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Feature Service

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Therapeutic Bacteria

Biologics are the pharmaceuticals of the future. Instead of by chemical synthesis, they are produced in living organisms such as bacterial cells. Wacker Biotech's technology turns bacteria into tiny pharmaceutical factories producing large quantities of extraordinarily high-quality actives at acceptable prices. This unique science is in demand among pharmaceutical companies the world over. The market for biologics is growing, and Wacker Biotech is growing right along with it.

They float in a murky soup of nutrients in huge steel tanks: life forms too small to be seen by the naked eye. These are bacterial strains, which grow and reproduce. At the same time, they perform valuable work, generating therapeutics to combat cancer or multiple sclerosis – diseases that push chemically synthesized actives to their limits. Drugs that are made by genetic engineering, are referred to as biopharmaceuticals or biologics – and

they are taking the pharmaceutical market by storm.

The lion's share of pharmaceutical approvals

Demand for biopharmaceuticals is enormous: they are today's fastest growing market for therapeutic agents and already constitute 29 percent of the global pharmaceutical market. Last year was the first time that biologics accounted for over half of newly approved drugs in Germany. According to a recent study by Evaluate Pharma, the global market is expected to grow by an average of 9 percent each year between now and 2024, achieving sales of over US$380 billion.

Utilizing natural talents – biologics production

At Wacker Biotech, pharmaceutical actives are produced primarily by modified strains of *Escherichia coli*, which function like miniature drug factories. A single tank, or fermenter, full of *E. coli* can produce several hundred grams of protein – enough to treat tens of thousands of patients. Making the bacteria produce the largest possible amount of active ingredient reliably and economically is a science all on its own. The only way to harness these natural talents for large-scale actives production is to make as many microorganisms as possible "happy" at the same time. The trick lies in

sophisticated fermenter control: making sure that, at any given time, the bacteria always have the right amount of oxygen and the right nutrients – one of Wacker Biotech's specialties. As a contract manufacturer, the company works in the background for pharmaceutical companies and biotech firms, producing active ingredients for the medicines of tomorrow. "We have mastered bioengineering techniques for producing active ingredients on small and large scales, both for the clinical development phases involved in approving a drug, and for supplying the commercial market afterward," says Dr. Susanne Leonhartsberger, the managing director of Wacker Biotech GmbH.

Three sites: Jena, Halle and Amsterdam

Scientists at the company's headquarters in Jena, Germany, have been using biotech methods for developing and producing pharmaceutical proteins for 20 years. What is now known as Wacker Biotech GmbH started out as ProThera GmbH, which was spun off from the state-owned Hans Knöll Institute in Jena in 1999. The company has been a wholly owned subsidiary of the WACKER Group since 2005, and the biopharmaceuticals business has grown steadily in recent years. Acquisition

of Halle-based Scil Proteins Production in 2014 gave the company a second site and doubled the number of production facilities.

In 2018, WACKER acquired Netherlands-based SynCo Bio Partners, which was then renamed Wacker Biotech B.V. – once again doubling capacity for the biotech business. The acquisition added two fermentation lines in Amsterdam capable of handling 270 and 1,500 liters, respectively. It was a strategic move, as exceptional growth has gradually pushed the Halle and Jena sites to their limits. The additional capacity will allow the company to meet growing demand. “Production of biopharmaceuticals is time-consuming. Our production facilities, along with all of the upstream and downstream steps, are only ever reserved for one customer at a time – and that ties up our facilities for a few weeks to months,” Leonhartsberger explains. After that, everything has to be meticulously cleaned out so that the equipment will be ready for the next customer order.

Boot camp for microorganisms

The general procedure is usually the same: a ring-shaped bit of genetic material known as a plasmid is transferred to the microorganisms.

This material contains the genes that tell the bacterium to produce the desired protein. The plasmid is then passed on to subsequent generations of bacteria, ensuring that they will produce the biomolecule as well. Once the microorganisms have generated enough product, the experts at Wacker Biotech stop the fermentation process and subject the contents of the tank to multiple purification steps. This process involves separating cell components, genetic fragments and undesired proteins from each other via centrifugation and chromatography. The final product is the pure active substance that the customer has ordered. In some cases, live bacteria – probiotics – are used even without modifying their genes.

