cell therapeutics, take you on a journey around the world and share with you the exciting projects that, together with our partners, we have implemented worldwide.

Stay well and positive.

Yours,
Gerhard Breu

26 A race against time

With support from Optima Pharma, Catalent starts filling of vaccines in record time at its Bloomington site. An important contribution in the fight against the pandemic. More about this on pages 26-31.

8 CSPE reloaded

Three years on, it is time to take stock. What are CSPE's benefits, and how can we make it even better? Gerhard Breu, Chairman of the Optima Pharma Division, gives an outlook.

12 An innovation project for cell therapies

Optima Pharma, working in collaboration with the the Robert-Bosch-Krankenhaus in Stuttgart and the Universitätsklinikum Heidelberg, is developing an automated unit for the non-centralized production of cell therapeutics such as CAR-T cells within treatment centers. A milestone in the production of pharma-ceuticals.

NEWS

Innovative power in an industry comparison

The pharmaceutical industry has probably never been in the public eye to the extent that it is currently during the COVID-19 pandemic. Rapid development of multiple vaccines in an extremely short time casts the industry's innovative power in a positive light. A 2018 study by the German Association of Research-based Pharmaceutical Companies (VFA, Germany) shows that these innovations were preceded by in-depth development work, even under non-pandemic conditions. The (research-based) pharmaceutical companies are by far the leaders compared to the most important industries in Germany. In numbers: In the companies that are members of the association, 25 percent of the staff work in research and development (R&D) and 17 percent of the turnover flows into this area. The aerospace sector comes in second place. Here, 15 percent of the staff and eight percent of the turnover are devoted to R&D. The automotive sector, with almost identical figures, is in third place. Globally, pharmaceutical industry spending is even higher: According to a study*, the pharmaceutical industry has reinvested 23% of its turnover in research and development projects (excluding generics). *(*EvaluatePharma®, "World Preview 2018, Outlook to 2024")*

OPTIMA continues its growth curve

Optima can look back on a successful financial year in 2020, despite the ongoing challenges posed by the COVID-19 pandemic. "We are continuing to grow and we have a high backlog of orders," reports Hans Bühler, CEO of the Optima Group. The consolidated turnover stood at over €420 million. The share coming from exports remains at over 85 percent. There are over 2,650 employees working for Optima worldwide. Over 2,300 of them are employed in Germany and over 1,850 work in Schwäbisch Hall. Even during the pandemic, Optima trains an above-average number of young people, with over 190 apprentices and students in the company. "Thanks to the encouraging business conditions, we can offer our apprentices and students a good future, and our employees around the world have secure, exciting jobs, and we are constantly on the lookout for skilled professionals worldwide to enable us to continue to expand," says Bühler.

Digital communication platforms like customer webinars (pictured), virtual factory tours and factory acceptance tests enable Optima to remain successfully in touch during the pandemic.

New Managing Director at the OPTIMA packaging group: Dr. Stefan König

As of March 1, 2021, Dr. Stefan König is Managing Director at the OPTIMA packaging group GmbH. Together with Hans Bühler (CEO), Gerhard Breu (Chairman, Optima Pharma Division) and Jan Glass (CFO), König will be responsible for the ongoing development of the of the Optima Group. The primary focus will be on products and markets. Before he joined Optima, the 55-year-old König with a PhD. in Mechanical Engineering had held senior management positions for over 20 years, most recently as CEO of Bosch Packaging Technology (now known as Syntegon Technology).

More climate-friendly cooling

Optima's sustainability strategy is continuing to evolve. More sustainable production is also achievable in the pharmaceutical sector. In the pharmaceutical industry, many processes are in a state of transition due to political regulations relating to climate change. Refrigeration becomes particularly impacted as access to conventional technologies becomes more and more limited. For systems with lifespans of over 30 years, the focus is on future-proofing and the quality of the systems. Freeze drying systems rely on stable, available refrigerants. We are committed to not compromising on safety and plant performance, and to making freeze drying processes as environmentally friendly as possible. Optima wants to reduce environmentally harmful refrigerants in freeze dryers by 79 percent by 2030. That is why Optima has been successfully using refrigerants with relatively low global warming potential in freeze drying systems for some time, and provides solutions using natural refrigerants and nitrogen cooling.

Conservation of resources in pharmaceutical production

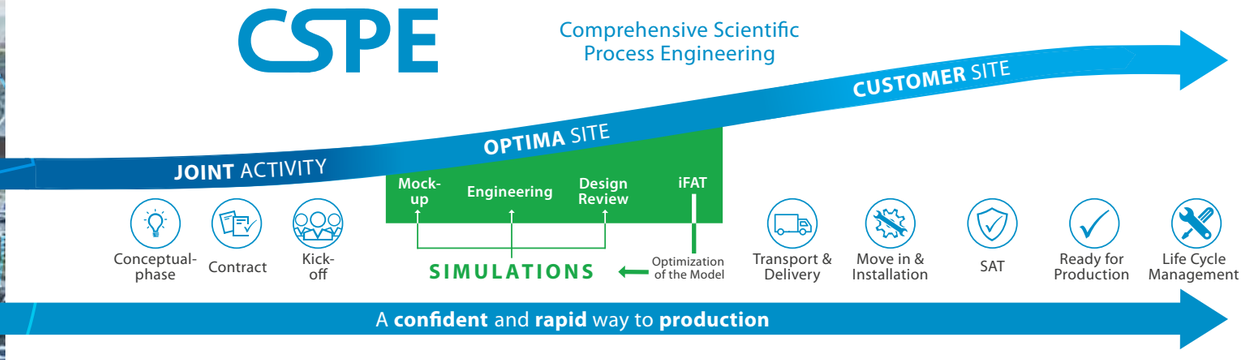
Water is a precious, limited commodity, especially in its pure form. Highly sterile water (WFI) is used for cleaning vials. Producing WFI is time-consuming and expensive. Reducing water consumption is an important issue both for us and for our customers. Long-term water conservation reduces costs and protects the environment. Optima is pursuing multiple means of reducing water consumption in washing machines. For instance, one new approach is to increase water's hydromechanical cleaning effect. New energy in the form of extra compressed air is introduced into the system. Real trials have shown that water consumption can be reduced by up to 45 percent compared to conventional options. All the information on the issue of sustainability at Optima is available in summary form on a single website.

More about this topic:
www.optima-packaging.com/sustainability

At the end of 2021, the CSPE Center in Schwaebisch-Hall will be complemented by another building, where integrated FATs for turnkey pharmaceutical lines can also be performed.

CSPE CONVINCES IN PRACTICAL TESTS

CSPE reduces the time span between designing the system and the start of production. After numerous turnkey projects involving the use of the turbo booster, Gerhard Breu, Chairman of the Optima Pharma Division, takes stock and gives an insight into how CSPE will become even more effective in the future.



CSPE is more than accelerated engineering. Performing risk analyses before the design starts is just as much a part of this as utilizing the potentiality offered by digital engineering in life cycle management.

"As part of CSPE 2.0, we will continue to increase the level of integration of the pharmaceutical lines."

Gerhard Breu, Chairman of the Optima Pharma Division

"Comprehensive Scientific Process Engineering" – the term coined at Optima Pharma in 2018 sounds rather awkward and complex. The idea behind it is no less complex. Large turnkey system construction projects would be accelerated sustainably and the associated risks minimized by using a comprehensive, scientifically based concept. Has it succeeded?

Filling of vaccines with no lost time

Many of the customers who have benefited from CSPE since then think – yes, definitely. Among them are two contract manufacturers that had already started up several new systems for filling COVID-19 vaccines in early 2021. The green light for developing these lines came in the spring of 2020, just as the first lockdown was paralyzing all of Europe and vaccine development was still in its infancy. At breakneck speed, three filling lines that had been intended for other products were reconfigured. They were able to be delivered in the shortest possible time. Three more filling systems are currently being built, and once again CSPE is ensuring that the phase leading up to the start of production can be considerably accelerated.

Optima Pharma has developed the CSPE concept to do everything in its power to shorten the time-to-market for its customers' products. Optima, as a total system provider, also performs a significantly higher proportion of the services involved in constructing complex pharmaceutical systems in-house. This drastically reduces the time required between the start of installation and starting production at the customer's site.

Simulation and Virtual Reality act as accelerators

Even the risk analysis performed before the actual project starts is shaped by CSPE. The consistency shown by all departments in identifying potential hurdles is exemplary. They draw on the workflows of similar, past projects to do this. Every work step that used to be a time-waster is now optimized. This paves the way for the current project to run smoothly. In the design phase, the developers rely on digital engineering, and do so in an extremely systematic manner. Methods like CFD (computational fluid dynamics) and strength calculations have been part of the engineering toolbox for many years. In the context of CSPE, they

STRATEGY

Modeling plant components in the context of digital engineering allows errors to be eliminated at an early engineering stage.

The systems, almost in the same way as in subsequent production, are supplied with ultra-pure water, steam, and coolant, etc. via the media channels in the CSPE Center.

The assembly hall of the first CSPE Center, with a height of twelve meters and an area of 3,600 square meters, is already almost at capacity.

Optima Pharma is a one-stop shop for the aseptic filling of high-quality pharmaceuticals. The CSPE process minimizes the risks associated with large-scale system construction projects. Short delivery times reduce the time-to-market for new pharmaceutical products.

are given an even higher priority throughout the entire life cycle of a system. For example, if the customer makes changes to certain process conditions at a later date, Optima Pharma can make a virtual "tweak". This makes it possible to anticipate any problems that may result from the change.

Simulation and digital engineering also assist with the planning of the sterilization process. At Optima, cycle development is already taking place. Simulation is used to optimize the dispersion of VHP (vaporized hydrogen peroxide) in the isolator. Suitable positions for the bio-indicators during pre-cycle development are defined. The simulation result can be used in the subsequent performance qualification as proof of a safe decontamination process.

Digital engineering also produces a virtual preliminary mock-up. With its help, the system's designers and future operators can experience it in virtual reality. Even before the wooden mock-up is built, they can get an idea of accessibility and are able to make quite a few suggestions for improvements. However, there is still a need for the wooden mock-up, among other things to test the handling of heavy or particularly sensitive components. The virtual mock-up can be used in two ways at once because it also does a good job for training purposes.

Second CSPE Center for complete lines

Another extremely helpful aspect is the option of carrying out an iFAT (integrated Factory Acceptance Test) for turnkey systems comprising filling and closing machines, isolators, and freeze dryers. To this end, Optima Pharma commissioned the CSPE Center with its 4,600 square meters of space in 2019. It provides enough space for the large turnkey lines. They can operate in real conditions here, almost in the same way as in the subsequent production phase. Media channels run along the floor, and all line components can be quickly connected to them. This is how the finished pharmaceutical line for the iFAT is supplied with process heating or cooling, demineralized water, and compressed air. The tests carried out in the CSPE Center ensure that the subsequent installation and the Site Acceptance Test (SAT) at the customer's site are both significantly faster. In the meantime, the CSPE Center is being fully utilized, and the next one is being built – and it will be 25 percent larger than the first one. It is scheduled for completion by the end of 2021 because the CSPE concept, including the pre-cycle development and iFAT, impresses Optima's customers across the board. Gerhard Breu, Chairman of the Optima Pharma Division, is pleased to receive their very positive feedback, as well as further input. These suggestions for improvement are already having an impact. Breu announces, "Integration levels are set to become even higher in future, as part of CSPE 2.0. Work that, up to now, has typically been done on the customer's construction site will be carried out to an even greater extent in one of our CSPE centers."

CSPE is taking hold – and it will be even better in the future

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

AUTOMATION IS KEY TO SAVING LIVES

Personalized tumor treatments are expensive. This particularly applies to individual cancer therapies based on gene-modified T cells. Currently, they are produced manually or, at best, in a partially automated process. In a collaboration project "ProCell for Patient" two hospitals are currently working with Optima Pharma to develop an automated unit for the decentralized production in treatment centers. This should significantly reduce the time and costs incurred in future manufacturing of those therapies.

Every year, more than 430,000 people are diagnosed with leukemia. Another 500,000 get sick with Non-Hodgkin's lymphoma. These include forms of the disease where chemotherapy and donating stem cells are unsuccessful. "Around a quarter of patients who have already undergone treatment can benefit from CAR-T cell therapy," says Prof. Dr. med. Michael Schmitt, Head of GMP Core Facility at the Universitätsklinikum Heidelberg (UKHD). He is considered as an absolute expert in cellular immunotherapy. T-cells are genetically modified there. "We modify the cells so that they can subsequently attack cancer cells in the form of what are called killer cells," explains Prof. Schmitt.

To do this, the cells are given a kind of "prehensile arm" that enables them to recognize the cancer cells. This is known as a chimeric antigen receptor (CAR). Using viral gene transfer vectors, the genetic information for the CAR is transferred ex vivo (outside the body) to the patient's T cells. The patient then receives back the CAR-T cells. They multiply within the patient and fight the cancer cells.

PROCELL

IMPORTANT FOR YOU

- Up to now, CAR-T cell therapeutics have only been produced on an industrial scale at a few sites worldwide, with high logistic, manual and time requirements.
- In the ProCell for Patient project, the Robert-Bosch-Krankenhaus in Stuttgart (RBK), the Universitätsklinikum Heidelberg and Optima Pharma have joined forces to facilitate the future decentralized, automated production of cell therapeutics such as CAR-T cells directly in treatment centers.
- The first production system prototype is scheduled to be installed at the RBK in the summer of 2022. After testing and further clinical studies, there are plans to roll this out to other treatment centers and industrial contract manufacturers.
- This could significantly reduce the cost of cell and gene therapies.

CAR-T cell therapeutics are currently produced manually in the GMP laboratory at at the Universitätsklinikum Heidelberg. This is extremely labor-intensive and has to be done in clean room environments at the highest Class A or B levels. *(Image: Universitätsklinikum Heidelberg)*

Centralized manufacturing is slowing progress

Since 2017, five CAR-T cell products have been approved worldwide: Kymriah (Novartis), Yescarta and Tecartus (Kite/Gilead), and most recently Breyanzi (BMS) and Abecma (bluebird bio & BMS). There are around 1,200 further cell and gene therapies in the clinical pipeline. Several thousand patients could benefit from this treatment every year. However, the complex industrial production of CAR-T cells currently takes place at just a few pharmaceutical industry sites worldwide, or at what are known as CDMOs (Contract Development and Manufacturing Organizations). The logistics involved and the largely manual production in class B or A clean rooms generate high costs. Meanwhile, there are many university hospitals that already have the expertise to produce CAR-T cell therapies, but their manufacturing processes originate in research, and they are therefore manual and individualized. Standardized and automated manufacturing at these clinics would lead to significant improvements in patient care.

