O-COM

THE OPTIMA MAGAZINE

Digital power, minimized glove interventions and risks

Innovative solutions:

Annex 1 in pharmaceutical production

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OPTIMA packaging group GmbH
Alfred-Leikam-Str. 25 | 74523 Schwaebisch Hall | Germany

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

Editorial Team
Felix Henning, Julia Völker

Responsible for content according to German media law
Dr. Stefan König

MIX
Paper | Supporting responsible forestry
FSC® C155291

Printed product
CO_2 compensated
klima-druck.de
ID-No. 24187203
VDM+
You can find more information on the calculation methodology, offsetting and the selected gold standard climate protection project at klima-druck.de/ID.

Challenges – **or opportunities?**

Dr. Johannes-Thomas Grobe
Chairman and CEO
Optima Pharma

Dear readers,

The pharmaceutical industry continues to develop with great momentum. Drivers include new, e.g. complex therapeutic procedures and weight loss injections with “blockbuster potential” – just after the pandemic had disrupted many investment plans, including replacement investments. On the technical side, Annex 1 requires a growing variety of technologies, extending to digitalization.

We implement these extensive requirements into the best, safest, and most efficient system technology, including innovative services for customers. In the project, we minimize complexity and risks, while optimizing quality. Our most valuable tool is the turnkey strategy that we developed over the years. This, coupled with concentrated innovative strength, has allowed us to grow into a globally positioned, preferred partner in the industry.

What does that mean for you? Read the articles in this edition of the o-com. Learn more about a turnkey project that was implemented specifically for highly active ingredients in a customer-specific design. It is also interesting how new system functions respond to the new Annex 1 guidelines. We also support operating processes with innovative digitalization and offer new services that increase efficiency. With 15 years of consistent turnkey strategy, we also provide an overview of the most important and latest turnkey innovations.

Enjoy!

Yours
Dr. Johannes-Thomas Grobe

16

Glove minimization

How to reduce glove interventions correctly – and why not all glove ports are the same.

25

Technical innovations for Annex 1

Updated regulatory requirements for fill-and-finish processes: Modular technology increasingly offers options, including fully automated solutions. This takes the individual needs of pharmaceutical companies into account.

44

Project: Integrated for highly active ingredients

Turnkey hands-on. Highly active ingredients require perfectly coordinated system components. Customers benefit from a system that has already been extensively tested at Optima. The (advance) cycle development was also performed in-house.

News

Strategy

Innovation

Insights

News

Management Board at OPTIMA pharma

Dr. Johannes-Thomas Grobe, Chairman of Optima pharma GmbH, has also taken over the role of CEO Pharma on July 1, 2024. The 58-year-old Doctor of Engineering has many years of experience in mechanical and plant engineering as well as in drive and control technology. His management team consists of: Matthias Poslovski (Chief Sales Officer), Matthias Naser (Chief Operating Officer), Prof. Dr. Thomas Pospiech (Chief Technology Officer), Holger Burgermeister (Director Service), Stefan Knellwolf (Managing Director OPTIMA pharma containment GmbH in Radolfzell), Stephan Reuter (Managing Director OPTIMA pharma GmbH with responsibility for freeze-drying in Mornshausen).

OPTIMA on course of growth

The Optima Group can look back on a successful 2023 financial year. The family-owned company's turnover rises to 620 million euros, and the number of employees to over 3,150 at over 20 locations worldwide. The high level of order intake will ensure further growth in 2024.

Realignment of the OPTIMA Executive Board

Setting up the management team for the coming years: That was the task for the successful Optima Group this year. Due to age, two positions had to be filled. After a structured one-year handover process, this has now been successfully completed. Marco Beyl (CFO) and Dr. Johannes-Thomas Grobe (Chairman and CEO at Optima Pharma) have taken over the responsibility from their predecessors. They complement the Executive Board with CEO Dr. Stefan König and Managing Partner Hans Bühler.

Ground-breaking ceremony in Radolfzell

In September 2024, the official groundbreaking ceremony took place for the extension of Optima Pharma Containment in Radolfzell, where isolators for state-of-the-art turnkey systems are developed and built. A 1,700 m² assembly hall and a separate administration building made of timber construction are being built. The planned construction time is one year. The extension building has become necessary against the backdrop of a significant increase in demand for insulators in recent years and the increasing number of employees.

Award for digitalization strategy

With the "Allianz Industrie 4.0 Award Baden-Württemberg", Optima received an award for its comprehensive digitalization strategy and the customer-focused implementation of digitalization solutions. The award with the highest level "Excellence", is presented by Baden-Württemberg's Minister of Economic Affairs, Labor and Tourism, Dr. Nicole Hoffmeister-Kraut, to companies with holistic approaches to digital transformation.

New headquarter

After 65 years, Optima has moved its headquarters from the Stadtheide to the Alfred-Leikam-Straße in the Solpark. For several years, management had been pursuing the combining of the central services in the Solpark, where most of the employees now work. This has now been achieved with the purchase of the former "Solar Factory" with enough space for central services, the new training center, which is currently completed, and a large assembly area.

IMPORTANT FOR YOU

- Holistic concept for fill-and-finish systems with isolators and freeze dryers
- Established: Comprehensive Scientific Process Engineering (CSPE) – optimized engineering, project organization and execution of turnkey systems
- Alignment of the corporate organization with turnkey: From the design phase to life cycle management
- Setting the pace for turnkey innovations with 15+ years of turnkey experience
- Early and continuous investment: Dedicated CSPE centers for system integration and implementation of integrated FATs

Turnkey lines: **Expertise paired with reliability**

Comprehensive Scientific Process Engineering (CSPE) offers digitally and physically optimized system integration for fill-and-finish systems, including isolators and freeze dryers as a complete turnkey line. Pharmaceutical companies benefit from minimized risks, reduced use of resources, and an expedited production start.

During cycle development, Optima utilizes different indicators, including enzyme indicators, leading to precise and fast results.

The CSPE center's own laboratory: One of several requirements for in-house cycle development for complete lines.

What is often simply referred to as "turnkey" is a package of coordinated services with the objective for the optimized system integration. Optima Pharma's CSPE approach simplifies the demanding task of manufacturing, installing, and subsequently operating fill-and-finish systems with isolators, and freeze-drying systems for its customers.

Isolators and filling and closing machines are complex process systems. For both to form a unit as a turnkey system, the software, controls, and mechanical interfaces must be closely coordinated. The same pertains to freeze dryers when part of the filling and closing process. Such highly automated, integrated fill-and-finish processes should be viewed holistically to find differentiated, optimal production strategies, says Dr. Mario Schwab, Director of Sales, Europe, and South America at Optima Pharma.

Completed in-house: Risk management

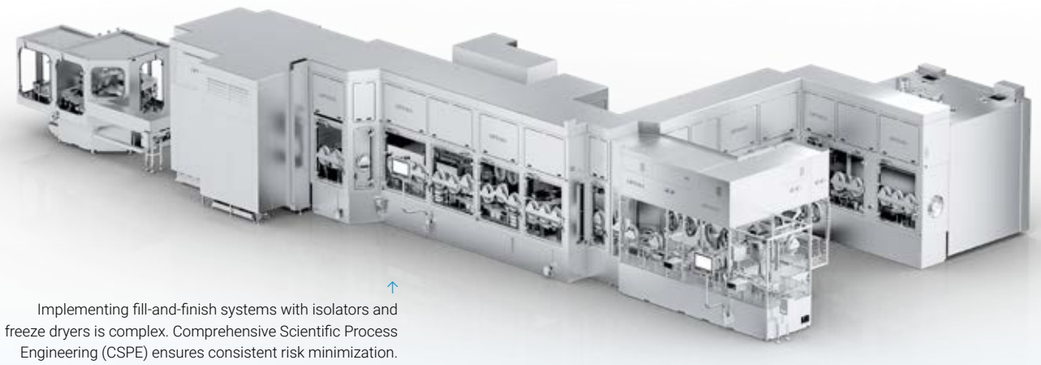
Within the scope of CSPE and five years of turnkey experience, Optima executes services in-house that would otherwise be performed at the customer's site, providing a seamless testing experience with the highest quality standards. Developing the CSPE capabilities required considerable investment, preparation, and expansion efforts.

Over the years, Optima has developed and continuously grown a holistic process understanding for integrated fill-and-finish lines with isolators and freeze dryers, while also establishing a systematic approach and methodology with CSPE. Today, Optima's CSPE centers in Schwäbisch Hall also offer services including comprehensive pre-testing of the system and the decontamination process pre-cycle development. The greatest benefit for pharmaceutical customers? Potential risks are identified and solved immediately at Optima - before the complete and complex system arrives for installation at the customer's site.

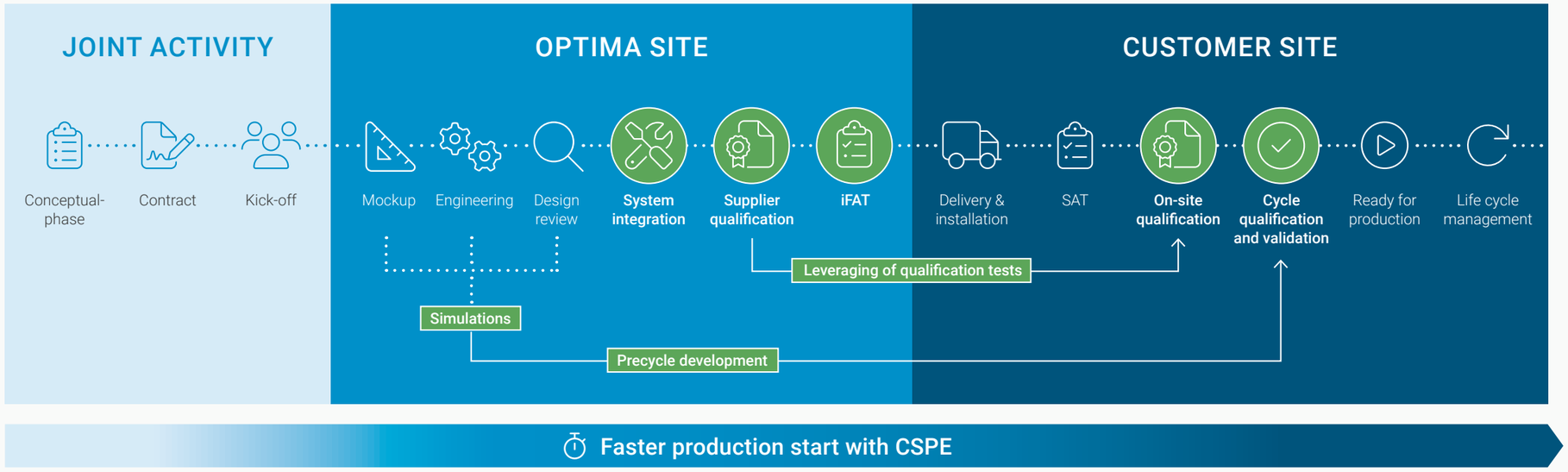
Ultimately, the Optima turnkey concept also reduces interference that would arise from work performed in the customer's cleanrooms. In addition, the CSPE approach also reduces the customer's efforts and use of resources. From project start to completion, all planning, coordination, and organization is carried out with a single point of contact at Optima – eliminating third party involvement for filling and closing, as well as containment and freeze-drying, saving cost and time. The single point of contact principle applies throughout the entire life cycle of the system.

