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Plant-wide automation and digitalization
in the pharma industry

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DIGITAL SOLUTIONS FOR THE PHARMACEUTICAL INDUSTRY

Win the race against time

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Be faster, better, safer

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BE FASTER, BETTER, SAFER

Digitalization an all-purpose tool

New diseases call for new medications, and growing competition calls for faster, leaner processes in all areas of business. Rebecca Vangenechten, 38, describes the potential offered by automation and digitalization for the pharmaceutical industry. She heads the pharmaceutical segment at Siemens and knows what makes the industry tick.

Rebecca Vangenechten, the recent years dominated by the pandemic have given the pharmaceutical industry even greater prominence: We've all experienced how long it can seem to take until a vaccine or medication reaches the market. What role does the time factor play in this sector?

A massive one! The reality is that the faster drugs or vaccines can be made market-ready, or manufactured in large volumes, the faster people can be protected from diseases, and the faster people who are already ill can be helped. That's a huge incentive. And at the same time, it's also true that early market-readiness keeps the costs as low as possible. And what's more, speed also means being faster than your competitors. The time factor is therefore of major importance.

In your view, what other urgent challenges is the industry facing?

There's a range of challenges for the pharmaceutical industry. What affects patients drives market growth for the pharmaceutical industry, especially in regions and countries that aren't financially strong. And that impacts on the products, because they have to be affordable. Another major question is how patient data will be used in the future. What influence will it have on treatment: will patients only be willing to pay for successful treatments?

The product range is also in transition. There are many innovations in the areas of pharmaceuticals and treatments. Innovations like customized medicine – in other words, the production of individual batches for a single person – create major challenges for production. Today's factories aren't designed for that, and a different infrastructure and supply chain will be needed. This also comes with uncertainty: How quickly can new technologies be incorporated in existing processes?

At Siemens, we firmly believe that when the real and digital worlds work together, the result is faster and safer production. That's why we've developed an end-to-end portfolio of software and automation solutions in the form of the Digital Enterprise to help us digitalize the entire value chain.

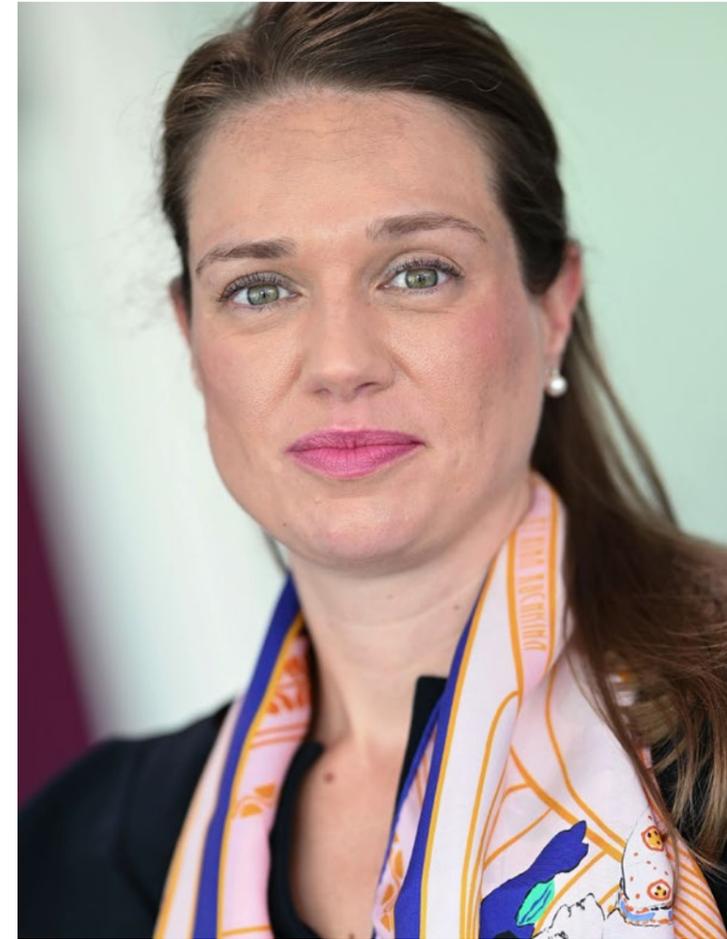
What does that mean for workflow validation?

