Wacker Chemie AG
Hanns-Seidel-Platz 4
81737 Munich, Germany
www.wacker.com

FEATURE SERVICE

June 2020

Vaccines: Training the Immune System

Polio, cholera, COVID-19: in part life-threatening illnesses caused by bacteria and viruses. Vaccines help the body defend itself against infection and get the immune system in shape to fight dangerous pathogens. The experts at Wacker Biotech have 20 years of experience producing vaccines.

They're on your skin, in your digestive tract, in the air and on the sea floor: we're surrounded by billions of bacteria and viruses. They live on us and in us. Invisible to the naked eye, most of these tiny organisms are harmless, and some of them are even critical to our survival. Some, however, make us sick, potentially triggering severe, even life-threatening illnesses.

Vaccines offer protection from an array of infectious diseases, such as polio, typhus, cholera, hepatitis A and B, HPV and smallpox, which, thanks to a global immunization campaign, was eradicated in 1980. Yet new pathogens or variants of known pathogens are emerging. The list is long. And it brings home one important lesson: vaccines are, along with the development of antibiotics, cornerstones of modern medicine. The World Health Organization (WHO) estimates that vaccines save the lives of two to three million people each year and prevent countless more from falling ill.

The immune system forms memory cells

Vaccines play a trick on the body, leading it to believe it has been infected with a pathogen. The trick works by selectively exposing the body to either all or part of a killed or weakened organism. Not enough to cause disease, but enough to alert the immune system, which reacts by forming antibodies to fight the virus or disease-causing bacterium – an immune response, in other words. This is also when cells known as memory cells are formed, allowing the body to remember the pathogen, even once the acute danger has passed. If the individual is infected again at a later point in time, the immune system will be prepared for it.

Researchers are now working round-the-clock on a vaccine for the SARS-CoV-2 virus, which can trigger the respiratory illness COVID-19. The disease was first detected in December 2019 in Wuhan, a city home to millions of people in the Hubei province of China. In January 2020, the illness developed into an epidemic in China, ultimately spreading around the world to become a pandemic. Because the SARS-CoV-2 coronavirus had been unknown up to that point, it is often referred to as the “novel” coronavirus. According to the WHO, 100 projects aimed at the development of a vaccine are currently underway (as of May 2020).

Not all vaccines are created equal

As part of that effort, pharmaceutical companies all over the world working on very different kinds of vaccines. “Not all vaccines are created equal,” explains Dr. Philippe Cronet, who leads the development of biotechnological production processes at Wacker Biotech – an area of responsibility that includes

vaccines. Pharmaceutical companies and research institutes have been contracting Wacker Biotech to produce vaccines for 20 years. The company's portfolio extends from classic live and killed vaccines to protein-based, polysaccharide and glycoconjugate vaccines. The field is large, and development is ongoing.

"One option is to use the pathogen itself in the vaccine – in either a weakened or inactive form," Cronet explains. The organisms in live vaccines are capable of reproducing, but they can no longer cause illness, and the resulting live vaccines are referred to as attenuated, i.e., weakened. Many of these vaccines – those that prevent childhood diseases such as mumps, measles and rubella – confer life-long immunity. Inactivated vaccines on the other hand, which are also referred to as killed vaccines, contain either a dead pathogen or part of an inactive virus to which the immune system responds. The protective immunity provided by killed vaccines generally only lasts for a few years, after which it will need to be stimulated again.

A new direction in the 1990s

Most of today's vaccines are inactivated varieties developed from only select molecules of a pathogen, and the use of genetic engineering technology to produce these has become increasingly common since the 1990s. These kinds of vaccines contain individual, characteristic proteins of a pathogen intended to produce an immune response within the body. For these to work, boosters known as adjuvants often need to be added. The same applies to what are known as polysaccharide vaccines,

which use polysaccharides taken from a bacterial capsule or virus shell to prompt an immune response. In order to amplify the effect, scientists in the 1990s also developed conjugated polysaccharide vaccines (conjugate vaccines), in which polysaccharides were bound to proteins. “These conjugates trigger a stronger immune response and provide longer-lasting protection than the antigen alone,” Cronet explains.

