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Increasing the Sustainability of API Production

Efficient Production Processes Not Only Have a Positive Impact on Economic Parameters, but Also on Sustainability.

For Siegfried, sustainability is much more than a phrase with a green coating. The term, which encompasses social and economic criteria in addition to ecological aspects, is one of five central corporate values. One of the biggest levers for reducing energy and resource consumption in the pharma supply chain lies in the efficient production of active ingredients and pharmaceuticals. The company therefore works consistently on optimizing its processes.

Sustainable entrepreneurial action has many aspects - social, environmental and also economic. For a CDMO like Siegfried, a key lever for sustainability is in particular in a more effective production of active pharmaceutical ingredients, so-called APIs.

One person who is instrumental in ensuring that Siegfried's sustainability goals—which in fact are also derived from the ambitious goals of customers—can be implemented in concrete terms, is Chief Scientific Officer (CSO) Jürgen Roos. He outlines the main measures: "We introduce second-generation processes, apply green chemistry, and continuously research new sustainable technologies. With these efforts, we reduce energy consumption, produce less waste, and at the same time, maximize our products' safety."

Reducing Resource Consumption in Production

A significant leverage for reducing energy and material consumption in particular he sees in the API (active pharmaceutical ingredient) production. APIs ultimately derive from petrochemical starting materials, which are converted in complex and energy-intensive syntheses. Roos is therefore concerned with the question of how the synthesis of APIs, i.e., their production, can be carried out at Siegfried with less effort. The company has developed and implemented various measures to achieve this. One lever, for example, is the implementation of green chemistry. This involves minimizing or completely eliminating the use of hazardous substances. "We target the simple things first as they can have a big impact. Some processes can operate just as effectively with less reagent and higher throughput. We design experiments to see how far we can 'green-shift' an existing process to reduce inputs."

In some cases, Siegfried goes further and fundamentally redesigns a manufacturing process by using more creative and innovative chemistry – a so-called 'second-generation process'. Thus, the company rethought the API synthesis route and optimized manufacturing processes for selected multi-client products. Such a method replaces the original API synthesis with more efficient approaches, e.g., shorter synthetic routes and more selective catalytic processes. Roos uses the example of the German Siegfried site in Minden to illustrate what this looks like in concrete terms: "For one of our multiclient products, the synthesis route was shortened from 17 to 10 process steps, producing the API faster than the traditional method. The raw material and energy consumption were also reduced by half. At the same time, the process generated 50% less waste and thus had a smaller environmental impact. Ultimately, all these benefits lead to higher product yields for our customers."

Computer Modelling for Scaling-up

Not only shorter processes, but also the tool of computer simulations

contribute to a better environmental footprint in active ingredient production at Siegfried. For example, data analysis enables Design of Experiments (DoE) for efficient laboratory development and Quality by Design (QbD) to achieve optimal product quality. And Big Data (process data) analysis helps to improve processes and to stabilize them at an optimum.

Computer modelling is also being used for 'scaling-up' from small lab equipment to large reactors in the production plant. This allows, for example, to predict heat transfers or flow conditions in the large reactor. Roos: "In the past, scientists would use an intermediate-scale reactor as a steppingstone, because quite a lot of things can go wrong with chemical processes as the reactor gets bigger or changes shape. Nowadays however, our laboratories have accurate, small-scale models of the large production reactors, and we combine these with computer modelling to guide us. This allows us to go straight to the desired manufacturing scale from the lab, without the wasteful and time-consuming experimentation at the intermediate pilot scale."

Membranes Reduce Waste

One example for a new process technology in API production processes is pervaporation. This is a sustainable solution for the removal of water and methanol from solvents during API manufacturing. This method uses semi-permeable membranes that allow water or methanol molecules to pass through them. "Through this process, we can reduce the waste produced by up to 15 times compared even to distillation", says Roos. "In addition, this approach has a smaller carbon footprint than incinerating the waste created in traditional methods. The use of pervaporation membranes offers an environmentally responsible way of managing solvent drying with lower energy requirements. At the moment, Siegfried is testing this technology to deploy it in the near future."