Since September 2018, Prof. Schmitt's GMP laboratory has had approval to manufacture CAR-T cells. His team has detailed knowledge of the manual manufacturing process, as well as all the regulations, efforts and costs involved. Commercial CAR-T cell products cost around €300,000. Health services are urgently calling for these huge costs to be lowered, as healthcare systems would quickly be overwhelmed by the growing number of patients. Decentralized automated CAR-T cell production can make an important contribution to curbing costs in this area.

It is therefore not surprising that the UKHD was the partner of choice for the strategic partnership between the Robert-Bosch-Krankenhaus (RBK), Stuttgart, and technology and systems provider Optima Pharma when they were considering developing an automated production unit for CAR-T cell products. As part of a previous project with Charité Berlin, Optima Pharma had already taken the first steps towards developing a suitable production platform.

"The automation of CAR-T cell production is long overdue. Not just for reasons of cost and quality. In the future, it will make the innovation process easier."

Prof. Dr. Walter E. Aulitzky, Chief Physician, Department of Oncology, Hematology and Palliative Medicine, Robert-Bosch-Krankenhaus Stuttgart (Image: Robert-Bosch-Krankenhaus/Fotostudio M42)

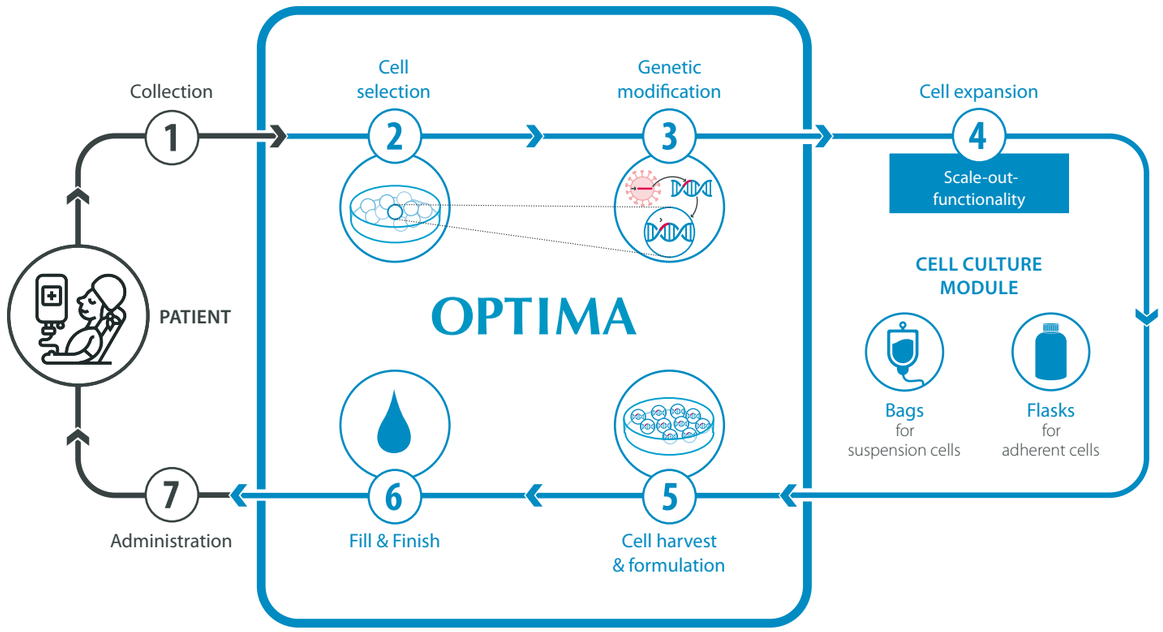
The RBK or its research unit, the Robert Bosch Society for Medical Research, has taken over management of the project. Prof. Dr. Walter E. Aulitzky, Chief Physician of the Department of Oncology, Hematology and Palliative Medicine at the RBK is extremely enthusiastic by the opportunities brought by CAR-T cell therapy, but when he thinks about the ways they've been made to date, he becomes impassioned: "When you have such a complex process with hundreds of different steps, you can't really have medical technicians filling pots on a "four-eyes" basis. Automation is long overdue. Not just for cost reasons. There is also a quality aspect. In the future, it will also foster innovation, because clinics that are involved in decentralized manufacturing can also contribute to optimizing and developing new cell therapies."

The first fully automated prototype system for producing CAR-T cell therapeutics using technology supplied by Optima Pharma will be installed in the GMP facility at the RBK. What was missing so far was the special expertise needed for manufacturing CAR-T cell products. "It quickly became clear to us that we had to recruit the Universitätsklinikum Heidelberg as a professional manufacturer and Prof. Schmitt as a specialist who knew the process inside out," recalls Prof. Aulitzky. This was not hard to do, because Prof. Schmitt is also anticipating significant improvements as a result of automation: "The workload will probably be reduced by at least 50 percent. Automated processes can also operate outside of regular working hours."

"ProCell for Patient" at the heart of a future reference center

The "ProCell for Patient" project started in October 2020, and is funded by the Ministry of Economic Affairs, Labour and Housing Baden-Württemberg as part of the "Forum Health Region Baden-Wuerttemberg" initiative. From Optima Pharma, Dr. Andrea Traube, who heads up Market Development with a focus on system solutions for cell and gene therapeutics at Optima Pharma, is accompanying the project. As Dr. Traube says, "The first steps have been mastered. These are the detailed process analysis of the CAR-T process in Heidelberg and the creation of the User Requirement Specification (URS)." Her expertise in automating cell culture processes, according to Prof. Aulitzky, is to ensure "that we not only map the manual process 1:1, but also make potential adjustments to the process to exploit the full potential of automation to optimize the manufacturing process." Optima has unique expertise in this area, he is convinced..

With support from the Baden-Wuerttemberg state government, stakeholders from the healthcare industry are developing programs designed to raise the state's profile as a healthcare location to the highest level possible.



In the Stuttgart/Heidelberg ProCell for Patient model, essential steps (blue) in the production of cell therapeutics are performed in an isolator in a fully automated process. The prototype will be installed at the Robert-Bosch-Krankenhaus in Stuttgart.

There are six main steps to the process: cell selection, cell activation, genetic modification to CAR-T cells, cell expansion, cell harvesting and formulation, and fill & finish. By using isolator technology from Optima, the system has not to be installed in the highest clean room class, as is the case in the Heidelberg GMP laboratory, but in class C or D clean rooms. The first challenges were already overcome during the preparation of the URS. Prof. Schmitt remembers: "To translate the manual process into a cybernetics format, a new way of thinking was required." Some process steps proved to be particularly challenging, such as the introduction of biological material. This is because isolator technology requires gassing by hydrogen peroxide, which can be damaging to unprotected cell material.

Operating concept to be integrated into hospital processes

Now Optima and the RBK are in the driver's seat. The experts at Optima Pharma are working on developing functional modules, while the RBK is working on the operating concept and developing a concept for a clinical trial to demonstrate the suitability of the system for use in decentralized CAR-T cell production.

In Q2 2021, work began on building and testing the first functional modules. As a result, it is assured at an early stage that the living cells are not damaged, for example by excessive shear forces. At the RBK, test operations will start in the summer of 2022. Even then, UKHD experts will still have an important role to play in making appropriate adjustments to any slight deviation. The ultimate goal is to produce a safe product that is given to the patient as an intravenous drip.

Possible use in hospitals and industry

If the ProCell for Patient model is a successful one, the intention is then to turn the prototype into a marketable product. Dr. Andrea Traube explains: "The system can be used in the future in both tumor treatment centers and in the pharmaceutical industry." Because of its modular design the project partners are anticipating that the production platform can be used to produce different types of cell and gene therapeutics. These have a great potential. By 2025, EU and US regulatory authorities anticipate ten to 20 new products per year.

In the long term, multiple hospitals and their patients may benefit from the ProCell for Patient project. First and foremost is the RBK. Prof. Aulitzky expects to obtain manufacturing approval three to six months after the project ends. The Universitätsklinikum Heidelberg, which will initially be supplied by the RBK, will also benefit from this. However, in the medium term, Prof. Schmitt wants to be one of the first to roll out the technology: "We want to set up a number of robot production isolators on a factory floor." Other clinics are also interested. Consequently, Baden-Wuerttemberg as a location will benefit by becoming a leader in technology for the decentralized production of personalized cell and gene therapeutics, and will help in gaining acceptance by health care providers and regulatory authorities. This means that in the future, patients will receive treatment more quickly, with the promise of successful treatment even when all other options have failed.

"With the help of the ProCell for Patient system, it will probably be possible to reduce the amount of work, i.e. the number of hours that qualified staff are spending today on the production of CAR-T cells, by at least 50 percent."

Univ.-Prof. Dr. med. Michael Schmitt, MHBA,
Siebeneicher-Endowment Professor for Cellular Immunotherapy, Head of GMP Core Facility,
Qualified Person acc. to §14 AMG, Medical Clinic V, Universitätsklinikum Heidelberg
(Image: Universitätsklinikum Heidelberg)

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FULL THROTTLE FOR VACCINE FILLING

The pharmaceutical industry started research on vaccines to fight COVID-19 in spring 2020. For Thermo Fisher Scientific, it meant upgrading its contract development and manufacturing business to support production of therapies and vaccines. Requests for suppliers like Optima to provide new sterile fill/finish lines with isolators were scheduled. New ultra-high speed fill/finish lines from Optima enabled by new technology vials from Corning now offer the possibility to further increase filling capacities within a very short period as is discussed in this joint in-depth evaluation.

Since the outbreak of the pandemic, Optima Pharma has been making great efforts to adapt existing filling systems for vaccine filling and to build new filling systems with isolators as quickly as possible. "Our employees have been extremely challenged and are delivering top performance worldwide," says Juergen Rothbauer, Managing Director of OPTIMA pharma GmbH. One example for a successful collaboration during the pandemic is with Thermo Fisher, headquartered in Waltham, Massachusetts.

Figure 1: The vaccine is dosed multi-digit into the vials. *(Optima)*

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The company's Pharma Services business provides contract development and manufacturing services, which includes sterile fill operations for COVID-19 vaccines and other critical care medications for pharma companies globally. As a strategic partner with the necessary technological know-how, and end to end drug substance and drug product development and manufacturing capabilities, Optima is helping the company increase capacity for vaccine filling at several of its sites as quickly as possible.

A record time from dispatch to starting production

Optima Pharma makes every effort to keep delivery times as tight as possible: "This is about nothing less than saving lives by expanding global vaccine filling. In this light, we have pulled out all the stops to expedite the completion and delivery of the filling lines for Thermo Fisher," Rothbauer reports. Besides the employees' high level of commitment, a whole package of measures contributed to the extremely rapid starts of production. These include the CSPE approach (Comprehensive Scientific Process Engineering), rapid modifications to machines that were already under construction, and the simultaneous development of vaccines and filling lines. The digitalization of engineering as part of CSPE has been a time saver. High levels of precision were already achieved in the 3D models and simulations, and this was carried over into installation, with high efficiency/high quality lines being created right from the start. A significant amount of time was also saved by assembling the isolator and the entire filling line together in the CSPE Center at Optima in Schwaebisch Hall before delivery as well as extensive testing of the complex technology.

Pathways to higher filling capacity

In addition to fast project processes, selecting the right primary packaging materials offers great potential for increasing filling capacities. As is the case for filling lines, the global demand for primary packaging materials has risen in response to the COVID-19 pandemic. Global supply chain leaders have identified vials as a supply chain vulnerability for both COVID-19 and non-COVID-19 products [1].
Recent US Food and Drug Administration guidance highlights this concern and helps to address it by outlining pathways to facilitate vial and stopper changes [2]. FDA points to Comparability Protocols (CPs) as well-suited for glass vial changes (such as shifts to Corning's Valor® Glass), as CPs can support vial changes broadly including across multiple products that use the same container (e.g., group supplements, trans-BLAs). In recent guidance, manufacturers are encouraged to contact the FDA to discuss specific cases that might warrant modified post-approval reporting categories and other risk-based approaches.

[1] Landscape of Current COVID-19 Supply Chain and Manufacturing Capacity, Potential Challenges, Initial Responses, and Possible "Solution Space," March 2021, https://www.ifpma.org/wp-content/uploads/2021/03/Summit_Landscape_Discussion_Document.pdf

[2] COVID-19 Container Closure System and Component Changes: Glass Vials and Stoppers, Guidance for Industry, March 2021, https://www.fda.gov/media/146428/download

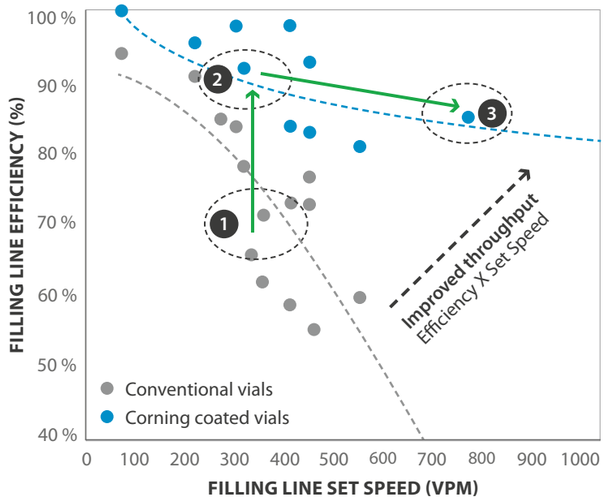


Figure 3: Filling line efficiency tends to rapidly decline with increasing line operating speed when using conventional vials. Corning Valor® vials maintain high line efficiency relative to conventional vials, even as line set speed is significantly increased. *(Corning)*

Line efficiency increase of up to 50 %

"Corning has tested its coated vial technology on numerous customer lines and has repeatedly demonstrated that line efficiency is improved by 20 to 50 percent relative to conventional vials", says Brendan Mosher, General Manager at Corning. Corning, headquartered in Corning, NY, and employing more than 50,000 worldwide.