A partner for the pharmaceutical industry

“Inducing bacteria to produce large quantities of highly pure actives efficiently requires a great deal of expertise. Plus, the equipment you need is expensive,” Leonhartsberger points out. “During the early stages of development, pharmaceutical companies don’t know whether their active agent will make it through the clinical phases and the approval marathon. That also makes acquiring the full complement of production equipment a risky

investment.” This is the reason why an increasing number of pharmaceutical companies are turning to contract manufacturers like Wacker Biotech. An important benefit for customers is that Wacker Biotech operations at all of its sites comply with pharmaceutical GMP (good manufacturing practice) requirements in order to ensure the high quality necessary for authorizing clinical trials or for market approval by the FDA (the US Food and Drug Administration) or EMA (European Medicines Agency).

Record yields thanks to top-of-the-line technologies

Jena, Halle, Amsterdam: each of these three sites contributes its own unique strengths, including a variety of different technologies, specialized fermentation systems, the accompanying biotech processes and downstream steps, and the necessary expertise that their teams contribute. The focus in Jena is on what is known as ESETEC® technology – a patented process developed by WACKER. The technology offers one key benefit in particular: “Bacteria normally retain the proteins they produce within the cell – including the desired active substance,” Leonhartsberger explains. “But that makes isolating and purifying those materials

complicated. The ESETEC® secretion system uses strains of *E. coli* where we've modified the genome to make them excrete the proteins into the surrounding culture medium in a soluble form." The bacteria regurgitate the active substances from their cells, so to speak – and that's a major advantage: cells and proteins can then be separated from each other via centrifugation alone. This reduces the need for complicated purification steps, which, in turn, saves money. In many cases, the method also produces record yields of several grams per liter. Yet another advantage is that complex biopharmaceuticals such as antibody fragments can be produced efficiently and cost-effectively.

Cryogenically preserved bacteria clones

What's more, the Jena site has another unique feature: it produces cell banks. Cell banks are treasure troves for individual customers. Like in a library, cell banks contain several hundred small glass vials lined up next to each other in storage boxes. These vials contain millions of bacterial clones that Wacker Biotech has genetically modified for their specific job – and then stored at cryogenic temperatures. This keeps them stable and reusable for decades. "For security reasons, we keep two copies of

each cell bank at two separate locations," notes Leonhartsberger. Whenever customers wish to produce their active substances, the biotech experts pull the corresponding cell bank, withdraw the bacteria, and cultivate them in fermenters for producing biopharmaceuticals. This can be done in a 350-liter system in Jena.

Cardiac medications from the fermenter

The fermentation line in Halle is four times that size, with a capacity of 1,500 liters. This WACKER site also brings another innovative technology to the table: FOLDTEC®. "Some proteins in bacterial cells simply remain insoluble," she points out. "That's the case with Reteplase, for example, a protein used for acute myocardial infarction. It aggregates in the cells to such an extent that the bacteria are unable to discharge it. In order to make proteins like these available as active substances, we use FOLDTEC® to retrieve them from our customized strains of *E. coli*." An important consideration here is that, while the bacteria assemble the desired proteins correctly, the three-dimensional configuration of the proteins must be right too – otherwise they will not be effective, as happens when they are present in cells in an insoluble form

known as inclusion bodies. FOLDTEC® allows the biotech experts to produce large amounts of the proteins in cells, dissolve and then convert them to their active form using special refolding technologies.