Enhanced Distillation Techniques

Distillation processes that have been in use for centuries and are a common method for separating chemical compounds, also offer the potential for greater efficiency and sustainability thanks to modern and sophisticated technologies. For example, enhanced distillation techniques enable higher product quality, yield, and a more efficient process while reducing waste. At Siegfried, distillation is used in numerous process steps of an API synthesis.

However, the classical distillation step is often long and thermally intensive. This results potentially in product degradation and yield losses. With increasing inefficiency and resource use, the sustainability of the process also decreases. To address these limitations, Siegfried optimizes the distillation with the help of subject matter experts and computer simulations. By doing this the chemical processes can be optimized significantly, and carbon emissions are going to be minimized. Furthermore, the use of solvents can be substantially reduced by selecting the right distillation equipment and conditions.

However, Roos points out, that many APIs are unstable and thus not suitable for standard distillation. Continuous distillation can be applied in these cases, as it minimizes the residence time at elevated temperatures - a few minutes compared with several hours for standard batch distillation. Roos: "Therefore, we decrease product degradation and increase quality, yield, and efficiency."

Limits of Sustainability

But Siegfried's sustainability efforts go far beyond optimizing processes. One of the core goals here is: by 2030, the company wants to halve its carbon footprint compared to 2020. On the other hand, the drive to optimize and thus reduce resource and energy consumption also has limits. This applies, for example, to the operation of cleanrooms, in which sterile or aseptic drugs are produced. Sterility in these environments is paramount. This requires a certain number of resources and energy, which cannot be dispensed with.

The CSO also points out that not every measure that would reduce the ecological footprint of pharmaceutical production can be implemented immediately. In many cases, approval must be obtained from the regulatory authorities. According to Roos, it can take as long as one year before this is obtained.

And whether a measure that is good for the environment is also good for the company in financial terms cannot always be guaranteed in advance. After all, more efficient production methods initially require substantial investments. Whether and when these will pay off in the form of lower costs cannot always be predicted.

Recognition by Rankings

All efforts and initiatives of Siegfried in terms of sustainability have been recognized by external parties and independent institutions. In 2022, Siegfried was again rated positively in the ISS ESG and the MSCI ESG Ratings, and was, for the second time in a row, included in the Dow Jones Sustainability Index Europe.

These awards are more than a nice figurehead for Siegfried. Nowadays, many customers expect the CDMO to operate and act sustainably. This also benefits the customers. "With our expertise in process optimization, we help our customers to develop greener production processes for their products and to achieve their ambitious sustainability targets," says Roos.

In 2023, Siegfried celebrates its 150th anniversary. Management's goal for the company is to continue to operate successfully for the next 150 years. One thing is clear: this will not be possible without a focus on sustainable action.

Thorsten Schüller, CHEManager

"Investments Always Pay Off"

CSO Jürgen Roos on Opportunities and Limits of Sustainability

CHEManager: How do you improve the environmental footprint of your production processes at Siegfried?

Jürgen Roos: We prioritize our sustainability efforts based on environmental impact. For example, we experiment with alternatives to harmful chemicals. Or we fundamentally redesign a manufacturing process by using more creative and innovative chemistry. This includes bio-transformations, in which enzymes catalyze highly selective reactions.

How much sustainability is possible? Where are the limits?

J. Roos: To give you an example: With our expertise in process optimization, we have reduced the number of process steps in the production of one of our APIs from 17 to 10, saving large amounts of solvent, energy and raw materials, and reducing process waste. The limit is often time: this research effort took over six years and cost nearly 2 million dollar.

What are the biggest challenges? And do investments in sustainability outweigh the financial benefits that you ultimately gain from them?

J. Roos: Sustainability and operational efficiency go hand in hand and investments always pay off over the long run. However, the optimization of production processes is resource and manpower intensive, one reason being that a new process requires a new regulatory approval. More regulatory flexibility would incentivize companies to revisit their production processes to make them more sustainable.

Thorsten Schüller

Jürgen Roos, Siegfried