This was also confirmed in a recent collaboration between Thermo Fisher, Corning and Optima Pharma. Corning Valor Glass was tested at Optima Pharma, Germany to evaluate two situations. On the one hand, retrofitting of existing Optima filling lines to reach higher speeds by use of Corning Valor Glass vials. On the other hand, building new lines that operate at even higher speeds without compromising established quality features such as 100 % in-process controls or product saving technologies such as re-dosing, re-stoppering and re-capping functions.

"Our employees have been extremely challenged and are delivering top performance worldwide."

Juergen Rothbauer, Managing Director of OPTIMA pharma GmbH

Improved production reliability and product quality

During the testing of Valor® Glass vials, no breakage occurred at any time, even though worst-case conditions were provoked, Tobias Dombrowski, Project Engineering Manager at Optima Pharma, reports. "The low friction of the vials surface combined with its very high strength are excellent properties", he says. Regarding the challenging situations for vial filling under the highest speeds, this results in an avoidance of negative cosmetic effects to the vial, breakage of the vial, static charge and less wear of the machinery equipment such as guidings and star wheels. Due to fewer interventions and a better processability in comparison with traditional borosilicate glass, line efficiency is increased.

Increase of line output by 70 %

"Simply substituting Valor vials for conventional vials under typical operating conditions can provide an immediate operational benefit," Mosher explains. This is illustrated by the difference between points 1 and 2 in Figure 3. "We have also observed that line efficiency tends to rapidly decrease when using conventional vials because of increased downtime," he adds. In contrast, the improved flow behavior, damage resistance, and other characteristics of Valor vials enable efficient operation at speeds up to 750 vials per minute as shown by point 3 on Figure 3.

To apply these findings to Thermo Fisher the joint team of experts from Corning, Thermo Fisher and Optima Pharma undertook more in-depth evaluation and further developed the concept onto a project to boost Thermo Fisher sterile fill/finish production with highest speed and quality. As not only investment costs, but also operating costs are very relevant for pharmaceutical companies, the estimation of required cleanroom and isolator space proved to be a major consideration during this project. While raising the speed by almost 70 % from 450 vials to 750 vials per minute, space requirements increased by only 25 % without compromising accessibility of the line. The results expected by Corning could be achieved in the in-depth investigations as shown in Figure 4.

Figure 2: Valor Glass vials *(Corning)*

Figure 4: Increase of vial output per minute (vpm) and space requirements using Corning Valor® vials on an Optima filling line. *(Optima)*

Speed at 2R	Relative speed	Space requirement
450 vpm	Standard line	Standard line
600 vpm	33 % faster	20 % larger
750 vpm	67 % faster	25 % larger

Luca Andretta, Sr. Director within the Pharma Services Technical Operations team at Thermo Fisher said this about his observations during technical assessments: "With Corning glass evaluation and trials we have seen improved quality through reduced risks of glass defects usually seen in normal operation due to Corning's lower coefficient of friction, higher yields as a result of reduced AVI rejects, all of which can allow us to operate our fill/finish lines at higher speeds, resulting in improved overall line outputs. In our experience with Corning glass options, we have concluded that substantial operational and quality improvements may be achieved, with minor qualification and regulatory impact," Andretta explains [2].

New vials as a retrofit option

Existing sterile fill/finish lines at Thermo Fisher plants were analyzed and requirements for retrofitting were defined. Downtime due to retrofitting had to be kept at the lowest level possible. An extension of complete stations or machine parts is not justifiable and causes further consequences, such as a revalidation of the isolator's decontamination cycle. With minimal well-thought interventions in the existing machine design, performance increases of 10 to 20 % can be achieved, depending on the current system. "The combination of a higher efficiency of up to 50 % at increased operating speeds ultimately provides a step change improvement in pharmaceutical manufacturing capacity," Mosher summarizes.

Primary packaging and high speed filling solutions as game changers

"In a time when the pharmaceutical industry and our customers need us to ramp up sterile fill/finish capacity to meet the growing needs of patients both for COVID-19 pandemic and emergency healthcare medications, as well as many livesaving mRNA and other treatments, we see the increased quality, output, and capacity potential of using Corning Valor® vials in combination with ultra-high speed fill/finish solutions by Optima as a game changer in our ability to serve patients in need of these products," Closs emphasizes.

MORE ABOUT THIS TOPIC

www.optima-packaging.com/whitepaper-vaccines

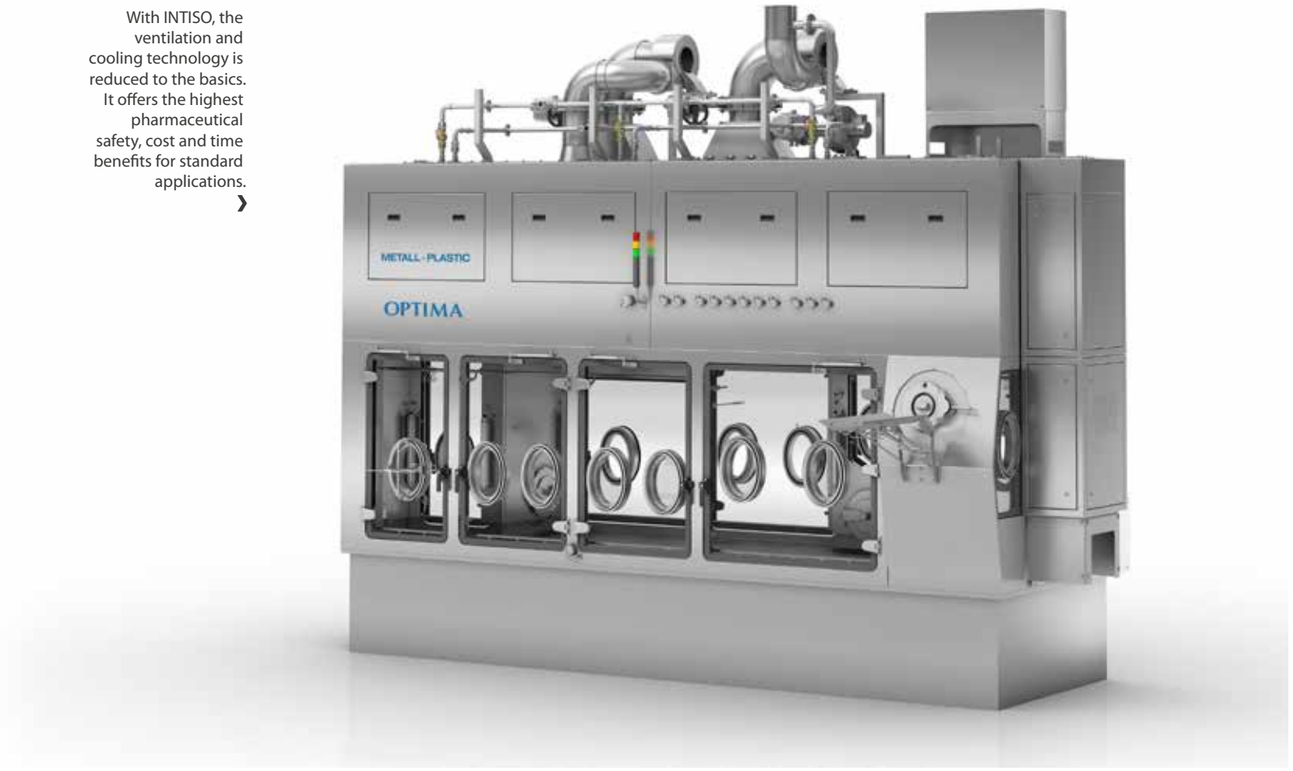
NEW INTISO: SMART ISOLATOR TECHNOLOGY FOR ASEPTIC PROCESSES

A new design for isolator technology: Metall+Plastic's INTISO is distinguished by the absence of an HVAC unit and the relocation of cooling and ventilation units from the mechanical floor to the isolator plenum. Even its modular construction is innovative. This article shows the advantages and practical application scenarios that result from this.

IMPORTANT FOR YOU

- New type of isolator: The INTISO from Metall+Plastic does not need an HVAC unit on the technical floor.
- Ventilation and cooling units are installed in the isolator plenum. The INTISO receives pre-conditioned air from the clean room.
- Significant time and cost savings
- Ideal for standard applications
- Improved accessibility
- The modular construction of the INTISO assists with time and cost savings.

With INTISO, the ventilation and cooling technology is reduced to the basics. It offers the highest pharmaceutical safety, cost and time benefits for standard applications.



The isolator plenum is the area located above the machine enclosure or the manipulation unit with the glove interfaces, and it is usually located flush with the cleanroom ceiling.

Photographs of isolators in cleanrooms are only able to show part of the overall complex isolator technology. The HVAC unit (HVAC: Heating, Ventilation and Air Conditioning) is located, almost invisibly, above the isolator on the technical floor. If it were possible to dispense with the large HVAC unit and extensive piping, it would be feasible to significantly reduce the amount of work involved in isolator construction, as well as the time and effort required for installation and commissioning.

Metall+Plastic has succeeded in relocating essential HVAC functions to the isolator plenum. The ventilation and cooling units are the newly repositioned technology. This design makes the INTISO suitable for standard applications carried out under the climatic conditions typically found in clean rooms, which roughly corresponds to a room temperature of about 20°C with a humidity level of about 40 to 50%. This is because INTISO uses the pre-conditioned air from the clean room and releases it back into the clean room (or even through the roof).

A new generation of isolators

What differentiates the INTISO and sets it completely apart from similar concepts available on the market is a supportive temperature control system. A temperature adjustment of around +/- 6° C can be carried out with a cooling unit that is integrated into the isolator plenum. In practice, this makes it possible, for example, to compensate for waste heat from fans or other isolator components and to create consistent temperature conditions, regardless of the batch size. The INTISO also compensates for the temperature fluctuations that occur in the clean room with its integrated cooling and ventilation technology.

Interim conclusion: This means that this type of isolator is just as safe for standard applications, but is also more cost-effective and available more quickly than customized designs. In scenarios that differ from standard applications, such as when pharmaceuticals require cold loading or highly active ingredients are being processed that require a very high air exchange rate, a tailor-made isolator from Metall+Plastic remains the better choice. But for almost all standard sterile fillings, from now on the INTISO will not just be an interesting alternative, it will be the first choice. Matthias Aster, Team Leader Sales at Metall+Plastic, is convinced of this.

For example, inactivated vaccines or insulin usually do not require special climatic requirements in aseptic processing – ideal areas of application for the new isolator type INTISO.

INTISO is equipped with a DECOpulse® decontamination unit. Consequently, compared to custom isolators, there is no difference in the decontamination times that can be achieved and the H_2O_2 residual concentration values. In a market comparison, the values achieved by Metall+Plastic are also at a very low level. The INTISO also conforms to all requirements according to cGMP Annex 1. For example, this includes individual filter integrity tests in accordance with DEHS/DOP. Likewise, the monitoring units are identical to customized systems in terms of their design. Furthermore, the INTISO's SCADA system corresponds to the earlier design, and can be combined with the HMI of filling and closing systems.

"This type of isolator is just as safe for standard applications, but is also more cost-effective and available more quickly than customized designs."

Matthias Aster, Team Leader Sales, Metall+Plastic

Modularity assists with time and cost savings

The thing that also sets the INTISO apart is its modular construction. To achieve this, Metall+Plastic has introduced a modular system for the INTISO manipulation unit, so that the frames are now pre-engineered. The resulting simplified engineering contributes to reducing costs, while at the same time, the system remains so flexible that adjustments to meet customer requirements can be made at any time. Similarly, connection to Optima and other manufacturers' filling and closing machines is unaffected.

Last but not least, INTISO improves access to technology, because filters or hoses, for instance, can be reached via the access panels on the plenum. Metall+Plastic performs all the engineering in this area without the need for tools, for example with crimp closures, so avoiding potential particle contamination in the clean room.

The new INTISO delivers persuasive benefits for standard applications in sterile filling. This is underlined by the range of orders Metall+Plastic has already received for the INTISO. The first project is about to go into operation.

Vaccination against COVID-19 is still considered to be the most important measure available for preventing severe disease progression.

CATALENT AGAINST COVID: A RACE AGAINST TIME

When the pharmaceutical industry started to research vaccines to fight COVID-19 in the spring of 2020, the concern that global manufacturing and packaging capacities would need to be increased arose almost simultaneously. At Catalent Pharma Solutions, a leading development and manufacturing partner to pharmaceutical companies, preparations began to boost vaccine production capabilities. As a part of this preparation Optima accelerated a program to make new Optima filling and closing lines, with isolators, ready to start almost at the push of a button as soon as emergency use authorizations were granted.

At Catalent, the OPTIMA VFVM 18000 filling and closing machine is used. The complete filling line handles washing, sterilizing, filling and closing of vials under isolator.

Catalent works closely with its customers to manufacture life-enhancing and life-saving medicines, including COVID-19 treatments and vaccines. Prior to the pandemic, Catalent had announced an expansion at its facility in Bloomington, Indiana, to meet customer demand and the projected growth of fill/finish within the industry. It quickly became apparent that an unprecedented number of treatments and vaccines would be needed to fight COVID-19, so Catalent accelerated its expansion to bring additional capacities online sooner.

New capacities in record time

Catalent placed an order with Optima for two vial filling lines to contribute to the new, globally required capacities. Typically, projects of this magnitude could take years until production can begin, however, both vial lines were accelerated to meet Catalent's customers' demand of biologics, including COVID-19 vaccines. Prior to the pandemic, Catalent had already announced an expansion to add capacity

IMPORTANT FOR YOU

- Extremely short project lead times for two filling lines to be used for vial filling, including COVID-19 vaccines
- The time factor was more important than ever during pandemic conditions. Only an exceptional team effort in close cooperation with the customer could deliver success.
- Measures to minimize delivery time included the CSPE process for complex turnkey solutions at Optima, a special logistics concept and the indefatigable commitment of all those involved in the project.
- The time and quality targets set were achieved, and Catalent was able to begin production at the end of 2020.
- The future-proof system concepts of both vial lines are marked by high speed, filling precision and flexibility.

High speed, precision filling: Up to 24,000 vials per hour are processed by the system. 100 percent of the containers are inspected by an in-process control.

in Bloomington, and had ordered a vial line from Optima. This pre-planned vial line turned out to be a very good option for vaccine production. Nonetheless, the technical concept still had to be modified in record time to meet the requirements of Catalent's customer's COVID-19 vaccine, and without compromise. For Catalent's second vial line, it was possible to transfer another Optima line, but again with the same time restrictions and a new, specific line design.