Digital engineering anchored with CSPE

CSPE also means consistently using the potential of digital engineering. "Without digital engineering, 'turnkey' in this form would not be nearly as effective and beneficial for our customers," says Schwab. Following more info on Optima's CSPE services.



Implementing fill-and-finish systems with isolators and freeze dryers is complex. Comprehensive Scientific Process Engineering (CSPE) ensures consistent risk minimization.



Wherever possible, all services are performed in-house at Optima Pharma. This shortens the commissioning phase at the pharmaceutical company and the overall delivery time from the order to "ready for production".

First, the simulations: Optima carries out air flow, fluid, and temperature simulations, as well as VHP cycle simulations as part of its digital engineering for turnkey systems. Since Annex 1 distinguishes between "first air" and "second air" (Eudralex Volume 4 - EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use) interferences of the laminar air flow, touching product contact parts, must be observed. At an early stage, simulations show where to make adjustments within the system. Comparisons with smoke studies performed at Optima, show the high level of consistency and precision of today's simulation results.

From digital simulations to hands-on tests

Simulations of the decontamination cycle also anticipate possible risks and precisely depict the VPHP distribution in the isolator. This type of simulation is executed early in the project phase to position the injectors perfectly. All required parameters, like injection pressures and rates are then established on the machine model and the final positioning determined with simulation.

Comprehensive tests: This covers the services that Optima provides before the system is delivered, including cable connection and labeling accuracy, as well as the safety circuit interfaces. Followed by filling line and isolator leak tests and, if necessary, the loading unit isolator of the freeze dryer.

Next, the system's automation and software framework are analyzed by a defined procedure, including the isolator technology software and the freeze dryer loading systems. Finally, the SCADA system assessment completes Optima's test series, ensuring the basic SCADA functionality for the integrated Factory Acceptance Test (iFAT), followed by the integration of the SCADA system into the customer's IT environment onsite.

From hands-on tests to qualification

The impressive CSPE centers in Schwäbisch Hall are fully functional test centers built to test and qualify complete turnkey fill-and-finish systems including the media supply up to the installation. Even small systems or freeze-drying equipment with side condensers can be installed, if required.

The decontamination cycle is developed in the CSPE center's own laboratory ("pre-cycle development"). In addition to the usual biological and chemical indicators for cycle development, Optima also utilizes enzymatic indicators, which lead to precise results more quickly.

Optima offers simulations of individual functions in motion up to simulations of the entire line.

One single point of contact: This principle applies throughout – including the coordinated introduction and installation of system technology in the clean rooms of pharmaceutical companies.

Optima Pharma already completed the qualification (IQ and OQ). After installation in the clean room, only interfaces that were separated for transport need to be retested.

System cycles must be slightly readjusted and verified after installation in the customer's clean room due to spatial conditions like room pressure cascades and surface temperatures, explains Schwab

Qualification once, not twice: "Leveraging"

If customers utilize the Optima Pharma qualification package (IQ and OQ), only those interfaces that are separated for transport, must be tested and qualified again in the clean room at the customer location. The approach in which the system has already been successfully qualified in-house by Optima, is called "leveraging."

The qualification and documents created by Optima can be used virtually as a complete basis. The customer's qualification only needs to be supplemented by those parts that had to be reconnected after transport. All documents have a uniform structure and can be used by authorities to validate the manufacturing process. This means that testing is carried out only once, saving time and effort for the customer.

In addition, Optima coordinates the entire introduction and installation process of the turnkey system using an integrated move-in concept. Optima turnkey project management offers shorter installation times onsite in the customer's clean room, and significantly less coordination effort for the customer.

Training and Optima Academy

Now the customer's turnkey system has been installed and production soon begins. This requires competent preparation – the operators and maintenance crew must be able to operate the complex system as quickly as possible.

The "Optima Academy" ensures that production begins quickly and efficiently. First, the individual training needs of the participants are determined. Then, professional, certified trainers build training content based on previously generated modules. Online training and face-to-face learning directly at the machine, both at Optima and onsite, are part of the academy.

Innovations and future plans

Freeze-drying and containment have been an integral part of Optima Pharma for nearly 15 years. There are countless development steps between the initial interface coordination and today's CSPE. Lots of experience and two CSPE centers later – have we achieved our goal?

There is always potential for improvement. Optima Pharma recently introduced an organizational innovation. Experienced experts for filling and closing, containment, and freeze-drying accompany a new project immediately after order receipt with a special approach. This ensures the best possible technical execution right from the project start.

The idea and philosophy of the Optima turnkey approach is to implement in-house systems that are fully tested, qualified, and almost "ready for media fill." What is the next step? Mario Schwab sees the future of Optima with complete fill-and-finish lines with or without freeze-drying delivered to the customer "ready for production" and installed reliably, in a short time. We are "Your home for turnkey."

What characterizes CSPE and "turnkey" at Optima Pharma?

- One single point of contact for the entire turnkey system
- The fill-and-finish line as a functional unit with isolators and freeze-drying: Consulting, engineering to installation, qualification, and "ready for production"
- Comprehensive digital engineering, including utilization of different simulation types for the entire line
- Uniform software and automation concepts for the entire line
- Cycle development of the decontamination process using simulations and hands-on implementation with indicators in the CSPE laboratory before delivery
- Comprehensive tests of the entire line before delivery, e.g., signals ("handshakes"), safety circuits and tightness of the isolator structure
- Uniform SCADA for the entire line: Functionality for iFAT, embedding in customer IT onsite
- "Leveraging": Virtually complete qualification of the entire line at Optima, only system parts separated for transport are requalified onsite
- Introduction concept and coordination of the installation with one contact
- Training, service, and entire life cycle management for the entire line with one central contact person

Glove minimization:

The path to risk minimization

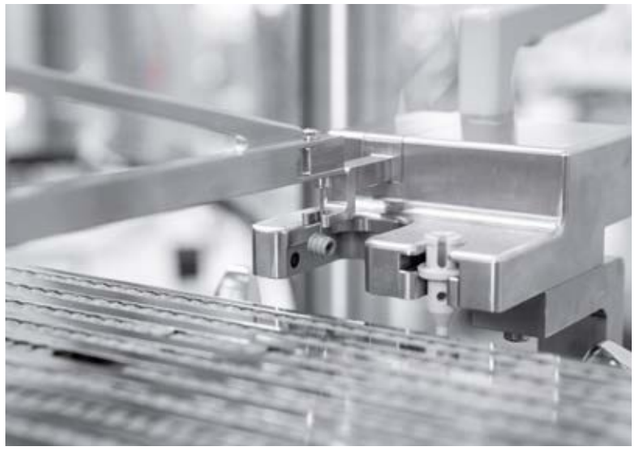
Reducing glove access on isolators and minimizing pharmaceutical risk – a clear regulatory mandate for the industry. There is no one solution, but instead a whole bundle of new, already implemented ideas and technologies to meet a wide range of requirements. This article explains each of these solutions in more detail.

IMPORTANT FOR YOU

- The individual risk of individual glove procedures depends on several factors
- Optima does not offer one machine type, but a portfolio of different solutions that are suitable for almost all machine types and functions
- The solutions are based on mechanical, software, and automation solutions, including AI
- The focus is a wide variety of specific customer needs, which will vary depending on the application
- Fully-integrated solutions according to Optima's turnkey and CSPE approaches: From flow optimization to in-house programming of all automation solutions

↑
Sorting bowls for stoppers and guide rails are considered a critical "hotspot." Optima offers solutions.

The regulatory objective is well-defined: Glove intervention in isolators should be avoided wherever possible. Annex 1 still permits glove interventions, but only as part of a contamination control strategy (CSS) as a risk-based procedure. The mission is clear – and machine manufacturers are continuously delivering new solutions to reduce glove interventions including scheduled interventions like sterile installations or unexpected troubleshooting problems.



Know the potential risks of glove interventions

In addition to minimized glove interference criterion, customers have highly specific requirements in every project. It makes sense to take a closer look at the risk assessment of glove procedures, which vary greatly from glove port to glove port. These factors in particular should be considered:

- Intervention frequency per glove position
- Position of the glove in the isolator
- Timeline of the process sequence
- Duration of a typical glove intervention at a location

Every glove installed on the isolator represents a certain basic risk simply because of its existence. However, for example, glove intervention in the filling area with open containers carries a comparatively much higher risk than glove operation after crimping, where the containers are already closed. Each glove port poses a different level of risk from another glove port.

No need for a new machine but a solution for all machine types

To reduce or eliminate glove interventions in a risk-based and customer-specific approach, Optima is convinced that a portfolio of glove-minimizing solutions is the best way to address these needs, since the question of the "suitable" solution is also a question of each customer's production process, budget, and business philosophy. Technology options should reflect each customer's requirements.

At Optima, new solutions must first pass several requirements. They should be practical – and thus ultimately offer a wide range of applications. They should be applicable to both low-output and high-performance systems like vaccine production, as well as in highly flexible systems for vials, syringes or cartridges, bulk, or nested containers. All these requirements are key to finding the best solution for all applications. In addition, new solutions should be compatible with other central system functions and properties.

Modular – including mechanics, software, and artificial intelligence

What options does Optima offer to reduce glove interventions? The spectrum ranges from AI-based error detection combined with robotics and autonomous path planning, to additional automation and software solutions, to innovative mechanical solutions. Combinations of the above-mentioned solutions are viable to design a customer-specific overall system.

According to Annex 1, components that come into direct or indirect contact with the product must be introduced into the system in an autoclaved state, whenever technically possible. This has to be accomplished (if possible) with closed isolator doors, for example with beta ports or material locks. Additionally, even during the subsequent setup processes, the components must not be touched directly with a glove. Handling and installation tools like removable handles on the equipment are an initial solution to comply with Annex 1. However, this requires well-trained personnel who know and can avoid first air risks during setup.

Innovative mechanical tools

Optima has developed innovative mechanical solutions to effectively minimize risks, as illustrated by a filling line with rotary piston pumps. The housing and pistons of a dismantled pump, which are product contact parts, are autoclaved together with a parts carrier and a protective sleeve. This carrier will later be part of the transport solution; the protective sleeve will in turn ensure that the operating personnel cannot touch the piston directly with gloves, neither during sterile transfer nor during assembly.