Promising new class of vaccines

Vaccines based on nucleic acids – the DNA or messenger RNA (mRNA) of a virus – represent a relatively new class of drugs offering a highly sophisticated immunization strategy. The vaccine contains only the blueprint of the DNA or mRNA of the virus, which the body uses as a basis for producing antigens. The immune system recognizes these antigens as foreign and fights them off – a trial run for a real infection without ever coming into contact with the pathogen itself.

“Vaccines based on nucleic acids are a very promising alternative to conventional vaccines,” Cronet observes. “They offer a number of advantages. The most significant of which is their minimalist structure, which reduces development and production time. The only thing you have to produce is genetic material, after all. You don’t have to culture the pathogen itself. And that eliminates a very time-consuming step.” Up to now, however, no nucleic-acid-based vaccines have been approved for human treatment – all of the candidates are still in the development phase. Some products have already been approved, however, in another relatively new class of vaccines:

viral vectors. Here the vaccine is based on a harmless virus that has been genetically engineered to contain a characteristic, but harmless component of the dangerous pathogen. A vaccine based on a viral vector has recently been approved for Ebola.

Quicker response to novel viruses

Several research institutes are also looking to this new class of vaccines to combat the SARS-CoV-2 virus. According to the journal *Nature*, 20 projects throughout the world are currently underway with the aim of bringing an RNA- or DNA-based vaccine for the novel coronavirus to the market. Twenty-five projects for developing viral vectors have been launched as well (as of April 2020). Current efforts to combat the coronavirus pandemic could pave the way for these new classes of vaccine.

“The rapid spread of severe infections like SARS, Ebola, and now the SARS-CoV-2 virus once again underscore the need for developing new vaccine technologies so that we can respond to novel viruses more quickly and effectively,” says Cronet. Wacker Biotech is looking into nucleic-acid-based vaccines as well.

Wacker Biotech’s role as a CDMO

As a CDMO (contract and development manufacturing organization), Wacker Biotech is a service provider. “We develop production processes and manufacture vaccines for our pharmaceutical industry customers, but we don’t do concept design or marketing ourselves,” Cronet explains. What Wacker Biotech experts do contribute are over 20 years of experience developing and producing living microorganisms, proteins and polysaccharides. These active substances are used both in

(pre)clinical studies and in commercial products. Wacker Biotech produces vaccines at three sites: one each in Jena and Halle, Germany (Wacker Biotech GmbH), and one in Amsterdam (Wacker Biotech B.V.). Wacker Biotech GmbH and Wacker Biotech B.V. are both wholly owned subsidiaries of Wacker Chemie AG.

“The concept behind a vaccine is simple,” Cronet observes. “But developing and manufacturing one is anything but simple.” It can take ten to twelve years on average to move from the research phase to approval. In the case of a vaccine for SARS-CoV-2, however, scientists are hoping that an accelerated process could bring us to that goal within 12 to 18 months. The only reason that might be possible is because most of the vaccine candidates rely on highly efficient discovery and clinical testing platforms that have been developed for other pathogens. Researchers have already re-engineered existing vaccines by swapping out their genetic sequences so that they will respond to SARS-CoV-2.

From preclinical to clinical development, from vaccine manufacturing to market delivery: Wacker Biotech supports its customers throughout the entire vaccine supply chain. An individual production process is developed for each vaccine (candidate) and adapted to the stage of development that a given vaccine has reached. “Depending on the vaccine, that takes ten to fifteen months,” says Cronet. Once the process is in place, millions of doses of vaccine can be produced within one to two weeks.

Broad vaccine portfolio

Wacker Biotech has already manufactured vaccines for a wide range of infectious diseases, such as cholera, meningitis A and C and Haemophilus influenza type B. “At this point we’ve provided over 650 vaccine batches for clinical and commercial applications,” Cronet notes. Whereas vaccine manufacturing at Jena and Halle focuses on protein-based agents produced through the use of the bacterium *Escherichia coli*, the Amsterdam site makes live attenuated, polysaccharide and conjugate vaccines. This involves the use of an array of additional microorganisms, such as *Corynebacterium diphtheriae, Salmonella typhi* or *Vibrio cholerae*.