And, of course, cost pressure plays a huge role. In this regard, companies have to consider where their core business lies and think about outsourcing, as appropriate.

How can we take a positive approach to these future-oriented trends?

At Siemens, we've derived five main industry drivers from these challenges: flexibility, speed, quality, sustainability, and efficiency. Entities that are well positioned in these areas will be equal to these challenges and will achieve a very strong market position. The direction is clear: We need more digitalization! It's the most valuable all-purpose tool.

In our personal lives, we're now accustomed to the fact that digital services make our day-to-day lives easier. A navigation app on your smartphone, for example, that takes us safely to our destination and helps us avoid current traffic congestion. Or messenger apps that enable us to stay in constant contact with our friends and family. And there are many other examples. Day-to-day business in the pharmaceutical industry is still much less digitalized, whereas other industries have certainly made more progress in this area. But there's huge potential for digitalization!



What does that mean, in concrete terms?

At Siemens, we firmly believe that when the real and digital worlds work together, the result is faster and safer production. That's why we've developed an end-to-end portfolio of software and automation solutions called the Digital Enterprise to help us digitalize the entire value chain. The important thing is to understand and use the vast amount of data supplied by the Industrial Internet of Things (IIoT). And that's exactly what the Digital Enterprise does! It combines the real and digital worlds so we can utilize our limited resources to make efficient use of the limitless volume of data and make our industry more sustainable. Specifically, we've developed eight portfolio modules that cover the entire value chain.

That includes digital twins and simulation. What opportunities do these technologies offer?

Depending on what's important to our customers, they can be used to create digital twins of products, product lines, processes, or buildings. A digital twin links the real and digital worlds – and by recording real-time data, the virtual counterpart can document the current condition and simulate the future condition, which lays the groundwork for optimization. It enables early recognition of problems, it can be used as the basis for in-silico tests, it and offers the opportunity to improve checking processes. With our customer GlaxoSmithKline (GSK), for example, we've developed a digital process twin for vaccine manufacture (p. 9). The digital twin not only makes it possible to check complex processes, it also predicts how changes would impact on those processes. This means that process engineers can perform simulations in just a few hours instead of having to construct trial facilities. This ultimately made the production process at GSK much more robust while improving the company's product quality and increasing its speed.

Can you name other examples of ways that automation and digitalization optimize production?

When facilities are designed or built, we provide support with Integrated Engineering. It's important in these cases to maintain an overview of the entire process lifecycle: Where is there potential for improvement? Where can we make improvements in speed? Where can processes be simplified? Siemens aims to create complete solutions that are in the customer's best interests. For Bayer AG in Bitterfeld, for example, we integrated a new type/instance concept incorporating both MES and DCS functions (p. 13).

We can also assist many pharmaceutical manufacturers with the transition to continuous production. This production method is used to manufacture active ingredients in compact, closed units with a high level of automation and less manual intervention. →



The Digital Enterprise portfolio from Siemens for you



Digital Twin and Simulation
Thanks to powerful simulation tools, pharmaceutical companies can develop medications and vaccinations even faster



Smart bioproduction
Next-generation production of biopharmaceuticals with data-driven processes



Paperless production with eBR solutions
A reliable system for effective batch handling and faster, paperless document handling in the pharmaceutical industry



Continuous production
We enable pharmaceutical companies to release products in real time and make continuous improvements



Integrated Engineering
Significantly reduced time from development to the manufacturing process and the patient



Integrated Secondary Lines
Shorter time to market thanks to integrated digital solutions and state-of-the-art automation systems for pharmaceutical packaging



Cell and gene therapies
Significantly shorter time to market for new therapies for genetic and rare diseases



Enterprise Recipe Management
Control and manage your workflow throughout the entire life-cycle of pharmaceutical products

The production stages that make up the sequential workflow in a traditional batch process are integrated into a comprehensive process, with quality measured in real time. Pfizer applies this method to its production in Freiburg, for example, and has just expanded its plant to include a high-containment facility – a facility where it can produce up to seven billion tablets every year. Along with several partner companies, Siemens played a role in making this production plant one of the most modern and sustainable facilities in the world (p. 14).