The autoclaved parts carrier with the components is transferred via the beta port to a rail system within the system for installation. The parts carrier snaps into a small cart that is transported to the installation position in the isolator. Only now, when the pump piston is inserted into the housing, can its protective sleeve be removed.

Handling tools increase the pharmaceutical safety of glove operations. Innovative mechanics open up additional great safety potential.
↓

Filling needle installation without contact

Precision and skill are required to insert the filling needles into the needle holders at the dosing station. Inserting the needles using gloves and manual movement makes this a difficult task, especially with multi-dosing configurations. The mechanical solution uses a precision guide to move the needle holder to the operating side of the isolator. This avoids the operator reaching over the conveyor. The needle holder on the isolator wall can also be rotated 90 degrees, giving the operator a clear view of the insertion position. The holder is ergonomically easy to reach as well as outside the first air critical area.

> The individual risk of individual glove procedures depends on several factors.

The holder with the filling needles is returned to the dosing station the same way, eliminating glove movement in the primary air area and accidental contact with critical parts. In addition, handles are now located outside of first air critical areas and the number of glove procedures, and the duration of glove interventions are greatly reduced.

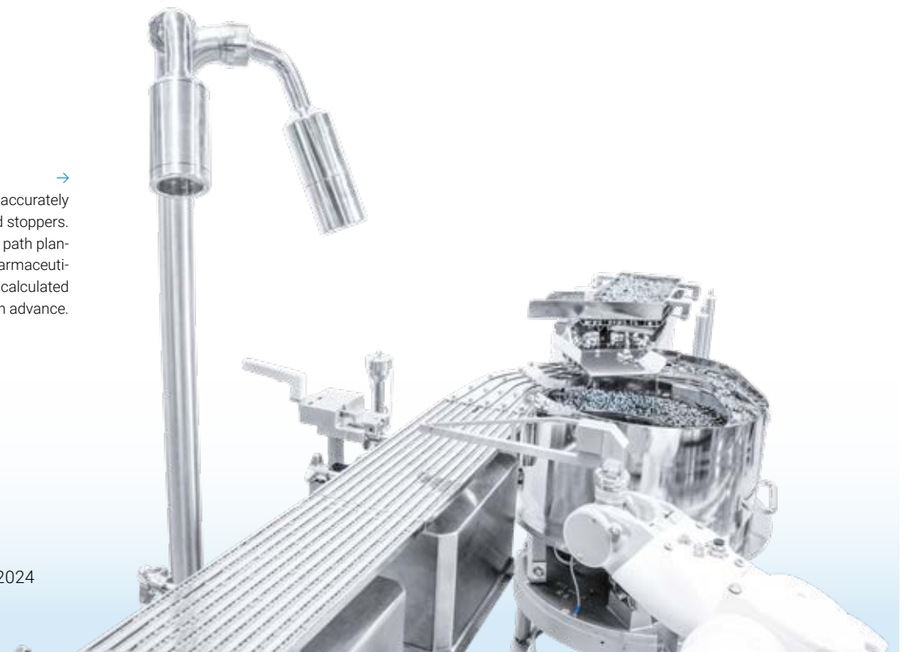
Save setup in seconds

Format parts must be connected safely and firmly to carriers during setup. Therefore, format parts are usually fastened with handheld screwdrivers, which can be difficult through glove ports when the isolator doors are closed, especially in difficult-to-reach, first-air-critical locations.

The new Optima system to install format parts without screws is “Plug, Click, and Play.” Springs, levers, and other mechanics almost completely replace the screw connections. Even “threading” the format parts is easy, and the guides still have defined play at the beginning of the path, which changes to zero tolerance in the final position. Once the format part snaps into the end position, a spring mechanism automatically fixes it into place, while another mechanism secures the position. The design utilizes the Poka-Yoke principle to ensure the installation of format parts and holders are in the correct order and location.

Customer input on engineering

This simple and user-friendly application includes intensive R&D. First, the forces acting on the format parts were determined. This information was used to test new solutions in FEM simulations – the first prototypes were produced using a 3D printer at Optima.



→ Artificial intelligence accurately detects misaligned stoppers. With autonomous path planning, the robot's pharmaceutical solution path is calculated in advance.

↑ Installing format parts with a simple “click” – Optima designed a special mechanism utilizing customer feedback and extensive testing

↑ Biotrak® detects germ contamination in real time. With its certification, numerous glove interventions can be eliminated. Optima has already integrated the system into several systems

Prototypes were sent to customers to provide feedback for improvements. Later, the washing and sterilization properties in the autoclave were also tested. Optima conducted endurance tests for the first format part series intended for customer machines at its in-house test station for several weeks, simulating actual production conditions. Only after this internal validation was the final approval for use in customer machines authorized.

This fixation system can be used across the entire system, significantly reducing the number of glove interventions in critical zones and their duration. Installing individual format parts was previously an arduous and time-consuming task. Now it takes just one quick glove intervention per position and the installation is complete – and it is first air optimized without the operator interrupting the primary air supply.

Software solutions to minimize risks

Software solutions are an ideal addition to these mechanical solutions. Many components, especially format parts, are attached to movable axes. These components can be driven by software-controlled motors into easily accessible installation positions, outside of first air-critical areas. When operators select this function on the HMI, numerous glove interventions are relocated to non-critical areas.

In addition to solutions for scheduled interventions, particularly supporting operators during setup, solutions for unscheduled interventions are part of the Optima portfolio – with the focus on potential malfunctions not corrected without critical glove intervention or completely automatically.

For example, if there is a production stop caused by a single track, due to a dosing pump defect, the effected track can be easily switched off on the HMI. Although the system performance is now reduced, this new software function eliminates the need for many glove interventions to troubleshoot the problem, allowing the batch to be completed.

Unscheduled interventions? Solved with robotics and AI!

With the introduction of Annex 1, the sorting bowl and the subsequent stopper feeding unit became an area of increased pharmaceutical criticality. During a glove intervention above the sorting bowl or the feed track the first air principal is violated and all stoppers in this zone must be classified as potentially contaminated. In addition, errors occur more frequently at the stopper sorting and feeding unit compared to other system zones. Optima estimates that more than half of all unscheduled glove interventions can be eliminated with a solution for this type of error.

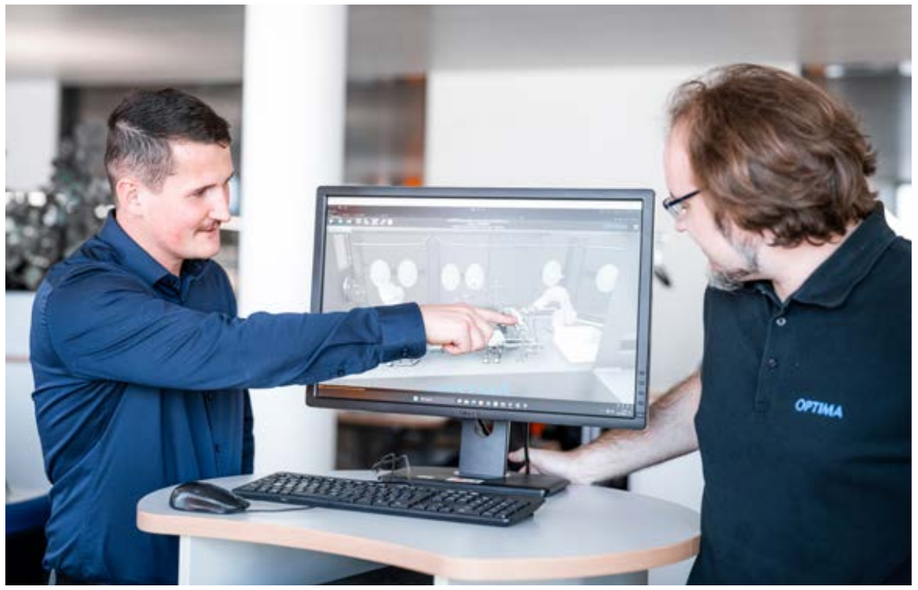
Therefore, Optima has developed a robotic system that nearly eliminates these glove interventions. The robot arm has an autoclaved tool with a needle as a "picker" and an optical system. Incorrectly oriented stoppers are identified, separated, picked up, and placed in a container. The first special feature of this module is the monitoring optics for the feed tracks, which, in combination with artificial intelligence, can recognize and classify different packaging materials and situations. This system is superior to classic image recognition and delivers remarkably reliable results. The second special feature of the new functional unit is the digital twin. This "twin" calculates possible solutions in advance – robot movement sequences - and takes various pharmaceutical-relevant criteria into account. This is called "autonomous path planning."

The faster twin

The digital twin knows and observes the pharmaceutical criticality scheme, particularly the first air principles. A robot has no access to "no-go zones," to avoid air turbulences over open containers.

A solution path is calculated with additional data, like the required processing time, which the robot then carries out. This also eliminates the collision risk in the system that could occur with this type of automatic intervention, avoiding a possible production stop. With autonomous path planning, the system can theoretically remove a misaligned stopper every 30 seconds without interrupting the process, ensuring compatibility with high-performance systems, and significantly increasing system productivity.

This complete solution, programmed and patented by Optima, creates the foundation for other application areas. Telemanipulation units also work according to the same principle. A robotic arm with tools inside the isolator assumes tasks that an operator would otherwise carry out manually. The robotic arm is activated and operated via a control from outside the isolator. This ensures spatial separation between the operator and the isolator interior. For example, a tipped empty vial on a turntable can be removed using telemanipulation. Critical zones are also inaccessible, so that movements in the systems are carried out in accordance with Annex 1.



The digital twin is specialized in calculating possible robot movements to remove misaligned stoppers in a pharmaceutical-friendly approach.

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Teamwork leads to the best solutions.

Just the same, installing the filling path can be achieved almost fully automatically with robotic support. The mechanical solutions and robotics work together to avoid glove interventions.

Special feature: System integration using CSPE

All solutions in the Optima portfolio are "fully integrated" and holistically developed as part of our Comprehensive Scientific Process Engineering (CSPE) approach. This applies to two aspects in particular:

The new glove-reducing functions are developed in simulations to optimize flow. As a turnkey provider, Optima carries out simulations with the complete design data including the isolator and freeze dryer (when applicable), as well as all installations of the system – mirroring the complete production line. This allows statements about the flow behavior, including mouseholes or different temperature conditions depending on the process phase of a freeze dryer.

Optima also carries out "in motion" flow visualizations (smoke studies) as required in Annex 1 in its own CSPE centers with an installed isolator and connected loading and unloading system.

