



# Every Drop Counts

At the German Site in Hameln, Siegfried Successfully Demonstrates Its Expertise in the Technologically Demanding Biologics Fill & Finish Segment. A Business with Future.

*The Fill & Finish of biologic drugs is expensive and poses special technological challenges for CDMOs. At the German site in Hameln, Siegfried has successfully proven these capabilities over the past two years by producing Covid-19 vaccines and a significant number of clinical batches for several biological companies. By investing in its competencies, capacities and flexibility, the company intends to further expand this demanding but promising business area.*

Siegfried entered new territory on September 14, 2020. On that day, the company announced that it had signed a collaboration and supply agreement with the German biotech company Biontech for the filling and packaging of commercial quantities of the innovative Covid-19 vaccine candidate BNT162b2. From mid-2021 to the end of 2022, the vaccine, which played a key role in the management of the Corona pandemic, was filled at Siegfried's German site in Hameln. For the aseptic filling and packaging ("Fill & Finish") of the vaccine, the company invested in a dedicated production facility and provided special storage capacity.

The next step followed in May 2021. Siegfried agreed with Novavax to handle the aseptic filling of the protein-based coronavirus vaccine NVX-CoV2373 for the US company in the future. The contract was ex-

tended the following year until the end of 2023.

The two vaccines are biologically manufactured drugs. In contrast to products with a chemical composition, biopharmaceuticals are characterized by a more complex molecular structure and a significantly more demanding production process. The demands on CDMOs like Siegfried are correspondingly high. Through these projects, the Swiss company demonstrated its ability to solve technologically demanding tasks even on short notice as well as to quickly ramp up capacities as required. With the investments in competencies and multi-purpose capacities in Hameln, Siegfried has already been able to support a number of customers with development and manufacturing services beyond vaccines.

## Every Drop is Important

In the biological Fill & Finish process, every drop counts, because the production of the active ingredient is very expensive. For example, 30 liters of drug substance yields 1 million doses of drug product. In this context, Siegfried points out that it has the equipment and experience to limit waste and leftovers and to ensure no interruptions in manufacturing. With the new production line, the CDMO is also able to perform 100% inline check weighing.

In addition, the company is very flexible in producing a wide range of quantities. For clinical trials, for example, Siegfried has a special line for small batches with minimal losses. Here the CDMO can produce batches of only 4 to 8 liters and doses of just 0.2 milliliters. But Siegfried can also do big things: In one of its projects they produced 760,000 cans in 500 liters—the company claims it is the only one that can do that.

Even though they are used to dealing with complex processes in Hameln, some products present a special challenge. Like Biontech's Covid-19 vaccine, which had to be cooled down to minus 80 degrees. The problem: The stoppers that seal the vials become as hard as stone at minus 50 degrees,

says Marianne Späne, Chief Business Officer (CBO) of Siegfried. Their ability to seal diminishes. That's why they developed their own solution. Which one? Späne only says: "IP"—intellectual property. Trade secret.

## The Future of Biologics

Up to now, the liquid pharmaceutical products they fill in Hameln have mostly been based on small molecules, i.e., chemically produced active ingredients. Biologics still account for a small proportion. But that is set to change in the future.

Given the growing pipeline of biologics, lack of technical expertise, and huge capital investment in the installation of Fill & Finish equipment, a rising number of pharmaceutical companies are turning to contract service providers in order to ensure the development of quality drug products. This surge in the demand for biologics Fill & Finish services has presented opportunities for service providers having such capabilities.

Digital screens at the entrances to the production halls in Hameln show, which products are currently being manufactured. Basically, they fill almost all sterile liquid pharmaceuticals, a total of more than 100 different products: anesthetics, water and also the Covid-19 vaccines from Biontech and Novavax, with which Siegfried has proven its capabilities "as one of the leading service providers in the CDMO sector for technologically demanding products such as Covid-19 vaccines," according to CEO Wolfgang Wienand.