Production in this case proceeds in multiple steps, and these vary depending on the type of vaccine. The first step takes place in the laboratory, where what are known as precultures are prepared of the vaccine candidate that the customer has provided. This is followed by scaling up production either in stainless steel tanks called fermenters or in single-use bioreactors. Here the bacteria produce the target active substance – in the case of a conjugate vaccine, they build the desired polysaccharides (see illustration). The polysaccharides next undergo multiple purification steps and lyophilization, after which they are chemically activated and, in the final step, bound to the carrier protein to form the finished conjugate vaccine.

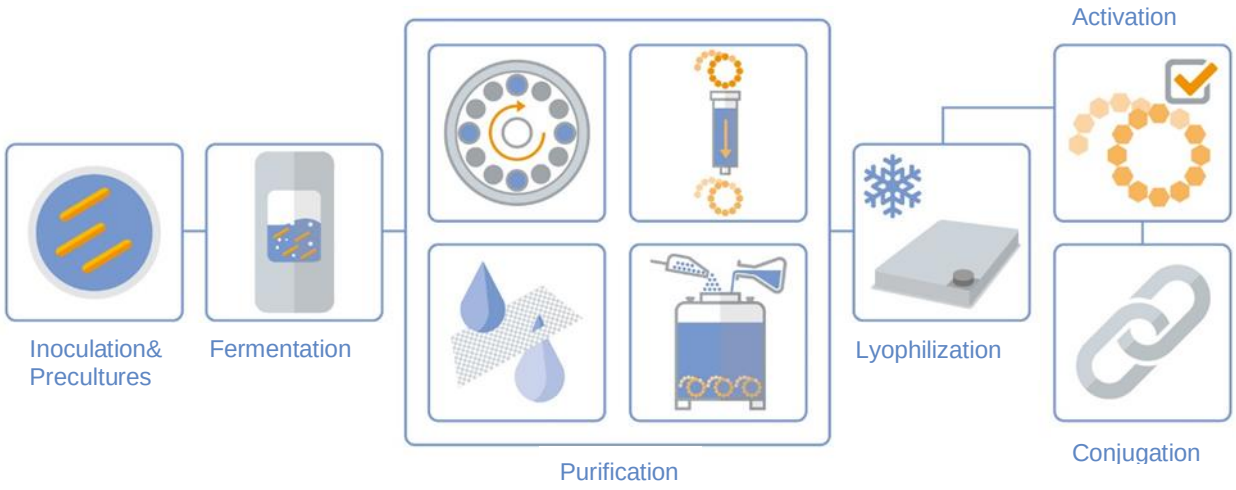
Wacker Biotech sites carry out this process in facilities meeting biosafety levels of 1 (Halle and Jena) and 2 (Amsterdam), on a

scale of 1 to 4. The sites produce vaccines in stainless steel tanks with capacities ranging from 270 to 1500 liters, as well as in a 250 L single-use reactor. This allows the company to adapt production volumes as needed – small quantities of vaccine for clinical trials, larger amounts for supplying the market later on. In Amsterdam, active substances can also be dispensed into as many as 20,000 vials per batch following production. Freeze-drying (lyophilization) at the end of the production process is an option as well. “All of our facilities meet the highest standards of quality. They’ve been approved both by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA), which means we can supply the global market,” says Cronet. Vaccines from Wacker Biotech are sent all over the world.

The vaccines market is constantly growing

Capacity utilization rates at all three Wacker Biotech sites are currently high, in part because the vaccine market is constantly growing – and not just because of the search for a SARS-CoV-2 vaccine. Scientists are continually discovering new pathogens, including many for which no vaccine currently exists. Also, because some pathogens possess the ability to adapt to their environments, there is a constant need for new vaccines to combat mutated organisms – this is why new flu vaccines are developed every year. Put in terms of actual numbers, the vaccine market is growing at an average rate of seven percent a year. Studies have indicated that this is not likely to change in the coming years. Keeping pathogens in check remains a never-ending task – and that goes for Wacker Biotech too.

Illustration: Producing a Conjugated Polysaccharide Vaccine



Box: How Bacteria and Viruses Make Us Sick

Infectious diseases can be caused by an extremely wide range of pathogens, the most important of which are viruses, bacteria, fungi and parasites. The infections that arise most commonly are those caused by bacteria and viruses – two groups that make people sick in very different ways.