In addition, Optima generally programs robotics and automation systems in-house, regardless of whether they were developed internally or from third-party vendors. Biotrak® is an alternative solution for system monitoring that is directly integrated into the Optima HMI and the batch reports (see page 31). This allows completely harmonized system integration of all components and functions and is a prerequisite for Optima to provide service support for all robotic components throughout the entire life cycle of the system.
This pool of modular solutions to minimize glove interventions is continually being expanded – and is becoming a real "game changer."

Optima's solutions to meet Annex 1 compliance go beyond minimizing glove interventions – learn more on page 25.

Technical innovations for Annex 1

IMPORTANT FOR YOU

- Annex 1 influences fill-and-finish processes: First Air principles, reduced glove interventions, increased monitoring
- The Contamination Control Strategy (CCS) is the basis of identifying and minimizing potential risks
- Simulations during engineering are the basis for consistently optimized first-air processes
- New functions and solutions support setup, the fill and finish process, and monitoring
- Modularity for individual customer-specific solutions

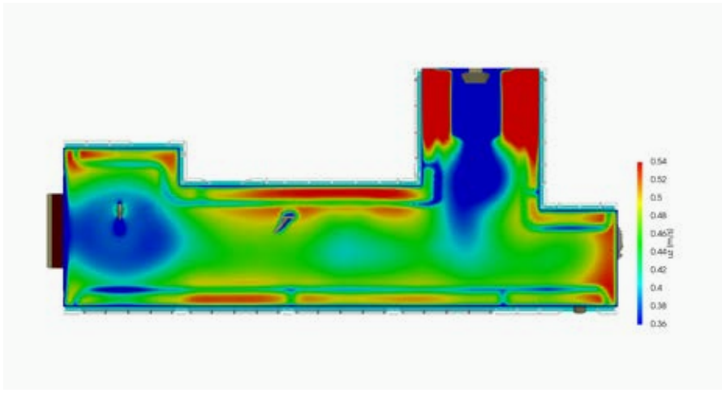
How does the current EU GMP Annex 1 affect fill-and-finish processes? What technical solutions and options does Optima offer to implement the new product and patient safety requirements?

Minimizing glove interventions in isolators is a key goal of Annex 1. You will find an in-depth article specifically about this topic in this edition of the o-com. Annex 1 also focuses on the First Air principle in fill-and-finish processes. Since glove interventions can undermine the First Air principle, there is a close connection between “First Air” and glove minimization – which also leads to overlap in the content of both contributions in terms of solutions. Therefore, some solutions are only mentioned in keywords and reference is made to the article, “Glove Minimization: The Path to Risk Minimization” (from page 16). The contributions thus complement each other.

Regulatory principles

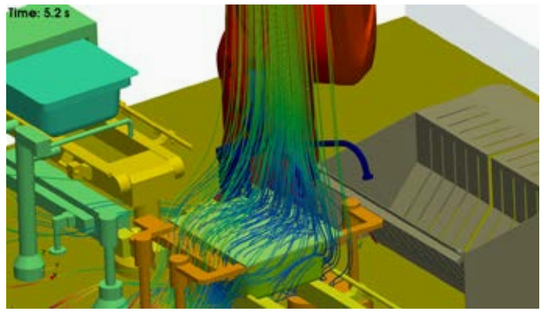
Today the Contamination Control Strategy (CCS) is the central basis for the handling processes of a pharmaceutical manufacturer. Another requirement of Annex 1 is Quality Risk Management (QRM). Processes must therefore be checked and evaluated according to a risk-based approach within the CCS. The QRM is, in turn, part of the overarching Pharmaceutical Quality System.

For the first time, “First Air” is explicitly mentioned in Annex 1 and a distinction is made between first and second air of the laminar flow. Simulations are initially suitable for implementing the First Air principle and laminar flow optimization. Complete turnkey lines with isolators and loading zones on freeze-drying systems can be simulated virtually allowing an iterative process. Simulations can then be used to document how a laminar flow can be optimized in the project regarding first and second air. Simulations do not replace actual smoke studies prior to production start. This can be done during acceptance testing at the manufacturer or at the customer site and must be video documented. Minimizing glove intervention, as communicated in Annex 1 is also essential. The pharmaceutical manufacturer must create an “authorized list” of qualified glove interventions in the fill-and-finish process. A distinction is made between non-qualified interventions, such as machine failure. Another fundamental aspect of Annex 1 concerns containment. RABS systems are still allowed in existing classified B-rooms. However, for new construction, isolator systems are preferred and have a majority market share according to Optima's experience. Isolators must create Grade A conditions in the critical zones and an unidirectional laminar flow.



The uninterrupted flow of First Air, here from a still closed tub with containers, is visible. Simulations of complete systems in operation, i.e. with moving components, are particularly meaningful. ↓

↑ Flow simulations created by the system manufacturer provide information about potentially problematic zones in the isolator that could contradict the first air principle of Annex 1. These zones are optimized during the engineering phase. Pharmaceutical companies and CDMOs can incorporate the flow simulations into their Contamination Control Strategy (CCS) to document the optimization of the system.



→ Handling and transfer solution for autoclaved rotary piston pumps in the isolator. With so-called peak devices, the rotary piston pumps can be installed without material product contact.

← New solutions for RTP ports reduce glove interventions in accordance with Annex 1. The ports are no longer operated from the inside via a glove opening, but from the outside. Mechanical and fully automatic solutions are available.

Annex 1: Setting up the system and batch preparation

When **handling the filling needles** and setting up the product path, direct glove interaction with materials that come into contact with the product must be avoided in accordance with Annex 1 (§5.5, §4.11). Optima has developed a variety of mechanical solutions to meet this requirement. These include the handling of autoclaved rotary piston pumps with appropriate transfer systems starting at the RTP port, mechanical guiding systems, and quick change over of components and format parts. (See report, page 19). In addition, regardless of the filling system, robotic technology can be used to set-up the fluid path and insert the needle almost automatically into the needle holder.

In the same regulatory context, **the RTP ports** for the equipment transfer, materials, and components to the Grade A system zone must be considered. Two solutions are available to open the RTP ports from the outside. Instead of the usual approach of operating the RTP port from the inside, using a glove (this is critical due to First Air supply), the new solutions are either manually operated mechanics or a fully automatic solution from a third-party supplier. Optima has already successfully installed both solutions.
The **sorting bowls** within the filling and closing systems must be sterilized in accordance with Annex 1 (§ 5.5) since they come into direct or indirect contact with the product. Bio-decontamination is no longer enough. The sorting bowl is now brought into the isolator area from a “parking position” through open doors without contaminating the isolator.

↑
Direct contact of product-contact parts through glove ports must be avoided in accordance with Annex 1. Handling tools are a solution.

Optima has developed an automated handling system with a swivel arm especially for high-speed systems with heavy sorting bowls. While the doors are open, a swivel arm takes the autoclaved sorting bowl (with a cover) from the front of the isolator and transports it to the intended position in the system. This improves working ergonomics while reducing the risk of contamination, as there is no need for the operating personnel to handle the sorting bowls. In addition, a smoke study can be used to identify how particles behave when the isolator door is open with existing overpressure while the sorting bowl is inserted into the isolator.

The following option was developed solely in accordance with § 8.16 (see below): **Verification weights** are placed individually on all load cells during batch preparation. Until now, these weights were moved manually using tweezers and gloves. An automated solution now places the weights on the load cells for calibration and then removes them. Since all tare and gross load cells, as well as the redosing load cells, must be calibrated individually, the new system eliminates the need for numerous glove interventions. A dynamic test also takes place.

Annex 1: Effects on the filling and closing process

The goal of §8.16 is to eliminate or reduce manual intervention by operating personnel wherever possible. This also includes the qualified, permitted interventions that are listed in an "authorized list" (§8.16 permits glove interventions provided that these processes can be analyzed on a risk-based basis and can be stringently justified in the CCS). Various solutions are available to meet this requirement.
Manual "start-up and emptying frames" or automatic line clearance pusher can be used in the handling process. This equipment distributes containers evenly at the discharge of the washing machine respectively at the infeed of the sterilization tunnel – ensuring safe, consistent sterilization. The removal of the clearing pusher in an A environment was previously performed manually, using gloves. In addition, according to the Annex 1 First Air principle, once a manual glove intervention is performed above the containers that could interrupt the airflow, all containers would have to be discarded. With the automated clearing pusher, there is no need to use gloves and no containers have to be discharged at this point.
Another innovation is the automated removal of misaligned stoppers in the stopper feeding tracks by means of a robotic arm using AI technology with an autoclavable picker with needle. This solution, which is also suitable for high-performance systems, significantly minimizes interventions and reduces downtimes (explained in more detail on page 22).

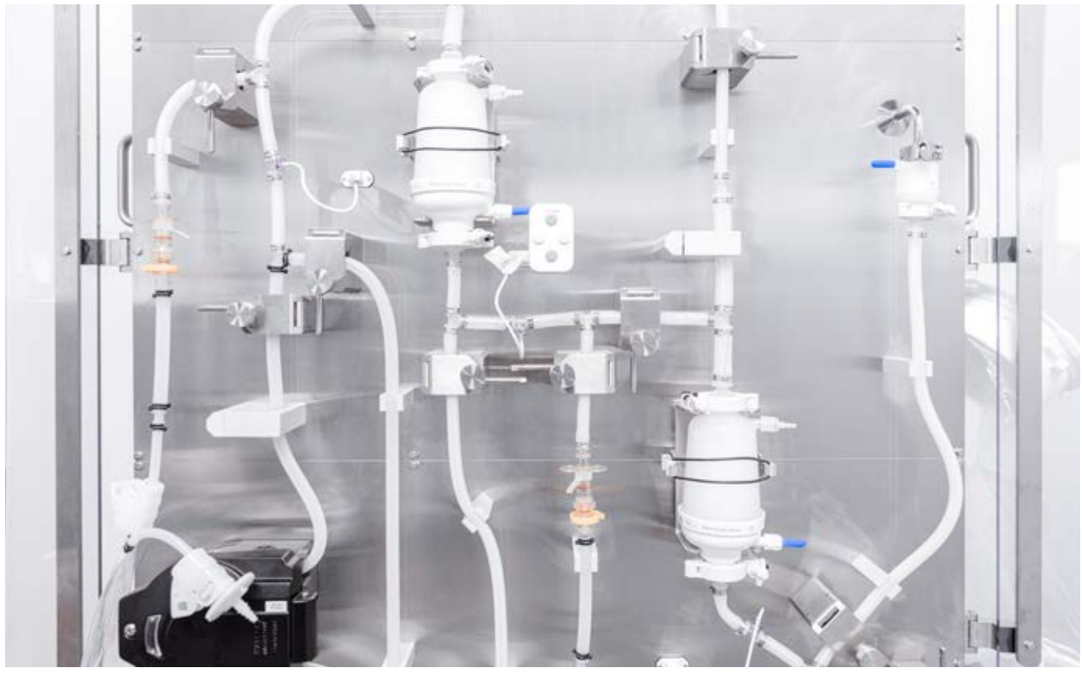
The solutions for opening the isolator RTP ports from the outside, as mentioned earlier, can be supplemented with **automated pivoting chutes** for stopper feeding. During the opening of the RTP port, the laminar flow or First Air supply is potentially briefly affected in this sensitive area. Since these are parts that indirectly come into contact with the product, slides must be autoclaved in accordance with Annex 1.
Optima has developed an enhanced solution to remove the **second Tyvek layer** of the tub. Previously, the Tyvek layers would bulge downward at the outer ends during automated removal, which would allow the possibility of particles entering the nest or open containers.
The new solution uses suction cups to grip the outer edges of the Tyvek paper, creating a consistently flat paper surface. De-ionization rods also ensure that the Tyvek paper is not statically charged, particles do not accumulate, and are not released unevenly. Therefore, the risk of particle contamination for containers is minimized.