Many manufacturers would like to switch to paperless production. What does this involve, and how can Siemens help them?

I'd like to make one point clear to begin with, to deal with a false impression that still persists in some cases: The added value of paperless production is much more than what a purely digital version of paper documents would offer. The major advantage is that workflows become transparent! In paperless production, the process data, conditions, and results are recorded in detail, saved, and displayed. The processes are made more error-resistant – in other words, more robust and less susceptible to deviations – and the cost and effort of data input and documentation are reduced. Siemens can realize this using its MES solution Opcenter Execution Pharma, which fully complies with GMP (Good Manufacturing Practice) requirements and is pre-validated for its observance of all current standards for pharmaceutical production. When BioNTech converted a new plant in Marburg to produce its very popular vaccine during the COVID-19 pandemic, it was essential to begin production as quickly as possible. Part of the solution therefore involved paperless manufacturing (p. 10).



What is Siemens doing to drive digitalization in the pharmaceutical industry?

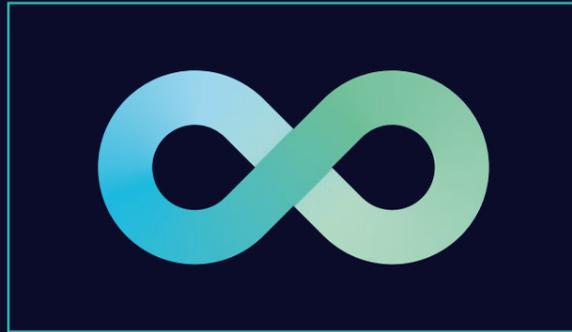
We know from studies that more than half of the digitalization projects that are initiated fail, that brownfield facilities are rarely touched, and that expertise in digitalization is often lacking. That's something we want to change! Siemens wants to speed up the digital transformation. That's possible with Siemens Xcelerator, a new, open, digital business platform that provides a curated portfolio of IoT-capable hardware and software, a marketplace for them, and a powerful ecosystem of partners. Siemens makes three promises with Siemens Xcelerator: First, to turn super-complicated into super-simple. Second, to make Siemens Xcelerator products flexible by making them fully modular and interoperable in stages so that customers can select exactly what they want. And third, to focus on openness and ensure that Siemens software works well with other systems. In all these ways, Siemens will continue to be a powerful partner in the advancement of digitalization.

Rebecca Vangenechten, thank you for the interview.

Solutions in brief

In focus

Digital twin



Using the digital twin, a virtual representation of the real thing, it's possible to test stages in the process and gain insights in a virtual environment right at the outset. Connecting the digital twin to a running process, it predicts the performance of the process, anticipates any deviation and steers the control back to the optimal production. The data obtained from real runs is fed back with machine learning into the models, the "brain" of the digital twin and thus helps optimize both the digital twin and the products and processes from an early stage.

Paperless production



Paperless production offers advantages over traditional procedures in the pharmaceutical industry in particular: Process data, conditions, and results are recorded in detail to ensure processes are more resistant to error, in other words, they are made more robust and less susceptible to deviations. At the same time, the tasks of data input and documentation are now less complex. Electronic Master Batch Record Management enables users to create, execute, review, and release Master Batch Records (MBR), and Electronic Batch Records (eBR) are made faster. The individuals in charge can easily monitor, observe and, if necessary, record every stage of production and every base material. Testing is based on the principle of "review by exception" – in other words, deviations are dealt with when the system recognizes them based on exception rules. That makes the testing process less labor-intensive and much faster, since otherwise the individuals in charge would have to check several thousand pages on paper. As a result, digital production is a significant factor in making the process faster and improving quality.