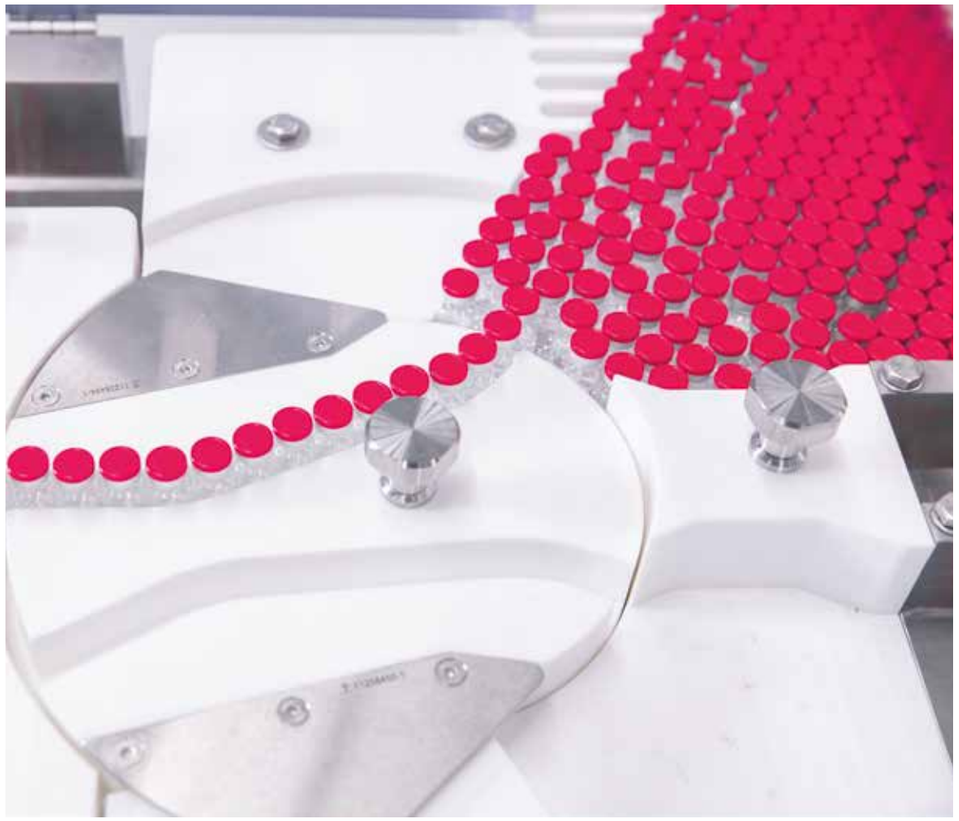
"Catalent wanted a high-speed line to bring life-saving medications to market as safely and quickly as possible."

Rebecca Mullis, Lead Process Engineer at Catalent Biologics

Now, Optima and Catalent, who share a long-standing relationship, were being challenged to make the impossible happen. The first requirement for the systems was a new Catalent building. Here, Catalent expedited its own planning and construction to bring the program forward by ten months. At Optima, both lines were given priority.

Line planning and vaccine development were running in parallel, so a certain degree of flexibility in the technical design of the line was initially required. Rebecca Mullis, Lead Process Engineer at Catalent Biologics, commented, "The output of the line is very important. Catalent wanted a high-speed line to bring life-saving medications to market safely, and as quickly as possible."

Output was designed at up to 24,000 vials per hour, which can be achieved with 2R vials and ten-digit processing. The second line dispenses at a rate of up to 16,200 vials per hour into 10R vials. At the same time, high filling accuracy had to be achieved. Both lines were to operate with 100% in-process control and were to be equipped with Optima's isolator technology.



Vials filled with vaccines and tested are lined up and compactly grouped with a tray loader.

Technology provides a (time) advantage

The turnkey line engineering used by Optima Pharma meant that Catalent was able to enjoy a single point of contact for the entire solution. Both lines subsequently benefited from the fact that the isolator, filling, and closing machines were fundamentally aligned, from the mechanical fits to Environmental Monitoring Systems (EMS) to the electronics and controls. Outwardly, this can best be seen in the software integration of the isolator into the machine control system – all parts of the system are operated via a central Human-Machine Interface (HMI). This greatly reduces potential sources of error, which, along with simplified project organization, yields considerable time benefits.

Comprehensive Scientific Process Engineering (CSPE) is another process employed by Optima Pharma. CSPE has made it possible to perform advanced virtual testing of the interfaces between the isolator and the filling and closing machine across different locations. In the CSPE Center, both lines were set up complete with isolator. The high complexity of such systems means that, even in a turnkey project, it makes sense to test the entire unit as comprehensively as possible for the Factory Acceptance Test (FAT), so that massive time savings can be achieved once installed at a customer's own premises.

In addition, Optima Pharma has a library of software modules that also function as a programing standard. These tried and tested modules were able to be used for many of the functions of both lines, and this also saved time; software development and configuration was done simultaneously with the system design.

Finally, there were also some very practical things that facilitated rapid implementation. "Optima has shown very high commitment to helping Catalent," says Mullis. She added, "We were assisted in the fast-track of both projects, and Optima provided all the resources needed to do so, enabling us to meet the extremely tight schedule. There were frequent conference calls scheduled overnight, so that we could initiate a dialogue with the experts the very next day."

› EMS stands for Environmental Monitoring Systems. Multiple parameters are measured and assessed in the isolator-protected machine. Specifically, these include particle counters for air quality, germ collectors, and sensors for air temperature and humidity.

Catalent's second line at Optima Pharma's CSPE Center: There is adequate space for the air handling units.

Assembly of the CG membrane. The filling machine and the isolator are tested together in the subsequent integrated Factory Acceptance Test (iFAT).

High-value freight: Several heavy-duty transporters first transport parts of the filling and closing technology from Schwaebisch Hall to an European cargo airport.

A layover at a cargo airport: One of the world's largest cargo aircraft, the Antonov An-124, is being loaded.

At the same time as the equipment was being built, Optima was already working on logistics. In early August, part of the first line was shipped to the U.S. by sea. Then, at the end of August, one of the world's largest cargo aircraft, an Antonov An-124, took off from Europe bound for the U.S. On board: 38 tons of high-tech line modules, which had previously been transported using several heavy-duty trucks from the Schwaebisch Hall and Radolfzell sites (isolator technology) to an European cargo airport. In the time gained by air freighting, the filling machine and the isolator were fully completed.

All the components arrived at Catalent together and on time to the very day. These special shipping channels also made it possible to speed up the re-commissioning process, i.e., the reassembly of the line at the customer's site using as few components as possible.

High tech in the air and vaccines on the way

"Optima manufactures quality equipment that has precision built into all of its parts and systems, and is precisely engineered. Even the 3D models show a high level of detail with which Optima achieves high precision and reproducibility. This makes it possible to build high-quality lines right from the get-go," says Mullis. Software parameters from similar projects that had already been implemented also helped to quickly breathe life into the system functions during the commissioning of this new vial line.

The first Site Acceptance Test (SAT) was conducted at the Catalent site in the fall of 2020. Since the system installation began, Optima's experts from Green Bay, U.S. were on hand to assist. Work was carried out in two shifts and during weekends, based on COVID-19 health and safety protocols in order to maximize the (working) time available.

The first engineering runs to fine-tune the system were performed at the end of 2020. Even the isolator cycle development benefited from turnkey system integration and prior experience. The DECOpulse® decontamination system was set up and the cycle development was completed within weeks. Catalent then performed the process qualification. In close cooperation with the authorities and in compliance with all regulations, Catalent was able to include several values which were obtained and collected by Optima during the project phase as a reference. With this approach, the process qualification could be accelerated.

Optima succeeded in hugely expediting both vial line projects. But it was not just the scheduled deadlines that were met. Much more importantly, the work resulted in equipment and processing that met the extremely high quality standards of the pharmaceutical industry and Catalent. Close, trusting cooperation between the parties was a precondition for this success.

The commitment of everyone involved

As Catalent began filling vaccines on its new vial line, the fight to respond to the COVID-19 pandemic continued with line two. An integrated FAT of the second filling machine with isolator was carried out in the fall of 2020, followed by SAT in the beginning of 2021, and production commencing shortly after. Catalent has also processed vaccines and treatments to protect against COVID-19 using pre-existing Optima equipment. The flexibility of formats and filling systems are integral parts of the design concept.

Like everyone involved at Optima and Catalent, David Di Palo, Optima's project manager, worked very hard over a period of months; his conclusion is remarkable: "The issue of COVID-19 affects us all, and I am definitely proud to be part of a project that is helping to bring a vaccine to market that will help people all over the world."

The significance of these efforts made by Catalent and all partner companies was made clear, in particular by a visit from former U.S. Vice President Mike Pence, who visited the Bloomington site on December 15, 2020, where he viewed filling and closing capacities at the site.

MORE ABOUT THIS TOPIC

You can find a TV report about it at:
https://bit.ly/3ascQkO

FLAGSHIP PROJECT FOR BIO-S STRATEGY

The French pharmaceutical company Servier is expanding its business model. As it moves towards becoming a recognized player in oncology, as part of its BIO-S strategy it is investing in production capacities for biologics and small molecules. The greatest degree of flexibility possible is ensured by a MultiUse line that can fill injectable solutions into syringes and vials. Servier opted for a complete system including a high-potent isolator and freeze dryer, the likes of which only Optima can supply.

'Les Laboratoires Servier Industrie' operates worldwide, employing 22,500 workers. The pharmaceutical company has historically had a strong presence in treating cardiovascular diseases, and it reinvests over 20 percent of its sales in research and development. The Servier Group has an exceptional manufacturing strategy, with a network of 16 production sites. 98 percent of its active ingredients are produced in France.

› Servier has also expanded its oncology and hematology pipeline by making several acquisitions: Shire, Ireland's oncology business in 2018, and Symphogen, Denmark, in 2020 and Agios, USA in spring 2021

Even with its current expansion of its strategic direction into oncology the French pharmaceutical firm is sticking to this line. In Gidy, around 15 km north of the city of Orléans, Servier operates its largest factory with three manufacturing facilities. One of these has been under conversion since 2018: In the future, the production facility known as Bio-S will be producing monoclonal antibodies for preclinical and clinical phases for cancer treatments, among other things. Servier's first biopharmaceutical manufacturing facility is scheduled to start operating in 2023.

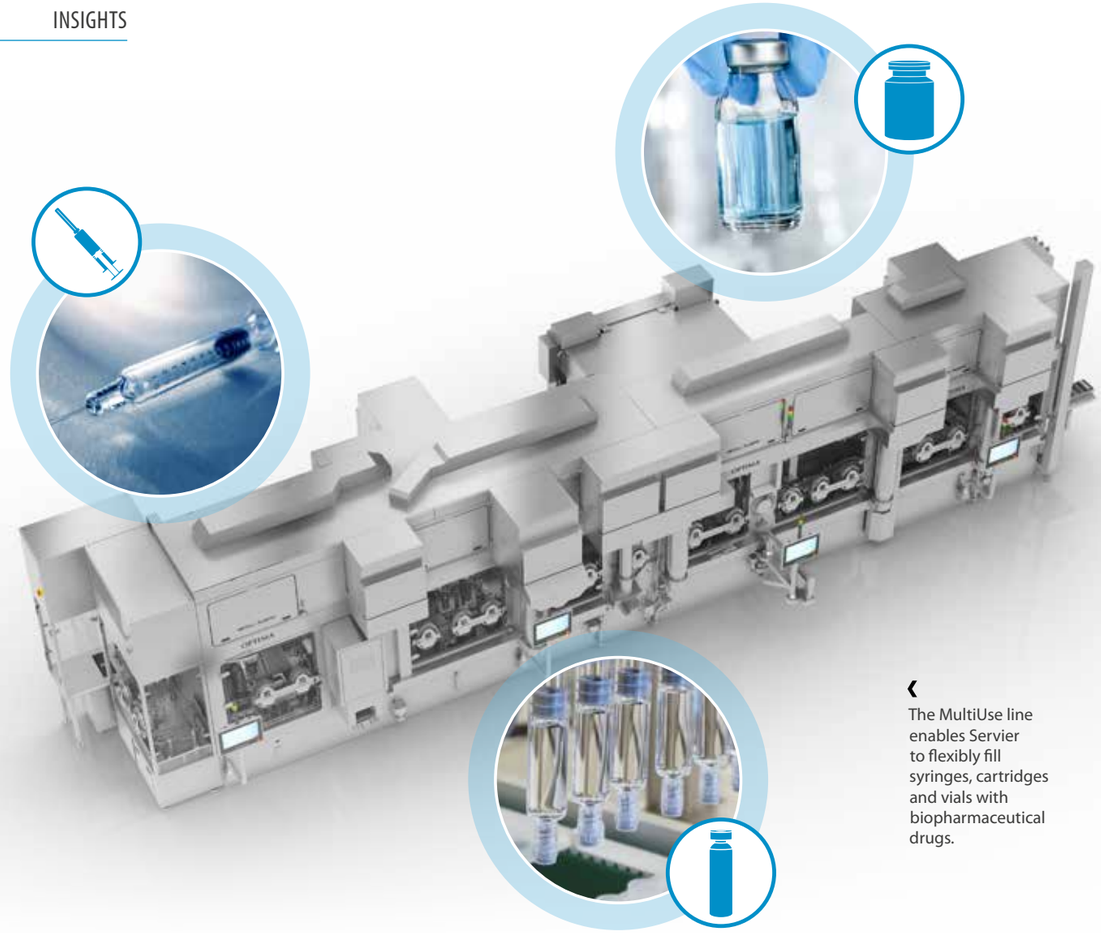
The development of its capacity for the biotechnological production of living cells is not the only challenge facing the manufacturer, which so far has focused on solid forms of drug administration. The filling of the new drugs in the future also poses different requirements than in the past, because they are intended for injection. Christophe Aussourd, Head of Pharmaceutical Industrial Development explained: "We wanted a flexible production line to meet initial clinical needs for biologicals and small molecules, as well as potential commercial manufacturing in the future." As early as 2016, Servier was putting out feelers for suitable suppliers. Fortunately, Optima's name was by no means unfamiliar to some Servier employees with expertise in biologicals production.