↑
New Tyvek paper removal solution: Efficiently avoids particle contamination in containers.

The simplified handling of this agar plate system considerably reduces the need for glove interventions
Source: Particle Measuring Systems
↓

→
Integrity tests for gloves are completed using glove testing systems. The determined data is transferred to the batch protocol via WLAN for documentation. The correct assignment of the test cover, glove port, and glove is completed utilizing RFID technology.

Camera systems with ring memory automatically record and save as soon as a glove is used during batch processing. This offers subsequent assessment and documentation if it was carried out according to regulations.



PUPSIT filter tests have been mandatory since the introduction of Annex 1. Highly automated test systems offer a rational approach to this integrity test.

Annex 1: Monitoring and process controls

In accordance with Annex 1, various monitoring aspects must be considered or offer potential for optimization. This includes monitoring of filling and closing processes, as well as glove interventions. Pre-use post sterilization integrity tests **(PUPSIT)** are now mandatory for product filters with Annex 1 (§8.82 ff.) and various aspects and procedures are defined for integrity tests. For example, the pore size of the product filter can be a maximum of 0.2 or 0.22 µm and a test must be performed "in-place," i.e., when installed in or on the system. Additional regulations are specified, and it is emphasized that tests require a profound understanding of the process planning and execution (§8.87). To achieve a high level of security in execution and a rational approach, Optima offers highly automated PUPSIT test systems.

> Annex 1 has a diverse influence on the fill and finish.

In existing filling and sealing systems, agar plates are usually used to **monitor the potential particles**. These plates must be removed or changed at specified intervals using glove openings and then incubated according to specifications. This procedure leads to numerous manual glove interventions. A new biofluorescence particle detector, Biotrak®, works without agar plates and continuously measures the potential particles in real time. After expected regulatory approval, all glove interventions in the agar plate system can be eliminated. Optima has now equipped the first customer systems exclusively with the Biotrak® system. Continuous measurements and real time evaluations reduce product losses significantly. Alternatively, a single-use system is available, which simplifies the handling of agar plates using glove ports.

Isolator glove ports: Leak tests must be conducted at the beginning and at the end of a batch, a run, or even more frequently according to Annex 1 (§4.21). In addition, the manufacturer must define, in the CCS, how often gloves on the isolator are replaced. Annex 1, § 4.22 also describes leak tests and bio-decontamination procedures for the glove openings. For example, a glove stretcher spreads the fingers of the glove. Optima offers special glove testing systems to verify glove integrity. Measurement data is documented by transferring it to the batch protocol via WLAN. RFID technology assures the correct assignment of the test cover, glove port, and glove.
Since glove procedures cannot be totally eliminated from aseptic processing in the foreseeable future, camera systems are a useful addition. **High-speed cameras with a ring buffer** are designed to continuously record processes at workstations and delete them again with a time delay. However, if the system stops, the sequence before and after a glove intervention or another error is automatically saved permanently.
This allows the assessment of the potential effects on the production process and its documentation. Camera controls can also help with error analysis and process optimization.

Conclusion: Modularity for more choices

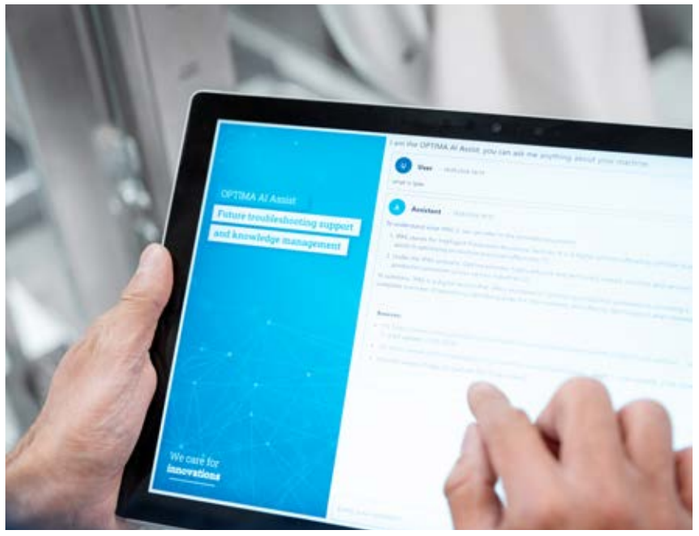
Annex 1 has many effects on the filling and finish process for pharmaceutical companies. New technical solutions for processing, setup, and monitoring are required – unless an alternative approach can be stringently justified in the CCS. Optima offers a wide range of solutions that provide options for system flexibility. The glove-minimizing solutions that are presented in the article on page 17 feature more detailed information.

IMPORTANT FOR YOU

- The IPAS digitalization portfolio currently includes 14 tools for pharmaceuticals, four of which are presented in this article
- New: An OLED display within the isolator pane shows information like an HMI, is operable and is a transparent “window” when not in use
- New: The AI Assist is available as a digital expert directly on the machine and answers operator questions that can be formulated without expertise knowledge
- Best seller: Camera systems record processes for analysis, only sequences that took place before interventions or alarms are saved permanently
- Improved processes: The Changeover Assist improves safety, prevents errors, and creates efficiency; Digital identification of format parts, as well as a supported and controlled sequence for format change work

Digitalization **meets customer requirements**

All Optima digitalization products have one thing in common: They provide significant benefits to our customers. This article explains how the control of fill-and-finish processes and camera interventions can be automated – and what a “digital expert” can do to improve processes and safety. In addition, we’ll describe the safe and efficient setup of systems using a digital tool, as well as a controllable OLED display within the isolator panes.



Operators do not always know the “correct” technical term to find specific information. The Optima AI-Assist helps to find a solution including additional sources.

Before installation, format parts are scanned. Systems are therefore completely equipped with the correct format parts and the correct installation order is followed.

To make fill-and-finish processes more productive and safer, Optima currently offers 14 digital products in its Intelligence Production Assistant Services (IPAS) portfolio. This article explains two new and two established products. All IPAS products have one thing in common: They must understand customer applications. Only then will an idea become a digital product at Optima.

A display integrated in the isolator panes? Yes!

The OLED display, which is integrated into the double-walled isolator panes, celebrated its public premiere at Achema 2024. This display complements the HMI as an additional display. In its final version it will be controllable via touch. One special feature: When the OLED display is inactive, it is transparent and allows a “window” view of the machine. Waldemar Mayer, head of the digitalization and robotics departments at Optima Pharma, explains the practical advantages, “Often questions arise when components are introduced, stoppers fed into the machine, or the filling path is setup. With the OLED display, system operators have video instructions, SOPs (Standard Operating Procedures) and other information directly in front of them.”

> Commonality of all IPAS products: Customers must be able to solve Use cases.

The OLED display also shows critical alarms. Operators may even have their hands in the glove ports and view instructions while they troubleshoot. The “Changeover Assist” (see below) is also available with directions for format changes directly on the isolator pane. Here too, the operator can immediately execute what he sees. With this innovation, Mayer expects new employees to become familiar with the machine more quickly. Ultimately, operating safety will generally increase.

Checking format changes – preventing errors

How can operators be better supported during format changes and machine set-up? This is a question that Waldemar Mayer and his team asked themselves for several reasons. Often when setting up a machine, a format part is selected or assembled incorrectly, which could lead to a machine error. For example, if a 2 ml format part is installed instead of a 10 ml format part, it can lead to a “crash.” Another scenario could be a forgotten format part that would cause production interruptions after the decontamination cycle. In the best-case scenario, it can then be introduced later via a port to avoid the restart of the entire decontamination cycle.

However, the consequences of such mistakes can be even more drastic. If it is a sensitive drug that must be freeze-dried immediately, production interruptions create significant financial risk and a potential gap in patient care. Annex 1 provides another argument for digital support during setup: The correct installation sequence of components is a prerequisite for ensuring that required First Air conditions are consistently met for format parts that are product contact parts.
One system averts all potential errors mentioned: The Changeover Assist. It contains digital step-by-step instructions for machine operators and provides a clear sequence that begins with the removal of the previously used format parts. Changeover Assist also contains digital documents and video instructions that show and explain how to proceed and what needs to be considered. Since pharmaceutical practice varies greatly from one company to another, Changeover Assist can be individually adapted or supplemented at any time with your own content including SOPs.

Scanning to remember

Part of the Changeover Assist system includes data matrix codes on all format parts. This means that every format and its format parts can be digitally identified. Before an operator installs a format part, he scans the code. The system then tells him whether it is the correct format part in the correct order. The correct installation must be then confirmed by the operator. This ensures that every format part “fits,” that all the required format parts are used, and that they have been installed in the intended order before the decontamination process begins.
Another advantage: A system can be set up with two operators in parallel. The Changeover Assist keeps track of when to complete each step and can subsequently establish who carried out which step. Upon request, a pharmaceutical company can set time specifications, which the machine operators must follow during the individual actions.
To display the Changeover Assist, Optima offers the HMI, tablets, the “Hololens” data glasses, and soon also the OLED displays presented above. These tools guide the operator to the location of the next format change. The representation methods differ depending on the medium. But even a top view of the machine on the HMI is valuable information that guides the system operator to the relevant location more quickly than if he were left to his own devices. With Changeover Assist, setup is not only much safer, but also quicker, as experience already shows.

Cameras with memory

Monitoring cameras are already installed in many new systems. Optima distinguishes between two types of cameras: Those for an overall overview of the machine and high-speed cameras that focus on core processes and critical processes for sensitive pharmaceutical applications. Customers can choose one or the other - or both camera types for their systems.

A new type of OLED panel within the isolator pane can be operated and displays information and video instructions. It is transparent when not in use.