Products

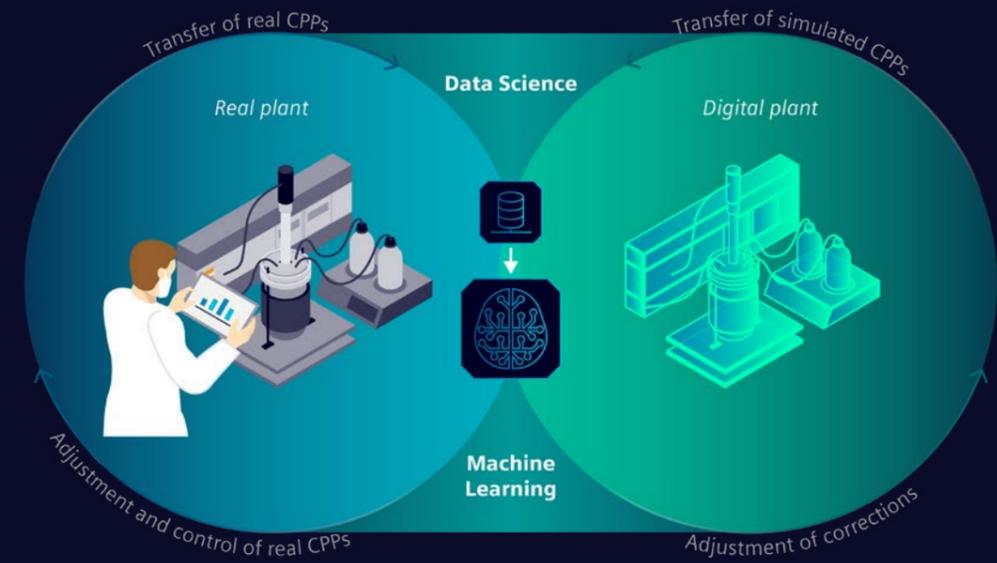
Distributed control system

SIMATIC PCS 7 is the automation solution from Siemens for discontinuous production of batch processes. Thanks to its modular architecture and the continuous scalability of its hardware and software, the process control system can be perfectly adapted to suit different system sizes and customer requirements. In addition to constant product quality and process reproducibility, there are other challenges when it comes to batch processes: Both the market and consumers demand product variety, product lifecycles are growing shorter, standards are being expanded, and checking procedures to ensure traceability in production (FDA compliance) are becoming more stringent. SIMATIC PCS 7 is recipe-based, enabling it to resolve even highly complex tasks involving changing control sequences easily and flexibly.

Manufacturing execution system

Opcenter Execution Pharma is the MES solution from Siemens for the pharmaceutical industry. It enables completely paperless manufacturing and fully electronic batch recording. Seamlessly integrating automation solutions makes it possible to develop, optimize, and manage production processes automatically. Opcenter Execution Pharma orchestrates the various sections of the system to ensure efficient production. The software enables real-time production and provides and analyzes process and quality information to optimize production activities from initial order to finished product.

GlaxoSmithKline (GSK): Stepping up the pace in vaccine development and production



For more information on the digital twin, see page 8

Global healthcare company GSK collaborated with Siemens and IT specialist Atos to optimize its vaccine development and production process. Together, the three companies developed a digital twin of the adjuvant production process which combines the virtual and real worlds in a closed loop. Using mechanical models and artificial intelligence (AI), the partners developed a hybrid model to simulate and monitor the process. As such, the digital twin links the process parameters to the quality of the adjuvant. The sensors and process analytical technology (PAT) provide information that feed the twin to predict the quality of the product. Digitalizing this process significantly shortens the lengthy development time: It enables easier and earlier access to results, faster and more comprehensive feedback, better ability to predict and share outcomes, and provides better oversight of the entire process. Digital twins offer particularly high added value in biological processes, or in cases where particular elements like physical models have to be better understood – as in the vaccines process. In the next step, GSK aims to collaborate with Siemens to create and introduce digital twins of the entire vaccine manufacturing process for all new vaccines. In other words, the digital twins of the product, production, and performance will be linked together.



BioNTech: High speed for vaccine production



For more information on paperless production and the products used, Opcenter Execution Pharma, and SIMATIC PCS 7, see page 8

Flashback to 2020: The COVID-19 pandemic dominates daily life, and all hopes are pinned on vaccinations. One of the vaccines that provides particularly good protection against COVID-19 is the BNT162b2 vaccine from Mainz-based biotech company BioNTech, which it manufactures in collaboration with U.S. pharmaceutical specialist Pfizer. To quickly expand the amount of vaccine available, BioNTech took over a large production site for vaccines in Marburg in order to set up the world's largest production of mRNA-based vaccines there. Siemens provided support in building the new production facility. A project of this magnitude normally takes at least a year, but in this case the participants completed the conversion in just five months. The Manufacturing Execution System (MES) for recording Electronic Batch Records (eBR) were completed in just 2½ months. "One factor that made it possible was the high level of cooperation between the teams and outstanding commitment by everyone involved: They all worked overtime and took no leave in order to advance the project as fast as possible," says Rebecca Vangenechten, head of the Pharmaceuticals segment at Siemens.