Turnkey thinking – the key to success

This set the scene for Optima's flagship project for the French market. The OPTIMA MultiUse line for highly active ingredients, implemented as a turnkey project with filling line, high-potent isolator, and freeze dryer from a single source, was to be the first of its kind in France. First, it was necessary to build trust. Fabrice Escourrou, Sales Manager Optima Pharma France, reports: "A lot of Servier employees were involved

IMPORTANT FOR YOU

- The OPTIMA MultiUse line, including the high-potent isolator and freeze dryer, completes the first Servier Bio-S biotech production facility in Gidy, France.
- The flexible line for vials, syringes and cartridges will fulfill the initial clinical demand for biologicals and small molecules in the future.
- The 100% weight control ensures high yield for the high value products.
- The dimensions of the integrated freeze dryer are such that it can be operated with the shortest possible processing times.
- The integration of the line SCADA into the higher-level IT enables Servier to manage electronic batch records via the in-house MES.



The MultiUse line enables Servier to flexibly fill syringes, cartridges and vials with biopharmaceutical drugs.

in the project, including quite a few who did not know us at all. After the project participants visited us in Schwaebisch Hall, we were able to convince them that we offer the right, innovative technologies from a single source. It was very important for Servier executives to have a single point of contact for the entire line."

"Besides the criteria of the integrated design and project management of the filling system, high-potent isolator and freeze dryer, we were convinced by the state-of-the-art technology of the flexible line and its '4.0 compliance'."

Christophe Assourd,
Head of Pharmaceutical Industrial Development at Servier

Christophe Aussourd says: "After an objective comparison of the offers from several competitors, we decided to go with Optima's solution. Besides the criteria of the integrated design and project management of the filling system, high-potent isolator and freeze dryer, we were convinced by the state-of-the-art technology of the flexible line and its '4.0 compliance'. Lastly, the spirit of partnership in terms of technical communication was also a decisive factor."

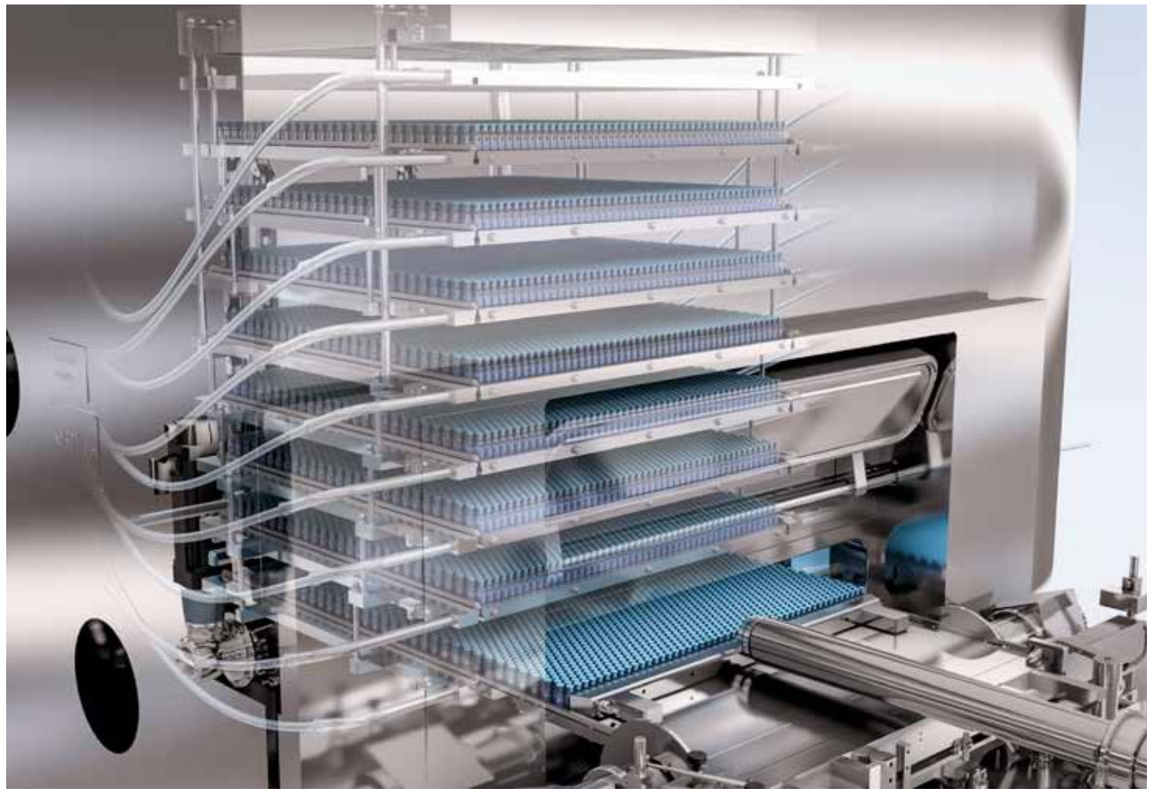
Optima Pharma has demonstrated its high level of expertise by designing the line as a MultiUse filling and closing line for syringes, cartridges and vials associated with high potency products. Rainer Goeller, who was responsible for the project planning of the filling system, remembers: "During the project planning phase, it quickly became clear that Servier was looking for a very

The Tyvek Removal Robot removes the sealed film from the nest before separating the containers inside.

compact system. We therefore scrapped an initial L-shaped layout and designed the system made up of a filling line and freeze dryer in a linear configuration. Rachid Azzouzi, F & F Workshop Manager says that he is satisfied with the project work: "We were involved at every stage of the project, particularly during the mock-up and design phases, to fine-tune the technical solutions that Optima proposed such as the pick-and-place technology and the filler set definition."

Maximum yield for high-value products

Servier's aim was not to achieve a high output, but rather the highest possible product yield. The Servier MultiUse line fills up to 3,000 containers per hour. All packaging materials are supplied pre-nested and pre-sterilized. Once the containers have been unpacked, partly manually and partly semi-automatically, and the protective slide has been removed by the Tyvek-Removal robot, they are separated and filled. 100% in-process control and, where necessary, refilling minimizes product loss. The Servier line uses peristaltic pumps for filling. They only introduce low shear forces, which is especially important for biological products. When there is a product changeover, the single-use product path coming into contact with the liquid can be easily replaced. There is no need for time-consuming cleaning and sterilization of this unit.



The integrated freeze dryer is accompanied by an automatic loading and unloading system that slides the vials into the freeze dryer row by row. The vials are separated again during unloading.

After filling, the syringes and cartridges are closed and derived. In contrast, vials can be freeze-dried in the next step. When designing this process, the requirements were precisely taken into account. The Optima team pays strict attention to every detail that can affect careful lyophilization. Harald Galonska, the lead Project Engineering Manager, explains: "For example, the size of the intermediate valve between the drying chamber and the condenser must be right. This is the only way that any water vapor that is generated can be removed quickly enough." Otherwise, the entire batch could thaw, making it unusable. For high-value biotech products such as the ones to be produced by Servier in the future, this would mean a loss of multiples of €100,000. So Galonska basically asks what the worst-case scenarios would be. He describes: "The compact Servier GT C-4 freeze dryer is designed to be usable for all products with the shortest possible process times."

The inclusion of the freeze dryer in an integrated line design requires close internal coordination in terms of design, documentation and time scheduling. "We deliver the majority of the freeze dryers as part of turnkey projects, so we are experienced in doing this," says Dominic Reeh, who was the Project Manager responsible for the freeze dryer. The entire plant is controlled centrally via a line SCADA. In addition, Servier was looking for integration with its higher-level systems. Franck Durtchi, Automation Manager at Servier explains: "Our 4.0 Servier Bio-S working group designed the requirements to ensure the MultiUse line, freeze dryer and isolator communicate with the Bio-S facility. Our goal is to manage electronic batch records via our MES (Manufacturing Execution System). To do this, product and environmental data will be collected, logged and analyzed."

Luc-André Claustres, Head of F & F and Project Manager at Servier sums up: "We are very satisfied with the project management. A collaborative and user-focused mindset was its key feature." In early March 2021, the freeze dryer, isolator and MultiUse filling line were delivered to Servier's Bio-S plant. "The system's flexibility provides real added value", says Luc-André Claustres, praising the system. "Thanks to its ability to handle both different types of containers and different kinds of pharmaceuticals, whether they are high-potent or not, liquid or freeze-dried, biologics or small molecules, we will be able to meet the needs of our clinical products going forward." He also feels that the automatic loading and unloading system for vials and the quick switchover of the format parts without the need for tools are a major advantage. This has made the state-of-the-art line an important factor in making Servier's Bio-S project a success.

"The system's flexibility provides real added value."

Luc-André Claustres,
Head of F & F and Project Manager at Servier

An important intermediate step on the path to an integrated line: The freeze dryer Factory Acceptance Test at Optima Pharma's Mornshausen site already took place in September 2020, in compliance with the COVID-19 regulations.

This turnkey project, which combined the MultiUse line with the freeze dryer and isolator, called for close coordination between Optima's different units.

INSIGHTS

IMPORTANT FOR YOU

- Extensive equipment customization to meet the customer's needs, specifically for on-site peptide production
- Optimal use of space, for example by using a monoblock design where the chamber, condenser, refrigeration system and control cabinet are installed on a single rack
- Short project run times, partly due to the monoblock construction method and simplified reassembly on site
- Bachem placed two further orders for additional freeze dryers, long before the f irst freeze dryer was operational.

FREEZE-DRYING PEPTIDES AT BACHEM

Linking amino acids to form stable peptides is one of the Swiss firm Bachem AG's special areas of expertise. Bachem supplies research institutions, laboratories and pharmaceutical companies. These pharma companies use the peptides produced at Bachem as active ingredients in final formulated medicines, and do so with great success, as demand is on the rise. Its highly specialized production is currently being expanded with freeze-drying equipment supplied by Optima.

At Bachem, peptides are dissolved in liquid at the end of the manufacturing process. Freeze-drying is used to convert these peptides into solid form by driving out the liquid. This process converts the peptides into a stable form that can be supplied to Bachem's customers, in amounts ranging from micrograms to large units, reports Alex Trippmacher, who, as Engineering Project Manager, was entrusted with the project planning, procurement and installation of the freeze-drying system, including the new clean room that had to be built.

Not off the shelf

The company's specialization in peptides includes two special features. On one hand, decades of experience with freeze-drying processes and the in-depth expertise that comes with it. On the other, over the years, freeze-drying processes and equipment have been continuously developing to meet the specific needs of peptide production, setting them apart from their peers in the pharmaceutical industry.

The management at Bachem decided to invest in a new freeze-drying system in 2019 to meet the steep rise in demand. Bachem placed the initial order with Optima as its new supplier in July 2019.

Optima Project Manager Dominic Reeh stresses how important it was, especially with this project, to incorporate Bachem's specific customer requirements and experience into the expansion of capacity as much as possible. For example, this involved incorporating defined components such as sensors that Bachem was already using in its existing plants. This was done in particular to simplify the supply of spare parts and stock-keeping.

In cooperation with a Swiss company, Bachem developed software that is also already used in existing freeze-drying systems and is precisely customized to the needs of the peptide specialist. This means that the operations staff are also perfectly accustomed to using this software. Optima then developed, supplied and installed the specific system hardware, including sensors and control cabinets, in a flexible way.

The OPTIMA LYO-S freeze dryer in two views. This was installed as part of the first order at Bachem and is already proving itself in practice. The first follow-up order is almost a copy of this type. These and others will be commissioned at Bachem before the end of 2021.

Limited space, customized concept

Optima's design engineers pulled out all the stops to make the best possible use of the limited space available on site. The OPTIMA LYO-S system type, with the freeze-drying chamber and the refrigeration system compactly arranged on a shared frame, is ideal in such cases. Bachem designed the footprint of the freeze dryer so that firstly it would fit the flexible production requirements and secondly, to make the increase in capacity as big as possible. This is currently the largest system of its kind used by Bachem.

"At Bachem, there is a very wide range of product variance. Our freeze drying systems are designed for typical multi-purpose operation," says Alex Trippmacher. "The products are also very high-value," he goes on to explain. Therefore, in the design of the Optima systems, the refrigeration compressor and vacuum unit are duplicated as backup. In the event of a component failing, they could salvage a batch.

"In the end," says Reeh, "we were also able to incorporate the customer's technical knowledge of the systems in a very transparent, open dialogue. The overall vibe was, and is, a team effort." The same principle was also carried on in internal meetings at Optima, and feedback from customers was consistently implemented.

The freeze dryer chamber with door can be seen. Bachem is now using freeze dryers from Optima for the first time.

A look at peptide production at Bachem.

Production at Bachem: The linking of amino acids to form stable peptides is one of the company's special areas of expertise.

Fast, but with a sure touch

At Bachem, another important aim was to grow the freeze-drying capabilities as quickly as possible. One year after the contract was awarded, the system's Factory Acceptance Test took place in July 2020. The monoblock design already mentioned has saved time. This particularly simplifies the reconstruction of the system on site using fewer components; this started in July 2020.

A sure touch was once again required on the way to the Bachem building. Heavy-duty rollers were used to transport the system through corridors to its final location. The route included a freight elevator, so Optima removed the adjusting plates from the system in advance to avoid exceeding the maximum load capacity of this goods elevator. In September, the Site Acceptance Test (SAT) was conducted alongside Bachem's internal certification, which once again helped to save time. Commercial production was able to start in October 2020.

More than just a vote of confidence

By no means is this the end of the story, because Optima had already received an order for additional freeze dryers in the middle of the implementation phase. This involves exact copies of the first system in the first tranche – only one of them needed to be mirrored. Somewhat smaller systems based on the same construction principle will follow in a second tranche. Here, the planned schedule puts the SAT for the first tranche in May 2021 and for the second tranche in late 2021.