Overview cameras record process interventions after an error message or alarm. This allows illustration where exactly the glove intervention occurred and how long the procedure took. Mayer explains how it works, “The camera system first sends all video recordings to a ring buffer. Without errors or interventions, these recordings will soon be deleted. However, after interventions or error alarms the recordings will be permanently saved by an automatic system.” This allows subsequent assessment whether a drug meets the pharmaceutical and regulatory requirements. On the other hand, if deviations were found in a medication, the recordings can simplify error analysis by showing how an intervention was carried out after an error and whether this could result in a contamination of the product.
This type of camera allows objective documentation after troubleshooting system faults.
Current regulations only require a second operator to record the process in writing after an error and a subsequent intervention. This can lead to inaccuracies and uncertainties. Another advantage: An image transfer from the machine interior can be activated at any time. Current video recordings can be sent directly to a production manager or live to other locations.

Process insight, overview, or both

High-speed cameras are usually installed for fast core processes or vital pharmaceutical applications. Typical core processes include filling and closing; one highly critical area is the stopper sorting bowl. Here, high-speed cameras offer numerous benefits. For example, if a filling needle drips, the solution could be to readjust the suction of the product. However, the error might also be caused by the needle movement or another incident.

Sometimes troubleshooting can be much more complex, says Marcel Klimmer. The product manager at Optima Pharma explains, “It happens that a machine goes into an alarm state and displays an error, which is not the actual cause of the machine malfunction,” explains the product manager. An important feature of high-speed cameras is that the recordings are stored in a ring buffer. This means that in response to an alarm, a defined period of video material is permanently saved. The origin of the error is therefore covered in the video sequences. Even if various details or partial functions within the core processes need to be examined for error analysis, viewing the video recordings remains timely manageable. Therefore, there is a higher likelihood of eliminating the root cause of the error in a targeted manner.
The two camera systems complement each other perfectly, allowing the user to analyze errors internally. In addition, the correct pharmaceutical and regulatory processes are documented to authorities in a simple, automated way.

Ask me!

The cameras are already a “best seller” with our customers.
The new AI-Assist is likely to become one as well. Like the OLED display, this digital machine expert is new to the IPAS portfolio. Operators can access the AI assistant as a resource at any time and ask questions in text format or verbally, depending on the acoustic conditions.

The camera system first sends all video recordings to a ring buffer.

↑
Video Monitoring: Core processes and highly critical processes can be traced at any time, whether for differentiated disruption analysis or the documentation of interventions.

The Change Over Assist includes video and other instructions for changing formats. Operators implement these directly on the machine.
→

A special feature of the AI-Assist is that it can be asked questions in a vague description, without keywords. “A table of contents, an index or FAQs are usually of little help if an operator does not know the correct terms or keywords,” says Waldemar Mayer, explaining the background. If you initially have only a vague idea of how to describe something, you won't get very far with the classic methods. However, a question to the AI-Assist does not have to be phrased precisely. As in a dialogue with a human expert, what you are looking for can be narrowed down (“prompted”) and found.
The AI-Assist searches the documents provided with the help of generative artificial intelligence and summarizes the relevant content for the operator to answer the question. With the source information that the AI-Assist inserts into its answers, in-depth knowledge or even a cross-check is quickly available. The technical and other documents that are to be learned and evaluated initially come from Optima. Pharmaceutical companies can also add their own documents like SOPs to the AI-Assist at any time to expand its knowledge base.

Strong team performance, strong products

Remote Service shows how important and promising digital products can be. This is now an indispensable IPAS product and is continuously developed to be state of the art. The area of Data Analytics, another IPAS product, currently offers new potential. The same applies to the area Sustainability, which is becoming increasingly important to the pharmaceutical industry. How can the use of energy and consumable media be controlled and reduced? This can be now digitally evaluated.
Optima's digital portfolio requires outstanding technical creativity and manpower - but results in improved productivity and safety for our customers. Together we care for the future!

STISO reengineered:

More compact, more powerful, faster delivery

Shortened delivery times, lower overall height: By reengineering the STISO, Optima has significantly increased the marketability of its proven sterility isolator!

IMPORTANT FOR YOU

- New sterility test isolator with compact design and significant reduction in system height
- New standardization concept enables faster delivery times of six to eight months
- Integrated cooler ensures stable temperature conditions between the working chamber and the installation room
- No external peripherals: control, operation, maintenance and service can be carried out within the laboratory space
- Rapid Transfer Port (RTP) allows operators to transport necessary tools, work, and waste materials into and out of the machine
- Maximum ergonomics for operating personnel: hardware and software are located in the immediate workspace
- Platform can also be used for applications in the cell and gene areas

STISO reengineered: Compact design with significant reduction in system height

Laterally mounted, integrated glove testing system – can be operated mechanically or via HMI

> As a result, we were able to achieve the desired system height of 2.50 meters and even a slightly narrower overall design.

Sterility tests are a central part of the aseptic pharmaceutical process and must be completed exactly in accordance with regulatory requirements. Commonly sterility tests are completed as close as possible to production conditions. The STISO sterility test isolator meets these high requirements. Operators and service personnel alike benefit from the sophisticated process technology of the STISO. The isolator is designed to complete all operations and processes of the system in the laboratory; therefore, even complex spatial situations can be solved onsite. The highlight of this configuration: The integrated cooler ensures stable temperature conditions between the work chamber and the installation room to avoid the use of external peripherals.

A more compact design with significant system height reduction

In the pharmaceutical sector, time and speed factors are increasingly proving to be crucial for pharmaceutical manufacturers and laboratory operators. Fast response times are also required from machine and system manufacturers.
Responding to the need for faster delivery times, Optima has reengineered the STISO this year. The requirements are based on experiences and customer feedback. The primary goal was to advance the standardization of the modular system concept to offer faster delivery times to align with market needs.
The second objective for the reengineering was the resizing of the system. Reducing the system height from 2.70 to 2.50 meters, with the goal of placing the existing work areas and the technology into a correspondingly more compact design without sacrificing quality in terms of technology and ergonomics.

"The experience of the past few years has shown us that not every laboratory has sufficient room height to set up the STISO," summarizes Matthias Aster, Director Sales at Optima Pharma Containment. "In some cases, the height of our isolator excluded it as an option for potential buyers."
Reducing the height by 20 centimeters required considerable effort for the system designers, as both the work chamber and the technical area above were reduced in size or compacted to save the required space.
The biggest challenge was the cooler integration. "We finally accomplished our goal and not only succeeded in achieving the desired system height of 2.50 meters, but even a slightly narrower overall design."

New standardization concept

The range of the STISO concept was examined for individual adaptation and standardization. Aster says, "Customer feedback has shown that the market tends to prefer short delivery times. People are more willing to forego one or two special equipment requests if they can benefit from significantly shorter delivery times in return. With our new standardization concept, we can guarantee a six to eight months delivery time. This would not have been possible with the previous version."

Material transfer via optional RTP port

↑
STISO work chamber in standard version with four glove ports

To achieve standardization, the following modifications were made to the initial design:

- The optional material lock is located exclusively on the left side of the new standard model
- The optional RTP port is installed on the right side (standard)
- The STISO's cooler is also spatially integrated
- Additional optimizations allow easy access for maintenance and services, as well as the replacement of some components as part of the redesign

Proven features are retained

Crucial for a new concept: USPs and clearly identifiable market advantages of the existing model must be maintained in the same quality. Aster explains, "Of course, this primarily includes process reliability, which we guarantee based on many years of experience. This is where we differentiate ourselves from our competitors, who purchase technology and parts and then must integrate them into a process. Optima, on the other hand, takes responsibility for the entire system, installs the system, qualifies it, and thereby ensures maximum availability."

> The platform we developed for the isolator is designed to be also suitable for applications in the cell and gene areas.

According to Aster, the integrated cooler was "untouchable" during the redesign. "The process of bio-decontamination with hydrogen peroxide requires stable and reproducible environmental parameters. The integration of the cooler into the STISO ensures that the temperature in the clean room always remains constant, as the machine does not have to give off ambient air in the room." Another benefit, relevant to the onsite room situation, is the option to work without any external peripherals. Control and operation, maintenance, and service: All related activities can be completed within the laboratory space.

Other applications – same platform

Another indispensable component of the STISO – the Rapid Transfer Port (RTP). This allows the operator to transport all the necessary tools, work, and waste materials into and out of the machine. No compromises were made regarding the ergonomics, which ensures a comfortable work environment for the operator. Everything required in terms of hardware and software is in the immediate workspace. The panel which is inclined at a six-degree angle for optimal work use, has also been retained.

According to Aster, "The platform we developed for the isolator is designed to be also suitable for applications in the cell and gene areas, among other things. The modifications e.g. for the product formulations or the preparation of cells are rather marginal in terms of design. The working chamber that we developed for the STISO offers an optimal basis for mapping other processes as well."

However, Optima still has a convincing solution for customers who prefer isolator equipment tailored to their specific requirements. Aster says, "Parallel to the current version, we continue to offer the more modular predecessor model. This means customers choose what they want, provided they are not tied to short delivery times!"

Optional: Material transfer lock →

Interior view: Material transfer lock (MTC) with pneumatically sealing sliding door ↓

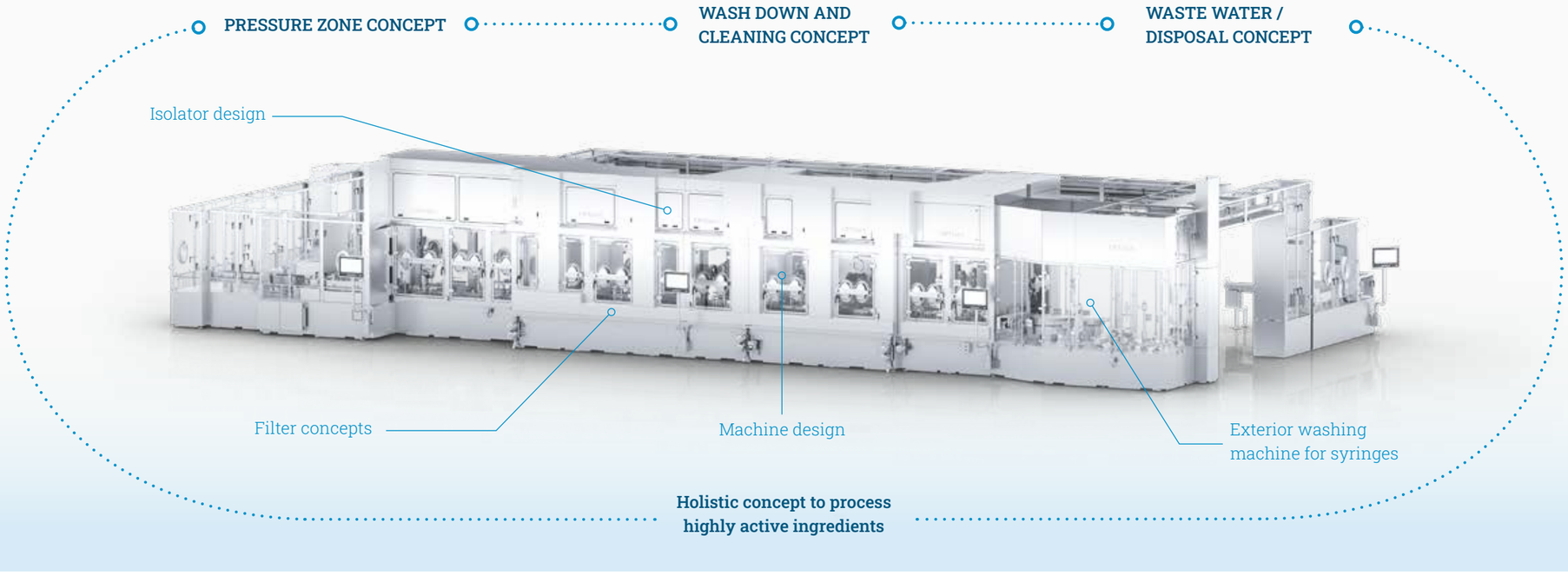
MTC with independent bio-decontamination cycle ←