Industrie 4.0 as a solution

One of the many challenges was the switch to mobile single-use components in production. Because that means: the operator must be precisely guided in the manual assembly of the components. The solution is paperless production. Another aspect in favor of this approach was that working with mRNA required a higher cleanroom class than was previously needed at the plant, and it would prevent paper becoming a "contamination factor" in digital production.

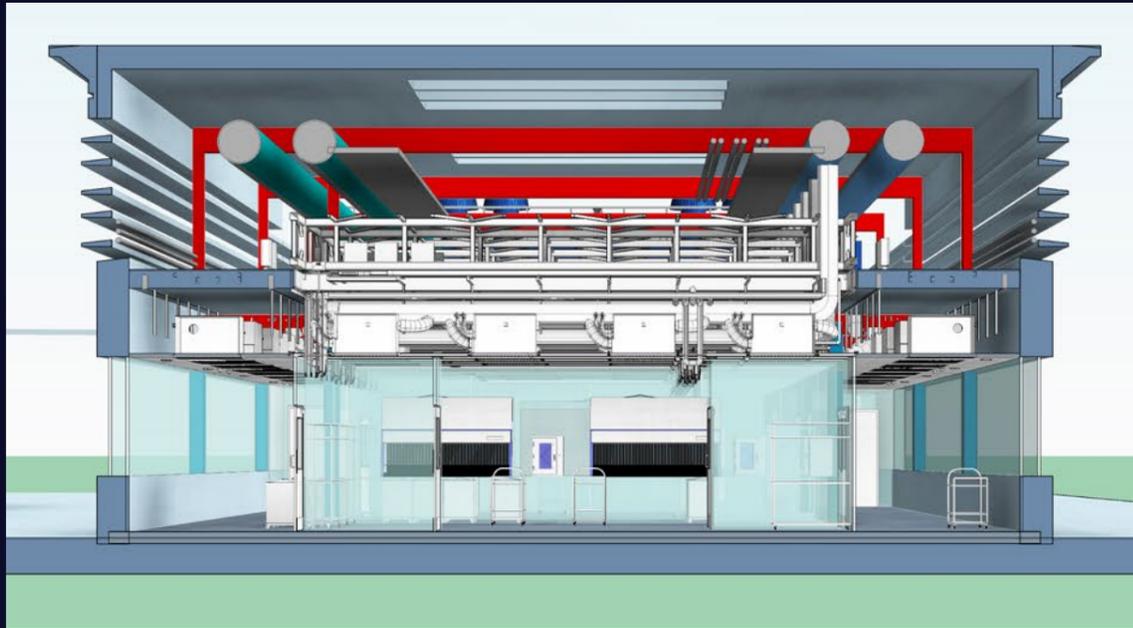
That was the basis for opting for the Opcenter Execution Pharma solution from Siemens as the new MES. Because mRNA processes include a lot of manual stages – weighing, for example – operators require guidance. This is provided by the workflow management component of the software. To automate the facility, all systems were converted to the latest version of SIMATIC PCS 7. The powerful, flexible, and scalable distributed control system steers and controls all the processes in the plant and takes digitalization to the field level.

AGC Pharma Chemicals: eBR-pioneer in Spain



For more information on paperless production and the products used, Opcenter Execution Pharma, and SIMATIC PCS 7, see page 8

At its location in Malgrat near Barcelona, AGC Pharma Chemicals produces active pharmaceutical ingredients (APIs) and intermediate products. It's a digital pioneer in this field: AGC Pharma Chemicals is the first pharmaceutical company in Spain to introduce an electronic batch record (eBR) and combine it with its distributed control system (DCS). The manufacturing execution system (MES) Opcenter Execution Pharma makes the digital transformation of production workflows possible. This digital platform seamlessly links the MES level with the distributed control system (DCS) level, which meant that AGC Pharma Chemicals was able to streamline its own processes and workflows – while simultaneously complying with all legal requirements – and also fully digitalize its production guidelines. That removed the need for more than 530 manual inputs from operators, guaranteeing data integrity and simplifying the process. In addition, the flow of materials is controlled using bar codes, which further improves quality and safety. That first required an upgrade and migration of the existing SIMATIC PCS 7 distributed control system. This was done while the system was live, which meant that the old and new systems had to be replicated, simulated, and migrated in parallel before being put into operation. The second step was to introduce the electronic batch record, which covers and documents the use of materials, production execution and batch testing.