From development to dispensing

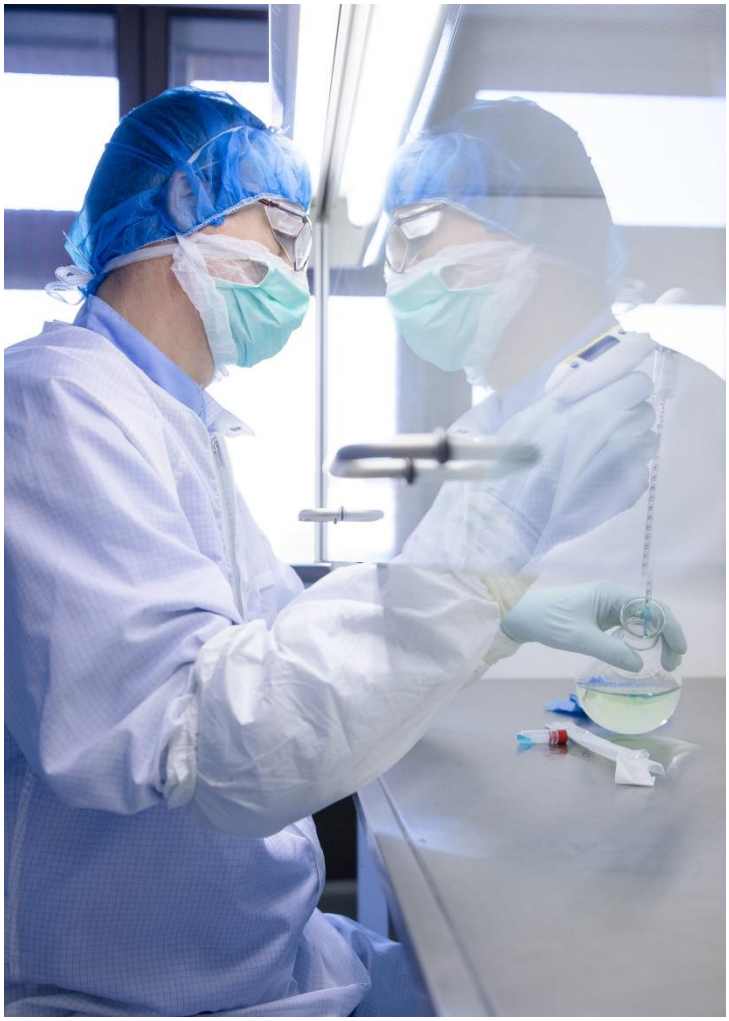
As a result, the solutions of active agents produced in Jena and Halle contain little bacteria when WACKER dispenses them either into bottles or into plastic bags that hold up to 50 liters. The company then delivers them to its customers for further processing. “The fill-and-finish plant at our Amsterdam site now gives us the option of dispensing sterile solutions directly into the vials,” says Leonhartsberger. For this reason, the Dutch site meets Class A cleanroom specifications – the highest possible level.The term cleanroom is used when the particles floating in the air in a room do not exceed a specific number or size per cubic meter. For Class A cleanrooms, that means a maximum of 3,520 particles greater than or equal to 0.5 µm in size and no more than 20 particles greater than or equal to 5 µm. Given that we are surrounded by billions of particles in our daily lives, those numbers are extremely small. And the complexity of the room equipment, alongside the cleaning

procedures that employees must undergo before entering the room, is correspondingly high.
Plus, the Amsterdam site has a lyophilization facility for freeze-drying solutions of active substances before they are sent to customers. This improves shelf life.

The heartbeat of pharmaceutical innovation

The new site in the Netherlands contributed another entirely new technology as well: LIBATEC® is used for developing and manufacturing Live Microbial Products (LMPs). LMPs are a promising class of therapeutic products that open the door to new medical treatments. “Applications involving live bacteria represent an exciting up-and-coming field that is now open to us,” Leonhartsberger notes. “This demonstrates once again what a technology-driven company we are and how we and our customers do our very best to deliver innovative treatments to patients.”

Wacker_Biotech_Fermenter.jpg
Production at Wacker Biotech GmbH: the Munich-based WACKER Group entered the field of contract manufacturing for pharmaceutical proteins when it acquired Prothera GmbH and subsequently renamed it Wacker Biotech in 2005. (Photo: Wacker Chemie AG)



Wacker_Biotech_Labor.jpg
Specialists in the field of microbial production: Wacker Biotech GmbH is a full-service contract manufacturer of biologics with more than 20 years of experience with microbial systems. The company's core competencies include the manufacture of active pharmaceutical ingredients, vaccines and live bacteria. (Photo: Wacker Chemie AG)

Wacker_Biotech_Amsterdam.jpg
Through its 2018 acquisition of SynCo Bio Partners B.V. in Amsterdam, the Netherlands, Wacker Chemie AG strengthened its pharmaceutical protein business and expanded its portfolio – an important step to keep pace with the rapidly growing biologics market. As a result, Wacker Biotech now has three sites: Jena, Halle and Amsterdam, with a total of about 330 employees. (Photo: Wacker Chemie AG)

Wacker_Biotech_Leonhartsberger.jpg
Dr. Susanne Leonhartsberger has been the managing director of Wacker Biotech GmbH since 2017, and, in her capacity as the head of the Biopharmaceuticals business line, is responsible for WACKER's biologics business. "What especially motivates me is that we're providing innovative medications for sick people all over the world – and that's how most of us feel," the biologist observes. (Photo: Wacker Chemie AG)

Note:
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The company in brief:
WACKER is a globally-active chemical company with some 14,500 employees and annual sales of around €4.98 billion (2018). WACKER has a global network of 24 production sites, 22 technical competence centers and 50 sales offices.

WACKER SILICONES
Silicone fluids, emulsions, rubber grades and resins; silanes; pyrogenic silicas; thermoplastic silicone elastomers

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