IMPORTANT FOR YOU

- Turnkey engineering and execution for highly active potent ingredients: specific pressure zone concept, cleaning functions, and filter concept
- Premiere: new exterior washing machine for all three container types (vials, syringes, cartridges)
- Advanced wash-down and separation of contaminated water
- No glass-to-glass contact throughout the entire processing process
- Completely tested system with isolator and AHU as part of the iFAT
- Special team approach with the customer

An **integrated HPAPI** project

Two complex technical systems that together form a functional unit. “Marrying” an isolator with a filling and closing line is vital to a fill-and-finish project - especially in systems that process highly potent active ingredients (HPAPIs). Another highlight of this customer project was the introduction of the first exterior washing machine that not only cleans vials, but also pre-filled syringes and cartridges.



For highly potent active ingredients: The pressure zone concept of the fill-and-finish system was tailored to specific ambient pressures. →

Highly potent active ingredients require fill/finish systems to meet the highest requirements to protect both system operators, as well as the sterile product. The Comprehensive Scientific Process Engineering (CSPE) approach offers several key advantages to accomplish these goals.
"With CSPE we always look at the entire fill and finish process, which is a special turnkey core competency. For example, as an isolator manufacturer, we have direct access to all data from the filling and closing line and our colleagues have direct access to ours," explains Matthias Aster (Director Sales at Optima Pharma Containment). Another common thread of this project: "A 'team approach' with the customer that I have never experienced before," notes Lucas Meyer (Project Manager at Optima Pharma).

Defined pressure zones

The new Optima system will process next-generation biologics that belong to the OEB 5 class. The "Occupational Exposure Band" describes the toxicology of the pure substance. OEB 5 corresponds to a load of less than 1µg/m³ – one cubic meter can only contain less than 1µg of the potent ingredient.
In addition to protection, these product types also require special safety features for employees. The pressure zone concept is a vital component of the safety equipment and the technology requirements. The system's isolator barrier and excess pressure in the filling and closing area, compared to the atmosphere of the installation room, initially prevent potential contamination of the drug. The filling and closing lines contain pressure cascades between the different zones. These zones are only connected to each other via "mouseholes" through which the containers are transported – using pressure cascades to contain potential particles.

The filling zone has negative pressure compared to the adjacent areas. This means that HPAPI aerosols, which can never be completely avoided during filling, remain within the filling zone. The pressure decreases from the closing station to the exterior washing machine. Ultimately, there is defined negative pressure on the exterior washing machine compared to the system's upstream zones and the surrounding atmosphere of the installation room. Potentially present particles are directed into this non-critical system zone – protecting the operator. Since the containers are already closed, they are cleaned with an exterior washing machine to remove potentially adhering particles – yet another step to improve operator safety.

For ergonomic reasons, the first filter stage of the bag-in-bag-out filter was relocated from the technical floor to the clean room as part of the mock-up. →

One valve, two drainages: Contaminated and non-contaminated wastewater are separated. The cost of disposal is reduced. ←

This pressure zone principle, which is often utilized for highly potent active ingredients, was specifically adapted according to the customer's requirements. The installation room (class C) and an adjoining surrounding room (class D) have positive pressures differentials compared to the atmosphere in other rooms. If an accident should occur, these "air bubbles" create a locking effect and the potent active ingredients remain within the installation room (cleanroom class C).

HPAPI engineering requirements

Another core element in HPAPI systems are specific filter concepts. Different filter variants ensure protection of the product, the operator, and the environment, depending on the customer's requirements and philosophy. The chosen 'bag-in-bag-out' principle uses standard filters, which are widely available and relatively inexpensive. These filters can be tested as a group or individually and replaced if necessary. Another safety advantage when changing filters, is that they can be sealed easily during the filter change. Most Optima customers opt for this version.
The system's cleaning functions are also fundamental to HPAPI processing. The still closed system is cleaned with water after each batch, which is partially automated here. The isolator's return air ducts, and for the first time, the transport system are cleaned automatically. Operators use glove ports and hand showers to manually clean other components according to SOPs. In general, simulations play a major role in CSPE. "For the washdown, we can use simulations to digitally run through the entire process steps at a very early stage. If we don't like something, we change it. Simulations even allow us to determine and document qualification activities," explains Aster.
Meyer says that HAZOP (Hazard and Operability) studies also examine how external or internal system errors could affect safety and how the filling and closing line must react. Different scenarios were analyzed together with the customer: What happens if an operator drops a tub? How does the system react after an emergency stop? A controlled machine downtime requires precise regulations for personnel, as well as system components. For example, defined valve positions that need to be programmed

Project handling: An integrated project

The MultiUse system was set up in Optima's CSPE Center with an isolator, including AHU (Air Handling Unit), and test runs performed. During an intensive iFAT phase, tests were conducted from cable labeling to the "handshakes" of the signal transmission between system components. The tests also included the mechanical and software interfaces between the isolator and the filling and closing unit, as well as the safety technology. In addition, leak tests ensured the isolator had the high-level of system tightness required for HPAPIs.
Parameter developments for the "wash-down" and a preliminary cycle development for the decontamination process were performed, including "worst-case positions" in the isolator. And finally, in cooperation with the customer's team, every single function of the isolator, including filling and closing line, was tested according to the specific functional description – leading to a successful iFAT.

“One team” – Flexibility and support

The aforementioned team approach was evident in many ways: For ergonomic reasons the customer wanted to move the first filter stage during the mock-up to the clean room. Today only the redundant “police filter” is located on the technical floor. The iFAT phase also reflects the close collaboration when the customer wanted to change a glove port. Both sides agreed that this change would be beneficial. With the now offset glove intervention, the system operates even while refilling stoppers.
The “one-team idea” was also evident when the customer in Schwäbisch Hall chose to work the late shift to enable Optima to work on the system during the day. And finally, from the moment the system arrived at the customer’s site in Northern Europe: Throughout the entire installation of the system, it was exemplary how Optima was supported by the customer and how well coordinated the entire project handling was, reports Meyer.

The system was installed in the company building shortly before Christmas 2023, and all SAT tests were passed as planned in the second half of 2024. This reduced timeline is feasible because the customer measured the system completely in 3D in Schwäbisch Hall. The system was then projected in the filling room at the customer’s site and peripheral equipment was ordered accordingly. The complete installation only took approximately six weeks.

New exterior washing machine and other innovations

A new exterior washing machine, which is part of the installed system, cleans the three container types: vials, pre-filled syringes, and cartridges for the first time. This requires a new, flexible transport system. In addition, details like sealing the container closure areas during washing are crucial, reports Project Engineer Benjamin Hofmann. Due to the capillary effect, water can hardly be removed

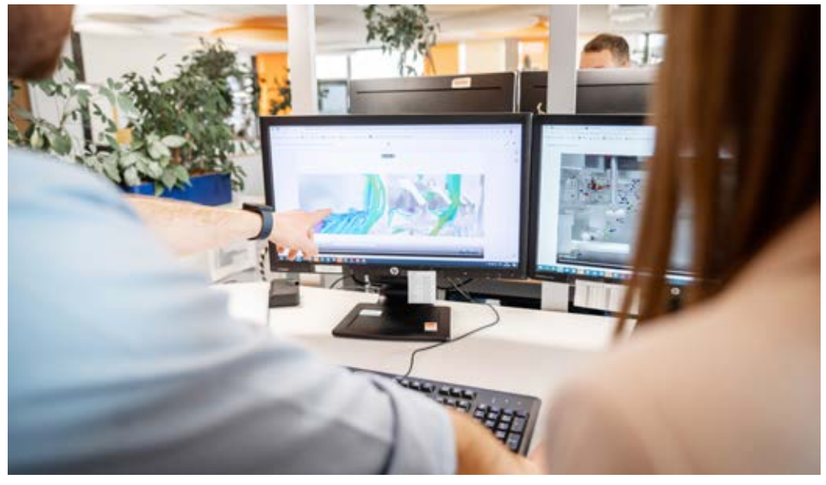
A complex project and lots of flexibility – the team approach left its mark. ↓

afterwards. The new exterior washing machine and the OPTIMA MultiUse, which was selected by the customer, complement each other perfectly. The MultiUse is also designed for all three container types and can process up to 9,000 RTU containers per hour.
As mentioned, for the first time a partially automated wet cleaning system was implemented for the filling machine’s transport area. This system operates with spray balls. The return air ducts of the isolator are washed fully automatically with spray lances and spray balls. Optima is convinced that this, in combination with hand showers and SOPs, results in the currently optimal partial automation. Full automation would result in many additional nozzles and greatly increased water consumption. Another new system function utilizes a valve to separate contaminated and non-contaminated water into different drainages. This reduces the effort required to treat and dispose of the contaminated water. Additional functions of the Optima MultiUse system have an impact when processing highly active potent ingredients. For example, a container-friendly transport system that grabs and passes on every container, avoiding glass-to-glass contact from start to finish of the fill-and-finish process, was installed instead of a conveyor belt, which would also “transport” potentially existing active ingredients.
Product-saving features such as re-dosing and re-capping, which the customer has opted for, have the welcome side effect of reducing potential waste and thus its costly disposal. The reject station was also adapted to customer specific requirements. Instead of vacuum wheels that could suck-in highly active ingredients, grippers are used for transport.