Exyte: A modular approach to the cleanroom



For more information on SIMATIC PCS 7, see page 8

Achieve sterile working conditions for medical research and production quickly and flexibly – the ExyCell modular system makes it possible. With the help of Siemens technology, Exyte, the expert in the development and supply of controlled and regulated manufacturing environments, manufactures individual, prefabricated and standardised cleanroom cells. Each cell is dimensioned to ensure that it will fit in any shipping container and therefore be suitable for transportation to any location. The cells can be used for the construction of turnkey greenfield plants as well as integrated into existing buildings. Because the cells are simply combined together, operators can easily scale the size of the system and design almost any floor plan. The cells are also neutral, meaning that

customers have the option of equipping them to meet their own requirements. But the key advantage of the modular system is that the cleanroom is available fast. Customers can start using smaller units within months and larger units within a year.

Systems used

Using the latest version of SIMATIC PCS 7, plant operators can manage automation processes in the ExyCells. They can also control the room climate. A supply of power to the cleanroom cells is ensured by the Sivacon low-voltage switchgear. With Desigo CC, Siemens also offers solutions for fire protection and access control. On request, the company also provides support for plant digitalization.



Bayer AG: Two hearts in one body



For more information on paperless production and the products used, Opcenter Execution Pharma, and SIMATIC PCS 7, see page 8

Bayer AG has modernized its highly automated plant in Bitterfeld, best known for aspirin manufacture, and has introduced a new manufacturing execution system (MES). For this project, the company opted for the complete solution from Siemens: With a combination of the SIMATIC PCS 7 process control system and the Opcenter Execution Pharma integrated in the PCS 7 interface, Bayer Bitterfeld isn't just acquiring a state-of-the-art MES, it's also getting an efficient automation solution (DCS) at the same time. This innovative solution is a multi-level type/instance concept: The entire process flow is modeled at the DCS level, where event-based MES workflows can be triggered when needed. Each individual specific process is cross-level as a library function or type, so the customer can create every new part-process exclusively in the batch recipe and implement any potential changes in automation much more easily and quickly.

All that's needed at that point is to revalidate the batch recipe, not the entire DCS/MES structure, as is the case with traditional separate systems. Another benefit of the complete solution is that it's easier to handle: Both systems are controlled via the same user interface.

Introduction with the system in operation

Because it's very important when manufacturing vital products like medications to ensure that the system migration doesn't cause any production outages, the new system was introduced in stages while production continued in parallel. The new and old MES operated in parallel for a period of time. Siemens supported the implementation of the system with Hypercare and a 24/7 project-based standby arrangement.