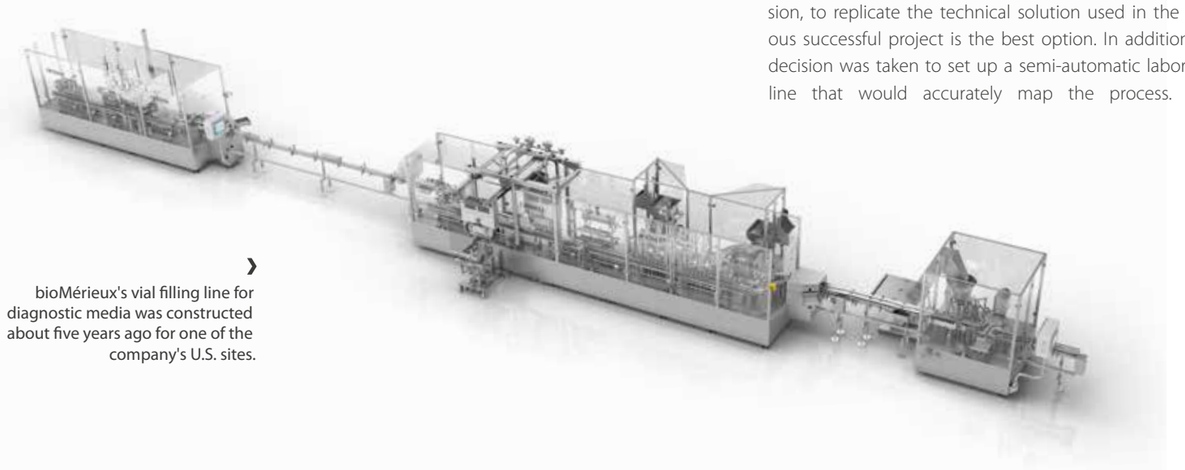
This means that within around 15 months, all the new freeze dryers that Bachem required from Optima will be up and running. Once again, there is a tight time constraint: The engineering phase, which is not necessary with identical systems, was taken into account, i.e. the time-to-market was reduced. Because of the increasing demand for Bachem's peptides, time remains a scarce resource.

And the first trial runs? "Everything went very well", says Alex Trippmacher. The interviewer follows up with "Everything went as you wanted and expected?" "Yes, reliably so." Nothing else to add.

TECHNOLOGY TRANSFER FOR DIAGNOSTICS IN CHINA

One vial, one filling material, one closure – done. But it is not always that simple. In fact, when diagnostic products from bioMérieux are filled, there are four very different media. In 2016, Optima Pharma has developed a specific production line for this. Because of the principle of "never changing a running system", the company has now decided to purchase a duplicate of this system for its Chinese production site in Suzhou. Operators there are able to familiarize themselves with the process in advance, using a laboratory pilot line from Optima Pharma to run the approval process.

Suzhou, with its many canals, is known as the Venice of the East. The city, with its numerous gardens and temples, attracts not just a large number of tourists. Numerous international companies such as Apple, Bosch and Glaxo-SmithKline have settled in this booming metropolis situated about 100 km west of Shanghai. bioMérieux is a global leader in in-vitro diagnostics and also operates one of a total of six Chinese subsidiaries there. As part of new production facilities, a vial filling line for one of the manufacturer's best-selling products is to be built there. bioMérieux is already producing the diagnostic product in the USA using a special, complex process line that was set up by Optima over five years ago.



bioMérieux's vial filling line for diagnostic media was constructed about five years ago for one of the company's U.S. sites.

Capacity increase and market conquest at the same time

The great market success of the product made it vital to increase capacity, and at the same time to conquer the Asian market. Firstly, the U.S.-based project team and the company's French headquarter thoroughly reviewed the options with a variety of line types from different manufacturers before making a decision: They came to the conclusion, to replicate the technical solution used in the previous successful project is the best option. In addition, the decision was taken to set up a semi-automatic laboratory line that would accurately map the process. Alain

IMPORTANT FOR YOU

- In the future, bioMérieux will produce a successful diagnostic product in China too.
- The engineering process has been made easier and faster by duplicating a proven Optima system from the USA.
- Dosing four different media requires a wide variety of dosing methods to be well mastered. Synergy effects within the Optima Group are a driver for success.
- The Chinese operating team familiarizes itself with the complex technology by using a semi-automatic laboratory pilot line.

In Asia the demand for diagnostic tests is rising continuously. bioMérieux's response to this demand is a new facility for manufacturing diagnostic products in China.

Gourmelon, Senior Vice President Global Manufacturing Support & Industrialization at bioMérieux, explains what the aim was: "By doing this, we want to develop the relevant expertise at our Chinese site ahead of time. The employees there can acquaint themselves with the technology they need right away. This will ensure the smooth ramp-up of the production line." In addition, the pilot line will support the product approval process for China ahead of time so that the filling line can go directly into production as soon as it is delivered.

It is worth taking a look at the USA to understand the process. This is where the big brother of the future Chinese line is already located, with twice the capacity. In the USA, the different dosing and filling modules, as well as the closing machine, have a double design. There, the two lines intersect at a furnace where the partly filled vials are heated. At Suzhou, all of this is only needed once.

Sharing its experience worldwide is part of the bioMérieux DNA

Almost a 100 % technology transfer – bioMérieux is extremely consistent in this respect. "Sharing experiences and practices worldwide is part of bioMérieux' s DNA as a way to learn and grow together. So we prefer to rely on the well-established technology of our proven solution," says Will Darrigrand, VP Engineering Americas at bioMérieux. This makes it easier for the U.S. team, who are familiar with the line, to provide future support for the Chinese team.

"The line includes several filling stations for very different media that are not easy to handle. This is due to the high complexity of bioMérieux's product."

Claudio Schneider,
Project Engineering Manager, Optima Pharma

The Project Engineering Managers, Claudio Schneider and Mark Seitz, who were entrusted with project planning for the new line at Optima Pharma in early 2019, were able to build on existing technology. "The line includes several filling stations for very different media that are not easy to handle. This is due to the high complexity of bioMérieux's product," explains Schneider. Different filling techniques for very different media and quantities have to be combined. Additionally, there is a great difference in the requirements for filling accuracy.

By combining different processes, the line masters the dosing of four media with very different properties – from spray dosing of a liquid to the addition of the resin-like reagent.

In addition to the fully automated production line, Optima Pharma supplied a laboratory pilot system for Chinese staff to get to know and train the process.

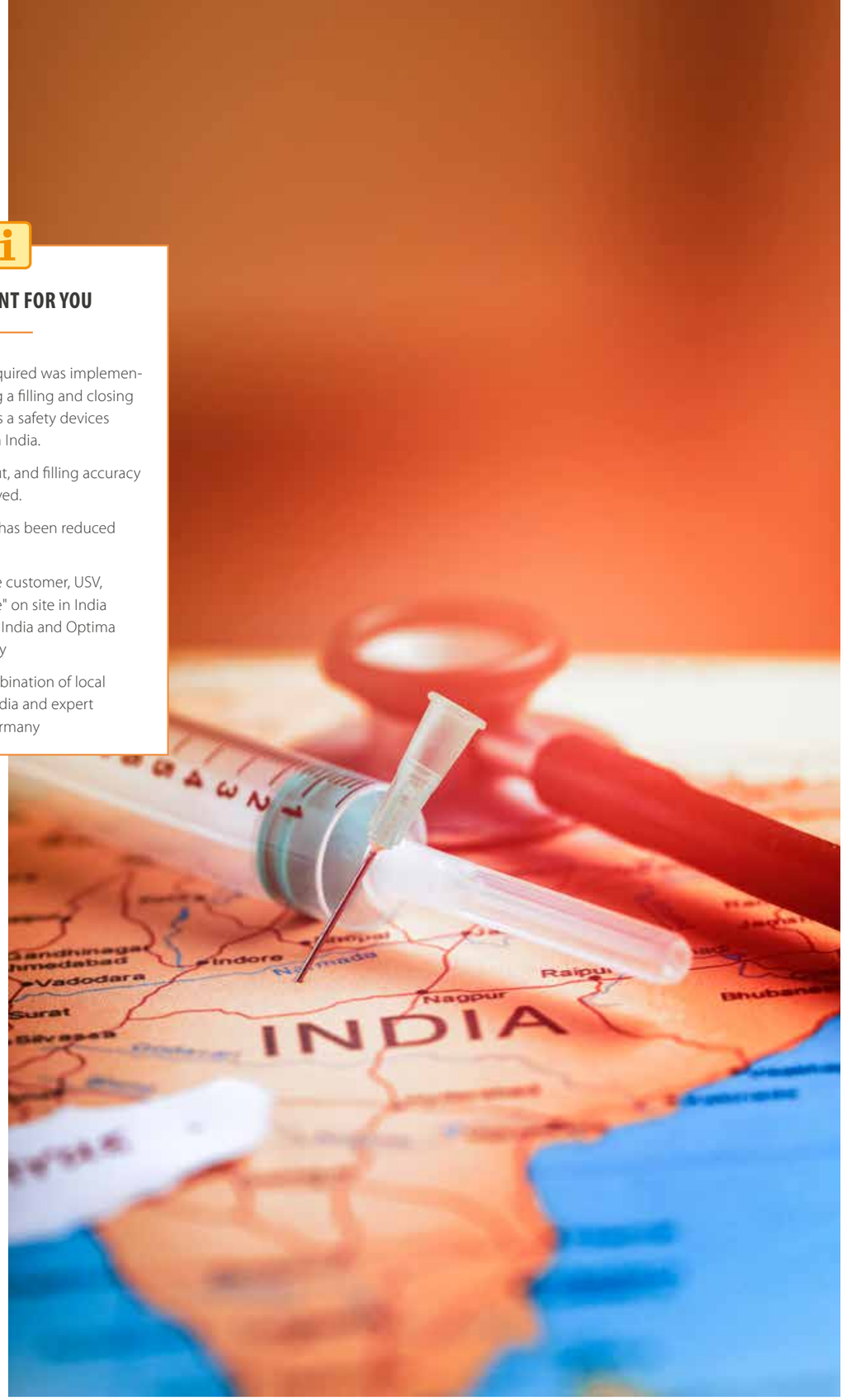
The line includes three dosing modules. After determining the exact tare, the vials reach the first station; here their inner walls are sprayed with the first medium by a micro-dosing device. Without any further intermediate weighing, the next station delivers a second liquid. After controlled weighing, the bottles pass through a tunnel oven where the added components are dried. This is followed by the second filling machine. Here a resin-like medium is introduced after a further weight check. Schneider explains that this stage, which is performed with the aid of an auger doser, as being particularly difficult: "The dosage of that component is highly dependent on its moisture content. In this respect, the experience gained in designing the U.S. line has been of great help." After the correct dosage has been checked by the next in-process control load cell, twelve vials are simultaneously filled with another liquid medium. Finally, they are closed with a stopper and fitted with a cap, which is subsequently crimped.

Complex technology in the laboratory pilot line too

This technology is also used in the laboratory pilot line, although a variety of steps are carried out by hand. It had already been delivered and is ready to run, around few months before the production line. A few thousand vials will probably have been produced by then, which will be used, among other things, for team training and local know-how development.

In each case, the technical platform for dosing the key components is the OPTIMA VFVM filling machine, where a rake ensures the safe transport of bottles. There is a total of five in-process control points that ensure quality by verifying correct filling with the individual components of the diagnostic product. At the end of the line, there is the OPTIMA VVM2428 closing machine, which also carefully transports the products.

The line is to be delivered to China in a couple of months. It is anticipated that set-up and start-up will run smoothly. Both the manufacturer and the users will be able to draw on the tried-and-tested processes of the preceding system, so technology transfer pays off. "In this way we will benefit once again from Optima's experience and the reliability of its technology," expects Foster Zhang, Senior Director of Manufacturing at bioMérieux China.



IMPORTANT FOR YOU

- The flexibility required was implemented by supplying a filling and closing system as well as a safety devices system to USV in India.
- Reliability, output, and filling accuracy were fully achieved.
- Time-to-market has been reduced by four months.
- According to the customer, USV, "excellent service" on site in India by both Optima India and Optima Pharma Germany
- The perfect combination of local knowledge in India and expert backup from Germany

INTERNATIONAL TEAMWORK FOR USV INDIA

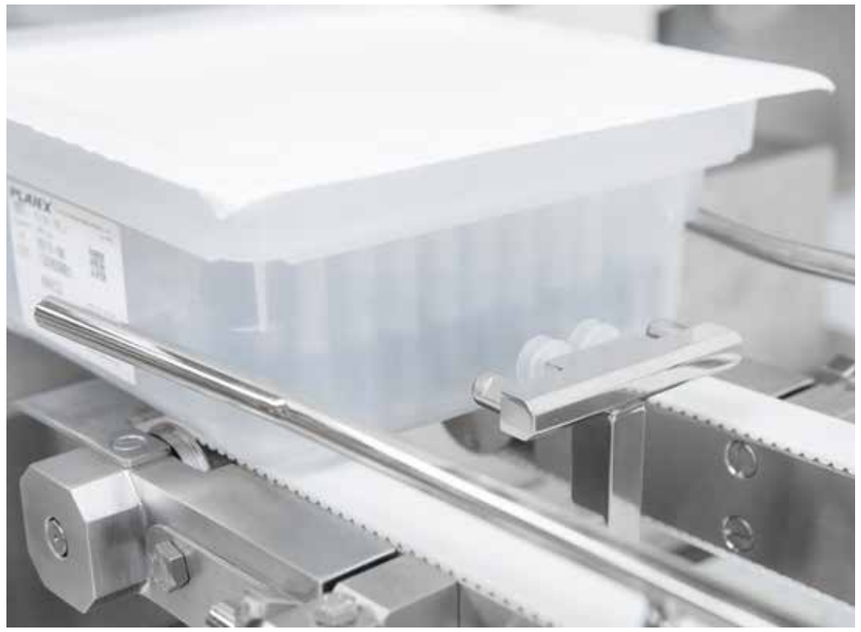
The Indian company USV Private Limited was founded in 1961, and now operates in 75 countries around the world – a success story based on entrepreneurial courage and pharmacological expertise. Since September 2019, USV has had two flexible Optima systems in commercial operation at its site in Daman (India). In this report, we show the close interaction between the expertise at Optima's Indian site and the German headquarters, and how USV benefits from this.

In January 2015, USV Private Limited placed its first order with Optima for a highly flexible, combined labelling and assembly machine for safety devices like finger flanges on syringes. Just four months later, there was a follow-up order. A highly flexible filling and closing machine was needed to replace an existing unit at USV. Following a lengthy approval process, USV can now look back on over one and a half years of industrial production with the systems.

Thanks to Optima, USV was initially able to save time and money through a joint Factory Acceptance Test (FAT) of the two machines in Schwaebisch Hall, reports Akshay Chikodi (Director Sales & Service at Optima India) looking back. However, by far the biggest advantage was achieved in the time-to-market. This was because the filling and closing machine was more complex in terms of qualification and approval, and was then able to be installed and qualified before the assembly machine. This meant that it was possible to save approximately four months time to start the important work for this and for media fills as soon as possible.

There is also close collaboration across the continents: Optima servicing uses digital technology.

Flexible filling processes for ready-to-use syringes syringes and vials. Depending on the batch sizes, the number of filling points can also be modified.