The turnkey factor

Looking back on the initial investment decision, the customer says that safety and design, technology, cost-effectiveness, and partnership were key considerations. The responsible project manager recalls: “We knew that Optima’s ability to deliver a turnkey project would provide an additional advantage that would address all these factors.”

Simulations always contribute to optimized results, in the basic development of new functions, as well as in specific projects. →



The transport system prevents potential carryover of active ingredients and assures gentle handling. Semi-automatic cleaning is introduced. ↓

Mouseholes connect the system zones. In coordination with the customer-specific pressure zone concept, the pharmaceuticals and the system operators are protected. ←

IMPORTANT FOR YOU

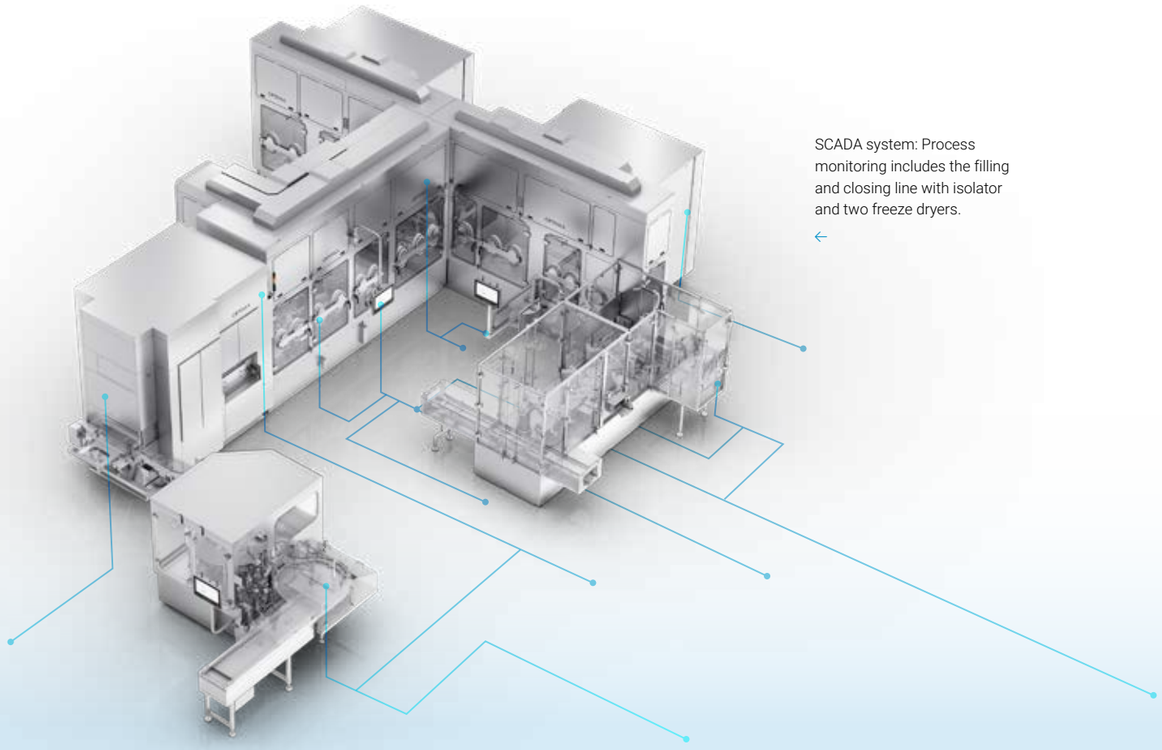
- Comprehensive SCADA system for a turnkey system, which also includes peripheral system functions and components
- Parallel freeze-drying batches are recorded and documented separately
- The technical documentation from Optima is also used by the customer for the GMP qualification of the system
- High standards also in formal collaboration, for example in the change control process
- Customer-specific “SCADA pilot project” at a very high level as a basis for future orders

SCADA with **maximized added value**

A new level of detail in the SCADA system:
A European pharmaceutical company secures the processes on a fill-and-finish system with an isolator and two connected freeze dryers and documents the product quality automatically. In addition to data transparency for the entire line, the SCADA system also offers comprehensive protection for the company itself.

During freeze-drying phases, the filling and capping section of the system remains operational.

Turnkey: With SCADA integration of all system functions, Optima benefits from end-to-end interface transparency.



SCADA system: Process monitoring includes the filling and closing line with isolator and two freeze dryers.

SCADA means Supervisory Control and Data Acquisition. Functions like glove testing systems and checkweighers, which exclusively monitor processes, are usually included in a SCADA system. This also applies to isolator data due to its protective, respective barrier properties, as well as freeze dryer temperature data. However, the customer sought even more. Optima project manager Daniel Keck reports that for the first time, data from the material transfer lock is now being imported into the SCADA system. Thus, even system data that has a very low probability of influencing the process and product quality will now be also monitored. In implementing these extensive requirements, Optima, as a turnkey provider, also benefited from the interface transparency to and into all functional areas of the line.

Pilot project: Raises the bar

The same applies to formal processes: The demands of the pharmaceutical company were significantly higher than anything that had previously been requested. For example, change control procedures, and very detailed qualification documents (discussed more below).

Keck explains why this is remarkable and worth reporting, “As a company, we learned something new in this project. Above all, as a partner to the pharmaceutical industry, we have proven that we always meet the highest technical and formal standards, even when it comes to SCADA systems. At the same time, this project created the foundation for future projects.” The vial system with freeze dryers served, as a “pilot project” in the SCADA area. In the next step, new syringe lines of the customer will benefit from the lessons learned in this project.

SCADA means security

The first task of a SCADA system is the continuous safeguarding and documentation of the fill-and-finish processes, including isolator and freeze dryer, in the interest of patient safety. The comprehensive data transparency created here also sets a broad foundation for successful audits. If any (partial) process is questioned even years later, the pharmaceutical company can access data and provide answers quickly.

However, the SCADA system is also extremely important for the pharmaceutical company internally. Structures and automation ensure SCADA-generated data can be accessed at any time, by any authorized employee of the customer – this is especially important for large and complex company organizations because data cannot be manually moved to arbitrary directories.

Tamper-proof

Data from the SCADA must also be tamper-proof. At large pharmaceutical companies, high-level administrators ensure conformance to procedures and the clearing of deviations between actual and target values. These procedures can, for example, clarify whether the drugs in question meet the quality criteria or what caused the deviations. For administrators to be able to initiate these complex processes at all, it is essential that the underlying data cannot be manipulated. In other words: Trust in employees is good, but automated, tamper-proof control and alarm systems are mandatory.

The SCADA system creates data and process transparency synchronously regardless of location. An administrator with the appropriate authorization can view almost every part of the system, from any location. GMP-critical parameters are the primary focus. Additional data and analysis provide insights in the event of deviations from target values that can be attributed solely to the so-called “business risk” i.e. they will not influence the product safety or quality, but are relevant to the economic efficiency of the processes at the customer company.
To protect the installed SCADA system from external assaults, specific password guidelines were set-up and tested for all functions. In addition, automatic-update servers are now part of the security standard.

A multi-batch system

The Optima turnkey line consists of a washing machine, sterilization tunnel, filling and closing machine (with capper), two RALUT loading systems for the two star-shaped arranged freeze dryers,

Multi-batch system for the entire system: Parallel freeze-drying and fill-and-finish processes are documented separately.

and another crimping machine for lyophilizates produced by the freeze dryers. Since a freeze-drying process can take several days, the system must be capable of vial filling and closing at the same time – and this is exactly how this line was designed. Consequently, the SCADA system must record multiple batches independently and in parallel.
Optima's SCADA system is based on the Siemens PCS7 control system. This comprehensive software is the standard for Optima SCADA projects due to its tamper-proof and automated data storage into directories. This ensures that the customer can execute data queries with batch reports and more from anywhere in the world (with Internet access).
Only raw data from the PLC machine controls transfer into the SCADA system. This data – values from sensor measurements or counts – is fed directly into the SCADA system and into the HMIs simultaneously. Additional networking between the HMIs and the SCADA is unnecessary. The SCADA system focuses on GMP-relevant data used for documentation, the remaining 90% of data is only fed into the HMIs and not into the SCADA, says Keck. For example, upcoming maintenance work or other similar data that would not benefit from additional processing is not input to the SCADA system.

Connecting to a higher-ranking system

The SCADA system is connected to the customer's primary MES system via an interface. Depending on the requirements, the raw data from the SCADA is transported unchanged to the MES system like a gateway or "translated" into another data protocol. What is initially implemented is an exclusive transfer of actual values to the company's production control system.
In the follow-up project, target values will be communicated to the fill-and-finish system allowing the pharmaceutical company to control batches from the primary system with the SCADA system. All Optima systems are equipped with the necessary functionality. The Optima software engineering department will develop a customer-specific solution, to initiate automated processes that are triggered when the system starts or stops.
The basic SCADA installation work was completed at the Optima division in Schwäbisch Hall for the filling and closing line with isolator and in Mornshausen for the freeze dryers. As per Optima standard, batch reports were created during the system's iFAT. The final SCADA integration took Keck to the customer's system at the installation site.

> We always meet the highest technical and formal standards, including SCADA systems.

From an organizational point of view, this makes sense, says Keck, since the SCADA ultimately must be embedded in the customers IT system on site. Preparing this "blindly" would hardly make sense, adds the SCADA expert. At the same time, the "formal shell" of the project is also adhered to since the final qualification must then focus on the self-contained overall system and not just its individual parts. Keck describes the close, cooperative collaboration with the customer with a wink, "The project manager at the customer could have passed as an Optima employee during this time and I could have passed as a colleague at the customer company."

Unique: Technical documentation becomes GMP document

As mentioned, the general criteria requirements in this project were high – with the emphasis on documentation. The Optima documentation was used for the SAT (performed by Optima) and will also be used by the customer for the system's qualification. It is easy to imagine that there is a significant difference between technical documentation that is typically created to describe system functionality and a document that a pharmaceutical company intends to use for qualification according to GMP criteria. Optima created documentation that satisfied both purposes in close coordination with the customer.
Another feature was the transparency in the project processes, which was ensured by Optima. One thing is already certain today: The current SCADA project is also a novelty for the customer – such a level of detail has never been implemented in a fill-and-finish project before. Future projects will soon benefit from joint achievements.

All parameters and potential process deviations are documented and can be tracked years later.

Optima's technical documentation will be included into the customer's GMP systems qualification.

A few facts about the **revised** **Annex 1 regulations** at a glance

The new **Annex 1 ...**

... aims to **prevent product contamination**

... was extended from **16 to 58 pages**

... the **Barrier Technologies chapter** has **quadrupled** in size

... regulates the **production of sterile drug products**

... is part of the **EU-GMP guidelines**

... entered into force in **August 2023**

EN 11880577