## Sophisticated Process

CBO Späne adds that the quality of the biologics and liquid drugs they produce in Hameln depends primarily on strict adherence to processes. One thing is to be avoided at all costs: That germs get into the production process or even into the drugs. After all, the products they manufacture here are highly sensitive. In addition to vaccines, they also include anesthetics that are injected into patients' bodies before operations. Nothing can be allowed to go wrong.



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Sterile and aseptic production means germ-free production. This kind of manufacturing process is one of the most demanding procedures in pharmaceutical production and places highest demands on rooms, air quality, starting materials, surfaces and personnel.

There are two ways to ensure sterility or aseptic conditions: One is heating the liquid drugs. For 15 minutes at 121 degrees in so-called autoclaves. These are basically oversized steam ovens that can hold several metal boxes, each containing thousands of ampoules or vials.

But not all drugs can withstand these temperatures, including most biologics. Then the only option is to manufacture them in a germ-free environment. The problem is that people always carry germs with them. They stick to their clothing, but they also adhere to tables, walls and work surfaces. And: You can't make them visible. There is no spray that can be used to detect the germs as small colorful dots in the environment.

Accordingly, the Siegfried employees at the Hameln site make great efforts with regard to purity. It already starts in the warehouse—the incoming crates are transferred here from wood to aluminum pallets. Employees can only enter the actual production area through locks and with special protective clothing. Particularly sensitive production steps are carried out fully automatically in specially separated rooms.

### From 5,000 to 30 Million Vials

The site has belonged to Siegfried since the takeover of the former family-owned company Hameln Pharma in 2014. Around 500 employees work here, in the southern part of Lower Saxony, in three shifts five days a week, sometimes seven days a week, in sterile and aseptic filling. They are specialists in this.

Hameln, says Späne, is the largest sterile filling site in the Siegfried family. Here they produce on eight filling and four packaging lines for about 30 to 50 pharmaceutical customers. Some have had production for years in the town known for the Pied Piper saga, others for just one production run. The volume of orders also varies greatly: sometimes it's just 5000 units for biopharmaceuticals, sometimes it's 50,000 or even 30 million ampoules or vials per customer and year.

The El Masnou site in northern Spain, 20 minutes north of Barcelona,



also specializes in handling aseptic products, in particular ophthalmics. Nearly 400 employees here manufacture and package sterile ophthalmic products including eye drops, eye ointments, ear and nose sprays. The Siegfried sterile and aseptic filling network also includes the US site in Irvine, California. The plant with its more than 120 employees has been part of the company since 2012 and primarily serves customers from the US market. watch.

### Constant Control, Constant Cleaning

Production is one thing, checking processes and sterility is another. At Siegfried's Hameln site, they check constantly, in the running process, so to speak. Employees take measurements on surfaces, they measure air quality, and employees are „wiped down“. Data is continuously collected and documented to prove that the batches are germ-free.

Visual inspections also have an important function. With an alert eye, employees check whether the heat-formed vials are properly sealed. Do they have a bulging head, i.e., is the glass around the top too thin? If so, the vials are sorted out by hand. It is a strenuous job that requires constant attention and is exhausting. That's why the inspectors take turns every 20 minutes.

Elsewhere, however, machines check whether the vials contain the correct amount of liquid and are re-

ally free of particles. To do this, the vials are set into rapid rotation, followed by an abrupt stop. And in order to test the tightness of the vials, they are subjected to high voltage.

### Twice a Year the Big Check

Twice a year, each production line undergoes a major check. The process is called Mediafill. In this process, a solution capable of strong growth is brought into contact with the surfaces of the production line. It is a demanding and technically challenging procedure. Contamination must be avoided at all costs. That's why cleaning, always cleaning. "In sterile production, they literally clean themselves to pieces," says the Chief Business Officer.

### 60 Employees in Quality Control

At the Hameln site alone, 60 employees work in quality control. Added to this are the production employees, who also make sure that processes and quality fit in the daily workflow.

In addition, they attach importance to service. Späne: "Our principle is: If someone comes to us with a problem, we'll find the solution." Or as Siegfried's corporate slogan says: "Expect more." In Hameln, this is brought to life in a very concrete way.

*Thorsten Schüller, CHEManager*

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