Pfizer: High, higher, HighCon

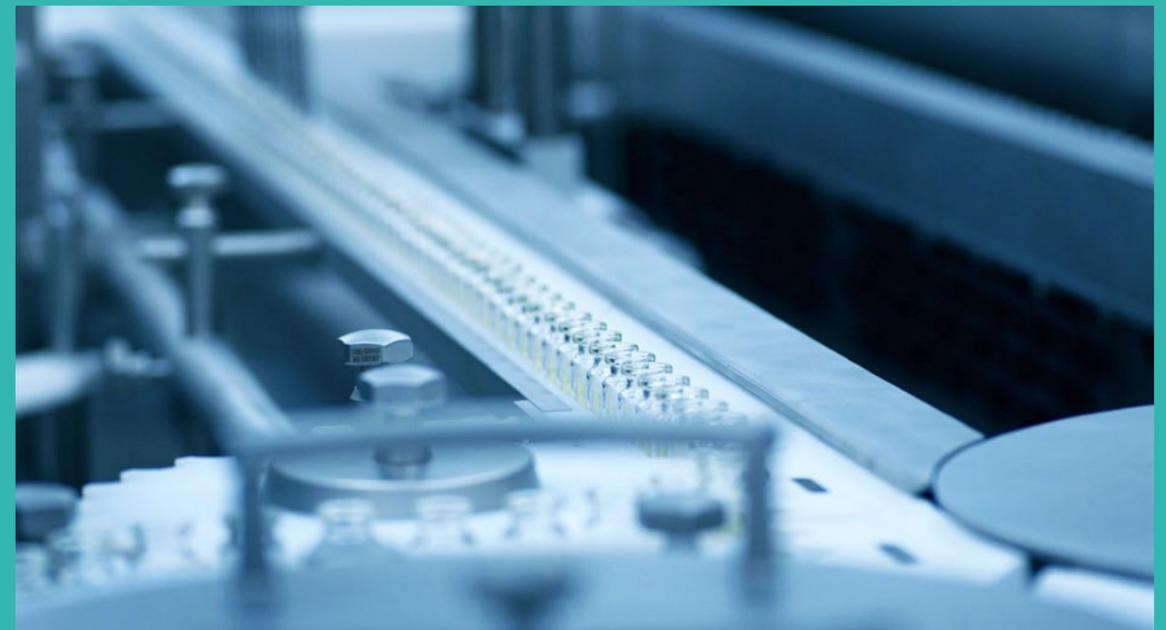


At its new high-containment plant in Freiburg, Pfizer's production can be more flexible, faster, and easier on resources thanks to the intelligent networking of machines and workflows. Along with several partner companies, Siemens played a role in making the production plant one of the most modern and sustainable facilities in the world.

For example, Siemens acted as a single-source provider of complete industrial logistics solutions, from the initial design through to a smoothly running system, the manufacturing operations management (MOM) solution to completely digitalize production operations, and the automation execution system (AES) based on the SIMATIC IT Production Suite, which coordinates the entire material flow. Networking and visualizing data in the Desigo CC management system helps Pfizer's new high-containment production plant consume about 40 percent less energy than traditional plants.

Working more safely with high-potency active pharmaceutical ingredients

High-potency active pharmaceutical ingredients (HPAPIs) are becoming increasingly popular in medicine. The reason is their elevated pharmacological action at low doses as well as their high selectivity, which reduces the risk of adverse drug effects. But maximum caution is required when manufacturing them. High-containment plants make that possible. What's special about Pfizer's new plant in Freiburg is that medications in category OEB4 can be made there, but employees only need protective clothing to the OEB3 level. This is made possible by a special containment concept and innovative technologies that are monitored and controlled by the Desigo CC building services from Siemens. This integrated, scalable, and open building management platform is linked to the SIMATIC WinCC visualization system, for example, which makes data sharing easy. From power distribution to automation, technologies like Desigo PX integrate the various building systems in Pfizer's new high-containment plant, including ventilation, air-conditioning, and heating.



Jinyu Bio: Digital animal vaccine production



For more information on the digital twin and the products used, SIMATIC PCS 7, and Opcenter Execution Pharma, see page 8

Animal vaccine manufacture is complex, and like human vaccines, it involves many separate stages. Chinese pharmaceutical company Jinyu Bio therefore wants to optimize the process and is turning to digitalization with that in mind. It introduced appropriate solutions aligned with shopfloor needs to cover the entire product lifecycle. The introduction of COMOS allows engineers at Jinyu Bio to access and modify design data anytime and anywhere, and the digital platform designs digital twins of the physical equipment, which significantly improves design accuracy. When COMOS and SIMATIC PCS 7 engineering is coupled, engineers can effectively share plant data. As a result, the teams work together more efficiently since real-time information-sharing is possible, and the error risk when designs are changed is reduced. In addition, the XHQ Operations Intelligence software combines the information from various backend data sources, which assists the management team with decision-making. The Opcenter Execution Pharma MES is a crucial tool in this regard, since it controls elements such as automated production and ensures end-to-end traceability. With comprehensive digital products such as Teamcenter, Opcenter RD&L, and SIMATIC SIPAT, Siemens also supports Jinyu Bio with horizontal data integration from the material supplier to the vaccine customer. The result is that Jinyu Bio has been able to create an IoT-based big data platform.