An OPTIMA TRR Tyvek Removal Robot will soon be peeling off the protective film.

At USV India, a second Optima system assembles safety devices. The syringes are also labelled.

Flexibility is the benchmark

Akshay Chikodi says that during the development phase, the filling and closing machine was initially supposed to be adapted to individual processes that existed at USV and that were dictated by the legacy machine. This is why the unpacking of the tubs from plastic film is not currently fully automated but rather semi-automated. In the process sequence that follows, there will be complete automation: the removal of the tubs sealed with film using the OPTIMA TRR robotic arm as well as the removal of the Tyvek cover, filling with integrated 100 % in-process control and, if required, with gas flushing, including when closing the containers with stoppers. The system with its five filling stations is designed to handle a capacity of up to 10,000 containers/h.

However, what primarily sets Optima's system designs apart is their flexibility. With the OPTIMA SV125, USV processes nested ready-to-use syringes in the formats 1 ml long, 3 ml (in different versions or formats) and 5 ml. In addition, cartridges are processed. A tool-free format changeover and coded format parts mean that the system can be changed over quickly and safely.

For maximum safety: in-process controls

Two filling systems cover the various product characteristics: Rotary piston pumps are installed as standard and are mainly used by USV for its peptide-based medicines. USV can fall back at any time on a five-position peristaltic pump system for other medicines, which is ready and waiting on a trolley. The in-process control ensures high filling accuracy and guarantees high product quality. The design of the machinery and the processes have been finalized in close cooperation with the project team at USV consisting of Hoshi Edulji (VP Commercial), Vijay Prabhu (Associate Vice President), Mangesh Gupte (General Manager – Projects), Shailesh Mukkirwar (General Manager – Projects) and Mahesh Italiya (Senior Assistant General Manager – Operation).

USV assesses filling accuracies for all formats against stringent acceptance criteria, reports Mahesh Italiya. In this regard, the system impresses the customers and, what's more, so far it has not experienced any significant failures. USV also processes smaller batches, so the number of filling stations on the Optima system can be reduced from five to two.

The second Optima system, the automatic assembly machine, was also designed primarily with flexibility in mind. Here, a variety of formats of filled and sealed ready-to-use syringes from different manufacturers are equipped with safety devices. Firstly, the syringes pass through the OPTIMA EKK labeler with printer, including for specific printing. These are checked inline by camera. Then the OPTIMA VSM assembly machine inserts the plunger rods into the syringes. Finally, the syringes are fitted with safety devices such as finger flanges, for instance. Here, too, the achieved format range is very large.

Networked locally and internationally – feedback from practice

But what does this close cooperation across borders and continents look like? According to Mahesh Italiya and the project team this was one of the key arguments in awarding the contract to Optima. Cooperation is intended to bring together the local knowledge of Optima's Indian subsidiary with the German site's in-depth pharmaceutical expertise.

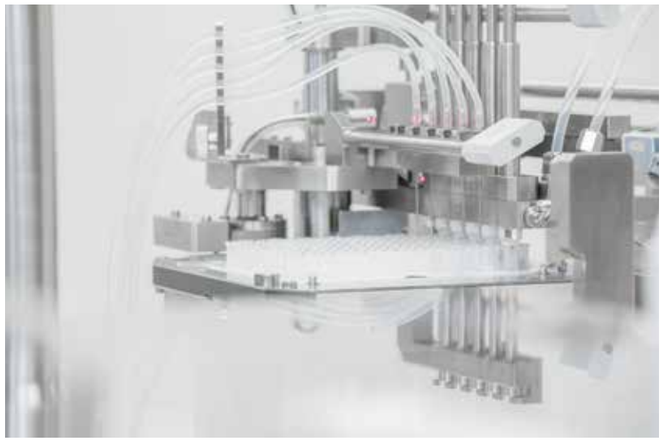
The pharmaceutical company USV in India placed the awarding of the contract on the flexibility of the filling solution. The OPTIMA SV125 currently processes nested ready-to-use syringes in the formats 1 ml long, 3 ml (in different formats) and 5 ml as well as cartridges.

What is particularly meant by local knowledge is a thorough understanding of the challenges faced in pharmaceutical production on the customer's site. This is how the German-Indian team succeeded in developing a concept that perfectly reflects these customer needs today. Again, a German-Indian Optima assembly team was on site at USV to install the equipment. The team became thoroughly acquainted with the customer-specific features and the design of the system. This was to offer benefits for servicing work later on. This international approach continued during the qualification process. Here, the Optima site in Germany provided support and backup for Optima India.

Initial training sessions were held by Optima India for the customer's staff, even before the commercial commissioning. It was also important to have direct contact with no language barriers when advising USV on which spare parts it should keep in stock. It was a matter of matching the customer's requirements and those of the machines as closely as possible, and setting up of spare parts management at the USV site in Daman, says Akshay Chikodi.

Additional local training sessions took place, firstly to qualify the USV staff to take ownership of "their" Optima machines and secondly, to be able to communicate accurately should any technical questions arise. It continued with the first new format parts, which were requested as additions to the USV product range. Expert on-site advice assured safety on both sides.

The removal of the sealed foil of the tub and the removal of the Tyvek cover is done fully automatically.



As a standard dosing system, USV uses rotary piston pumps in the OPTIMA SV125. In addition, USV can fall back on a five-position peristaltic pump system at any time.

Another Optima system labels and fits a wide variety of ready-to-use syringe formats with safety devices.

Aseptic processes and rapid on-site deployment

The close proximity would particularly pay off in the event of unplanned machine breakdowns. The fact that USV and Optima India are located within the same time zone is worth its weight in gold here when sensitive biological medicines have to be processed in aseptic processes within a limited time. In addition, if required, Optima employees would be able to be on site at USV within half a day at the latest.

Indian service staff have already used remote access to connect with service colleagues at the German headquarters in order to coordinate and implement solutions. Finally, Optima India carries out preventive maintenance on both systems.

"Optima India's and Optima Germany's service performance is excellent," says Ashok Saxena (Senior VP – Operations). His overall conclusion is unambiguous: "All our expectations have been fulfilled!" According to Mahesh Italiya, USV is operating equipment that is "completely reliable" and leads to results that are perfectly reproducible. They are an important asset in driving globalization forward. In the meantime, USV has concluded international licensing agreements with renowned global companies.

A HIGH-QUALITY ADDITION TO THE CDMO SERVICES

The growing biopharma market is an attractive sector for contract manufacturers including Biovian from Finland. The One-Stop-Shop Bio-CDMO has recently expanded its equipment portfolio with a fully automated vial filling line. There were two essential requirements the filling line needed to meet – the system had to minimize losses of valuable therapeutic drugs during filling and fit into the specific physical location in Turku Bioscience Centre.

CDMO: Contract Development and Manufacturing Organization, contract manufacturers and developers that provide support in research and development and the manufacturing of pharmaceutical products, especially in the pharmaceutical industry.

CDMOs support pharmaceutical manufacturers in many ways. They help with capacity problems, respond to needs through flexible process development, and they manage up-scaling to GMP production. Partnering with a CDMO can provide a head start to many biopharmaceutical drug developers. Therefore, there has been a rapid growth in the need for contract manufacturers. Especially for those who provide comprehensive services and can produce small to mid-sized batches for clinical studies and beyond.

One of the companies that can respond to the growing demand with comprehensive services is Biovian. The Finnish company was founded 18 years ago, and it has 1300 m^2 of GMP-compliant production space in Turku, located around 170 km west of Helsinki. Over the past few years, the plant has been further equipped with cutting-edge equipment such as single-use bioreactors. Growing demand for gene therapy drugs has driven the need for capacity expansion. The company describes itself as a One-Stop-Shop CDMO. This means it covers the entire service chain of biopharmaceutical manufacturing from early development to filling and labeling.

Contract manufacturers need flexible, user-friendly machines to fill a range of vials with various pharmaceuticals.

Fully automated filling

Biovian's customers are supported with commercial GMP batch manufacturing all the way to the fill and finish. For Pirkko Kortteinen, the Director of Development and Manufacturing, it became clear in early 2019 that there was a need for a fully automated filling system covering batch sizes of up to 10,000 vials that would also be ready for the revision of Annex 1 of the EU GMP Guide "Manufacture of Sterile Medicinal Products". Project manager, Ulla Myllymaa, was given a task to find a supplier, who could, in addition to above mentioned, meet the specific physical requirements of the facility. This challenge was also presented to Optima, the future supplier.

The quest to find the right machine turned out to be anything but easy. Ulla Myllymaa had to realize that the options available on the market were rather limited. So, she considered focusing on the manufacturers of individual components. Initially, she wanted to learn more about Optima Pharma's filling machines. Technical Sales Manager Thorsten Meiser recalls: "In discussions, we quickly concluded that Optima could provide the complete machine for vial filling with stoppering and capping, a Restricted Access Barrier System, RABS, and an integrated system for air sampling. This was exactly what Biovian was looking for. I was able to offer Ulla Myllymaa a newly relaunched concept, where certain improvements had been made compared to previous vial filling and stoppering and capping lines."

RABS: Restricted Access Barrier System, using fixed transparent cladding and safety-locked doors. All manual interventions are carried out using permanently fitted gloves.

Biovian's aseptic fill and finish completes its GMP-compliant biopharma manufacturing services.

IMPORTANT FOR YOU

- Biovian, as a Bio-CDMO, required a fully automated vial filling and closing machine that was ready for the revision of Annex 1 of the EU GMP Guide "Manufacture of Sterile Medicinal Products".
- The latest version of the VFVM231 vial system satisfies these requirements.
- Its flexible design means that it can fill different vial sizes and fill quantities. At Biovian, 2R to 100H vials are filled, with volumes ranging from 0.2 ml to 100 ml.
- A range of functions to minimize product loss are important when highly valuable pharmaceuticals with relatively small batches are being filled.
- The barrier system's customized low height and the machine's modular design mean that it could be installed in the planned location in the Biovian manufacturing facility in the Bioscience Centre.

Biovian in Turku, Finland, has equipped its production buildings with the latest equipment for manufacturing viral vectors for gene therapies and recombinant proteins. ❯

Luckily enough, a corresponding machine happened to be in Schwaebisch Hall waiting for delivery and Ulla Myllymaa was able to inspect all aspects of the system and test how each of its parts could be reached through the glove ports. Meiser says: "She was thrilled and would have loved to take the machine right away, just as it was." But the machine was reserved for a German customer to whom it was delivered shortly after a successful Factory Acceptance Test. Later on, Meiser and Sabine Wildenhain, the Project Manager for this project, also learned more about Biovian's specific requirements that would turn the seemingly standard filling machine into something unique.

Low ceiling heights challenged the Optima team

Biovian was planning to place the filling machine in its manufacturing facility on the seventh floor of the Bioscience Centre. There, the ceiling height was 2.40 m which is considerably lower than in standard production facilities. This had to be considered when designing the RABS containment. Meiser explains: "By conducting a trial, we were able to reduce the height of the laminar flow unit accordingly. Obviously, we needed to assess whether there was still enough airflow to ensure that the required particle-free performance was still there." That was the biggest hurdle. Once it was cleared and Optima was able to present the solution, everything progressed fast.

The specifications were created very quickly. Meiser thinks this was because of a strong mutual trust: "The Biovian management team perceived Optima as experts who know what they are doing." Consequently, the final meeting before placing the order also went smoothly. In summer of 2019, Ulla Myllymaa and Kaisa Paasimaa, an engineering expert from Biovian, discussed the final details with Optima's team. Two days were reserved for this, but everything was finalized in one day. One of the topics was how the new vial filling machine could be moved up to the seventh floor via narrow passageways and bends. Eventually, it was decided that the machine would be designed in two parts – from both mechanical and electrical standpoints – to allow easy transport and quick assembly on-site. The filling machine was to be equipped with compensation cells that damp any vibration that could affect the accuracy and stability of weighing when dosing.

Product loss is minimized

As requested by Biovian, the compact, customized VFVM231 vial system can support the use of various vial sizes from 2R to 100H and can handle fill volumes between 0.2 ml and 100 ml. The vials are supplied "ready for use" in trays and packed in sachets. Given the small batch sizes, the bags are manually removed within the containment environment, turned by a manual turning station, and pushed onto a turntable.

The next stage is fully automated. The objects to be filled are fed into a rake system where they are weighed and filled with a peristaltic pump. Its hose is single-use and can be easily replaced for every batch. Flexibility is required for filling, as the products can vary in viscosity and may, in some cases, tend to foam. Most biopharmaceutical products filled by Biovian are expensive. Optima's experts implemented special functions in the filling process, such as a so-called Redosing on Request (RoR) as part of the in-process control. In practice, the filling needle tracks an underfilled vial on the control load cell where it is refilled. This function also removes air from the filling tube at the beginning of the process and helps to recover all bulk material at the end of each batch. Product saving features are also built into the closing machine. For example, if a stopper is missing, a new stopper is fed from the sorting pot. Because these small batches are highly valuable, the aim is to minimize the number of partially filled or improperly closed vials that would need to be rejected. The final step of the process is sealing the vials with a final cap and crimping.

The new, fully automated vial filling and closing line with RABS started operating at Biovian in early 2021. It can process a range of vial sizes up to a batch size of 10,000 vials. ❮

Product losses are avoided with functions such as Redosing on Request, where insufficiently filled vials are redosed at the IPC point. ❮

In the CDMO sector, batch and product changeovers are frequent. Therefore, both the machine and its control system have been designed so that the Biovian staff, trained by Optima experts, can adapt the machine to new product characteristics or vial sizes. It has been made easy to handle the format parts and to replace them when necessary. The machine's highly compact design created some additional benefits. It allows even the shorter operators to reach all parts of the machine using gloves.

A trouble-free process and on-time delivery

The shipping and assembly of the machine went like clockwork. Optima delivered it before Christmas, "right on schedule," says a delighted Sabine Wildenhain, the Optima Project Manager. Seemingly satisfied, she talks about the perfect interaction of everyone involved and the fact that this project was characterized by female power from both Biovian's and Optima's sides. She says: "We had a female project engineer in sales, a female designer for the machine, one for the filling unit, a female qualifier, and we also had a woman in charge of air preparation and particle measurement." The assembly team also showed its best,

During stoppering, there is another product saving feature that prevents inadequately sealed vials. They are then closed with a cap and crimped. ❯

Automation is not yet used for unpacking the vials delivered "ready to use". The bags are removed manually within the containment environment. ❯

working hand in hand with the design engineer. The team's extensive experience and understanding of customer requirements greatly contributed to the smooth-running of procedures and to the building of a top quality machine.