How Viruses Trigger Infectious Diseases

Viruses are invisible to the naked eye and can only be seen with an electron microscope. Some look like tadpoles with tails, others are rod-shaped or resemble spheres. Their inner workings are relatively simple. Unlike bacteria, they have no metabolic processes of their own and consist of nothing but their genetic material. Strictly speaking, viruses are not even living things. And yet they can be hazardous to humans – the very simplicity of these tiny organisms is what makes them so dangerous. Viruses possess neither cytoplasma nor ribosomes, they cannot copy their

genetic material, and they cannot make their own shells. This is why they replicate by attacking foreign cells and injecting their genetic material into them. Once inside the host cell, the virus reprograms the cell's own genetic information, forcing the host to produce virus particles from that point onward. Those particles, in turn, attack new cells. Once set in motion, this process destroys cells in the body. Diseases caused by viruses include the flu, herpes, AIDS, hepatitis, and the respiratory illness COVID-19.

How Bacteria Trigger Infectious Diseases

Bacteria are many times larger than viruses: 0.1 to 700 micrometers. And, unlike viruses, bacteria are living things. More precisely, they are self-sufficient, single-celled organisms – tiny creatures that produce everything they need to live within their cell. They have their own genetic material, their own metabolism and they reproduce through cell division. They clone themselves, you might say. Most bacteria pose no threat to humans, and some are even highly beneficial, such as those that support digestion in the human intestinal tract. Only about one percent of these microorganisms cause disease. When these bacteria enter the body, they generate toxic metabolic products that result in an infection. Known pathogenic bacteria include those in the genus *Salmonella*, which trigger salmonellosis, a typical form of food poisoning. Diseases such as tuberculosis and whooping cough are caused by bacteria as well. Species of bacteria that are actually harmless and that live in or on the human body can also trigger an infection as soon as the immune system is weakened. One example of these are pneumococci, which can cause a variety of illnesses, such as meningitis. Pneumoccoci can be present in the noses and throats of many people without producing disease. Dangerous inflammations can develop, however, when these bacteria come into contact with older people, children or other immunocompromised individuals. In some cases, pneumococci can become established in the body long before the infection occurs – as soon as the immune system is compromised.

Box: About Wacker Biotech

Wacker Biotech GmbH and Wacker Biotech B.V. are full-service contract manufacturers of therapeutic proteins, live microbial products (LMPs) and vaccines based on microbial systems. The company's portfolio extends from strain/process development to analytical testing to GMP production for clinical and commercial applications. Wacker Biotech maintains three GMP-compliant, FDA- and EMA-certified production plants in Amsterdam and in the German cities of Jena and Halle. Wacker Biotech GmbH and Wacker Biotech B.V. are wholly owned subsidiaries of the Munich-based WACKER Group.

Before the large-scale production of a vaccine can begin, the first step is to develop the production process in the lab (photo: WACKER).

In stainless steel tanks known as fermenters, bacteria at Wacker Biotech produce the desired active substances (photo: WACKER).

From development to dispensing: at the Amsterdam site, vaccines can be dispensed into their final packaging for shipment to the customer. The vials then undergo one last quality check (photo: WACKER).

Please note:
These photos are available for download at:
http://www.wacker.com/featureservice

For further information, please contact:
Wacker Chemie AG
Media Relations & Information
Manuela Dollinger
Tel. +49 89 6279-1629
manuela.dollinger@wacker.com
www.wacker.com
follow us on:

The Company in Brief:
WACKER is a globally active chemical company with some 14,700 employees and annual sales of around € 4.93 billion (2019).
WACKER has a global network of 24 production sites, 23 technical competence centers and 51 sales offices.

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

WACKER POLYMERS
Polyvinyl acetates and vinyl acetate copolymers and terpolymers in the form of dispersible polymer powders, dispersions, solid resins and solutions

WACKER BIOSOLUTIONS
Biotech products such as cyclodextrins, cysteine and biologics, as well as fine chemicals and PVAc solid resins

WACKER POLYSILICON
Polysilicon for the semiconductor and photovoltaic industries