Project partners at the customer's site were understandably satisfied. Ulla Myllymaa confirms that "the cooperation with Optima was really good from start to finish. All the components were specified in the quotation. We received regular updates on all stages of the process in the form of images and teleconferences. Also, I appreciate the fact that we had a single point of contact at Optima, a deeply knowledgeable project manager. In the future, when customers visit Biovian we will be able to present high-quality filling equipment."

The customized RABS filling machine unit may one day be moved to another factory building. Its modular design will mean that this can be done easily. If needed, the machine guard (containment) could then be raised from the current 1.70 m, benefitting taller machine operators. With the new, flexible Optima machine, Biovian has future-proofed its One-Stop-Shop offering.

MORE ABOUT THIS TOPIC

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INTERVIEW

Comprehensive services for a global customer base

Three questions to Ulla Myllymaa
Project Manager at Biovian

What were your specific requirements for the new filling machine?

Biopharma companies that we work with as CDMO partners are developing the innovative medicines of the future. This means that the products we are entrusted with are extremely valuable. Many of the candidate drugs that we manufacture and aseptically fill in compliance with GMP are "first-in-human" products intended for unmet medical needs. This is why minimal product loss with the small batch sizes is a necessity. The filling system needs to be robust and reliable. The important features include full automation and automatic control of volumes.

How satisfied were you with the way the project was taken care of?

The way of working was highly professional from start to finish. Optima responded quickly to change requests that we made throughout the project. Moreover, Optima kept to the exact date for the delivery of the system.

How important will the new vial filling machine be for Biovian in the future?

Fill and Finish is one of Biovian's core competencies and an essential part of our One-Stop-Shop CDMO concept. For us, it was important to invest in the state-of-the-art automated system with RABS that meets current and future regulatory requirements (Annex 1 of the EU GMP Guide "Manufacture of Sterile Medicinal Products"). The Optima system will enhance our ability to provide high-quality, comprehensive services to our global customer base.

DIGITAL FEATURES FOR GREATER SAFETY

IMPORTANT FOR YOU

- A globally active pharmaceutical company has cooperated with Optima on a project for the first time.
- A turnkey filling line for vials with isolators and freeze-drying equipment was realized to fill hemophilia drugs and solvents.
- Smart digitalization technologies have been integrated, so increasing production reliability.
- The integrated mass spectrometers in the freeze dryers were used for the first time as SCADA integrations. These also boost production reliability and enable process control.
- Optima Smart Services "Changeover Scan" and "Video Monitoring" maximize line availability and product yield.
- The CSPE process can effectively shorten the time required to start production, even for complex turnkey projects.
- The customer is very satisfied with the progress of the project and the operational results of the system.

Optima Pharma has realized a complete vial filling line, including isolators and freeze-drying equipment that is equipped with various digital safety features and mass spectrometry. The customer, a globally active pharmaceutical company, places great value on production reliability and the use of future-oriented technology.

At the end of 2018, the global player faced the challenge of increasing production capacity. There were new products in the pipeline: Freeze-dried drugs for the treatment of hemophilia and other drugs to treat rare blood diseases were to be manufactured.

Optima scores with turnkey competence

Hemophilia is an inherited disease found predominantly in men, which inhibits blood clotting and leads to lifelong disability. Solvents are also filled on the line to be administered alongside the product.

It was clear from the outset that the supplier of the filling and closing line, which would include isolator and freeze-drying technology, should supply everything from one source as a typical turnkey project, thus making it a project that was predestined for Optima Pharma. In addition, the company would need to be a leader in isolator technology with the ability to deliver a complete qualification package. The company chose Optima as its partner for this first time on the basis of these factors. "Building a filling line project combined with freeze-drying equipment is complex. In addition, a new challenge for both sides was the almost full implementation of GMP qualification," says the responsible Senior Project Manager at the company, explaining the initial position.

Scanning format parts and verifying the DMC code ensures that the correct parts are fitted.

CSPE: In best time to production start

Optima Pharma has a proven and comprehensive technical and scientific process with CSPE that can shorten the time to production start-up using a range of measures such as digital engineering and many others. The customer has also benefited from this comprehensive approach: "Right from the sales phase and throughout the project, Optima Pharma's turnkey concept offered great benefits," says the Senior Project Manager. This had a positive effect on the coordination of overall design, communication, functional, electrical, mechanical and software interfaces and system control. Then there is the fact that there is one single contact person at Optima to advise on every aspect of the overall project.

As with the majority of filling line projects, in this case, Optima's supply scope also includes process functions for washing and sterilizing the vials. They are then filled and closed in the OPTIMA VFVM 7000 filling and closing machine. As a machine concept the OPTIMA VFVM is suitable for injection and infusion bottles with a dosage capacity of 0.1 ml to 500 ml. Output is up to 30,000 items an hour, depending on the product and filling quantity. This is connected to a loading and unloading unit for each of the two LYO-D freeze dryers. Each freeze dryer takes up nine square meters of floor space. An isolator was integrated above the filling machine and the two loading and unloading units. After the freeze-drying process, the vials are capped and stored. This is partially done under laminar flow. The initial purpose of the line is to fill hemophilia drugs and their corresponding solvents in vials of 2, 5 and 12 millliliters.

Mass spectrometry for even greater safety

100% in-process controls in the filling area and a range of cameras to check correct stoppering and closure with a cap ensure optimum process reliability. One special feature is the mass spectrometers integrated into the freeze dryers, supplied by Optima Pharma. These check the atmosphere inside the equipment for unwanted foreign substances at fixed intervals, and so are able to detect even the most minute quantities of oil both during and before freeze-drying. This is also why Optima's customer has chosen to include this process. Two additional goals can be achieved besides enhanced safety, due to the environment integrity test, explains Joerg Rosenbaum of Optima Pharma in Mornshausen, Hesse: "With the mass spectrometers, the freeze-drying process can be controlled very well. The device can also be used for process optimization to make even better use of production capacity." Mass spectrometers are also available as a stand-alone solution, and this means that they can also be used for maintenance purposes.

Another added benefit of Video Monitoring: Operators have an improved overview of the system as the cameras transmit live images to the HMI.

Assistance with changing formats

The pharmaceutical company did not only attach importance to the use of future-oriented technologies in freeze-drying. The system's second special feature is the digital functions. Digitalization is playing an increasingly important role in changeover and line clearance. For example, product paths are replaced or emptied manually and packaging materials are removed. Finally, the system is cleaned and sterilized before the next cycle can be carried out. Marcel Biedermann, Project Engineering Manager at Optima Pharma, says: "There are massive risks here that can severely affect the production process. We are therefore

"Now, almost two years later, we are seeing the fruits of our labor – a filling line that outperforms anything Optima Pharma and we have ever achieved."

The responsible Senior Project Manager at the customer

Keep a vigilant eye on production: Cameras located within the filling and closing line record every step.

currently providing operators with assistance here, and we will continue to do so in the future, via features from our IPAS (Intelligent Production Assistance System) digital product portfolio."

One of these features is the Changeover Scan. This Smart Service from Optima is a tool designed to assist system operators and is available to all Optima business unit customers. The customers' employees can use scanners to scan format parts that need to be changed and use a DMC code to verify that the right parts are being used. Correct installation has to be confirmed on the HMI. This way, the risk of machine downtime arising because the wrong format parts have been fitted can be effectively minimized, and machine availability is increased. Crashes within machines are therefore prevented, and product losses are also kept to a minimum. Another benefit is that operators can be trained more quickly.

Cameras: the production manager's extra set of eyes

Another Smart Service available in the system is Video Monitoring. Cameras inside the machine continuously record live images, which the customers' staff at their production site can view via their company network. In the event of a claim, this gives the company a means of providing proof to the authorities and eliminates the need to discard entire batches. Last but not least, the cameras improve the operators' visibility. It is also possible to use it 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 can be minimized. "When a production discrepancy is found in an aseptic production line, it is very time-consuming to investigate it. That' s why we need as much information as possible, as quickly as possible, to find the cause. Video Monitoring helps us with this", says the Senior Project Manager.

Working in combination, both tools increase system availability and deliver an even higher level of production reliability. "Our goal is for our products to be released immediately thanks to quality control and assurance in real time," he says, explaining the company's decision to use Optima's Smart Services. Consequently, continuous, automated, closed-loop production processes are very important to the company.

The pharmaceutical company is very satisfied with the ongoing operational results from Optima Pharma: "Now almost two years later, we are seeing the fruits of our labor – a filling line that outperforms anything Optima Pharma and we have ever achieved," says the responsible Senior Project Manager, summing up. "The line is functioning as anticipated, and we are now eagerly awaiting delivery to us." He particularly singles out for praise the simple, elegant design, the ease of cleaning and the filling accuracy, the high number of in-process controls, and careful product handling with minimal shear stress. "Compared to other suppliers, Optima's systems are the best we have ever tested," he says.

Ready to go

However, the majority of the qualification will be carried out at Optima, so the system will be staying at Optima Pharma's CSPE Center for a few more months. For the first time, installation, operation and initial pre-performance qualifications will all be carried out at Optima Pharma. The coordination of interfaces, the integrated Factory Acceptance Test (iFAT) under realistic conditions, which is part of CSPE, and the almost complete qualification significantly shorten the time to production start at the customer's site.

With Video Monitoring, the production process can be continuously recorded and film sequences can be saved in the event of an alarm.

The Changeover Scan effectively minimizes the risk of machine downtime and increases machine availability.

MORE ABOUT THIS TOPIC

www.optima-packaging.com/digitalization-pharma

168,5

million cases of infection
associated with COVID-19
worldwide

As of: May 27, 2021
Source: COVID-19 Dashboard | arcgis.com

150,8

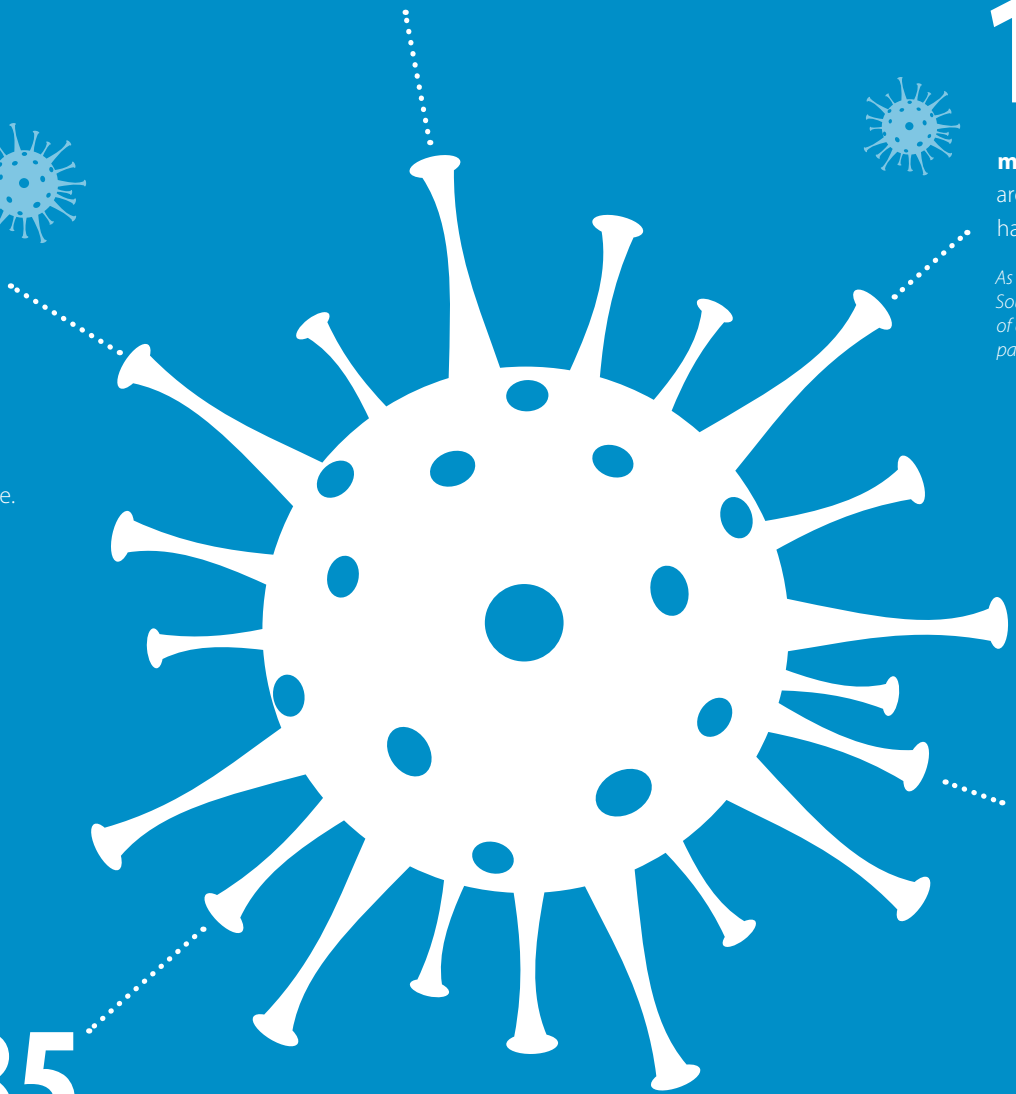
million people
around the world
have recovered.

As of: May 25, 2021
Source: Worldwide number of cases of coronavirus by patient status | Statista

16

vaccines against COVID-19
have already been
approved worldwide.

As of: May 24, 2021
Source: COVID-19 Vaccine Tracker | trackvaccines.org



10%

of the population of the world
has been vaccinated
so far.

As of: May 27, 2021
Source: Current corona situation on May 27, 2021: figures, maps & graphics for Germany and the world | Redaktionsnetzwerk Deutschland

285

vaccines against COVID-19
are in clinical trials.

As of: May 25, 2021
Source: Vaccines against the coronavirus – current development status | vfa

1,7

billions vaccinations
have been administered
since the start of the
vaccination campaign.

As of: May 25, 2021
Source: Coronavirus vaccinations by countries worldwide 2021 | Statista

Sources: *arcgis.com | Redaktionsnetzwerk Deutschland | Statista | trackvaccines.org | Verband Forschender Arzneimittelhersteller e. V. (vfa)*

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