# DEFENSIVE CHAIN

TEXT **ANNETTE LOCHER**

The use of therapeutic proteins is spreading worldwide. While these active ingredients promise to bring about major medical advances, some have the problem that they are quickly broken down in the human body before they can release their full therapeutic effect. This might be offset by chains of polyethylene glycol, which Evonik manufactures at pharmaceutical quality


All in green: Protective clothing that is impermeable to gases is obligatory for Evonik chemist Marius Mewald whenever he works with the raw material ethylene oxide

Marius Mewald loves to solve difficult tasks. He has a doctorate in chemistry, and his job at one of Evonik's research departments is to fulfill customers' wishes. Mewald, 36, has been working at the Exclusive Synthesis unit of Evonik's Health Care business line since 2015. The pharmaceutical customers that he serves, from startups to major corporations, all have very individual needs. In most cases, they want to launch a new drug on the market and are looking for a partner who can reliably produce the active pharmaceutical ingredient or a precursor of it, at the highest possible quality.

This desire often results in a research assignment for project managers like Mewald. "We have the know-how for advanced technologies that can synthesize certain classes of molecules," he says. "But each molecule needs its own process." It's Mewald's job—and his passion—to devise this process and later hand it over to his colleagues in the production department.

However, Mewald's daily work has changed considerably lately: His laboratory has evolved into a production facility. That's because a large-scale plant for the innovative technology that was tested and developed here doesn't yet exist. "Instead of trying out new things, we now have to do the same things the same way each and every day," says Mewald. "And we have to do this for months on end." It's clear that he doesn't really like this state of affairs, but he nevertheless seems satisfied and even proud. After all, this project enabled the team under his leadership to make it to the final round of the Evonik Innovation Award competition in 2019.

What was especially notable about the team's achievement is that the experts took just a few years to develop a technology for the production of polyethylene glycol (PEG) for pharmaceutical applications, to set up a pilot plant, and to land its first major contract from a customer. These long-chain molecules, which are made up of ethylene oxide building blocks, can be used to modify delicate active ingredients in such a way that they remain intact in the body long enough to achieve the desired therapeutic effect.

"Although many companies can manufacture PEGs, only a handful of them worldwide can produce PEGs for pharmaceutical use," says Mewald. Among other things, the trick is to create chains of molecules—polymers—with lengths that hardly vary and that always have specific chemical groups at both of their ends. "Any deviation can reduce the effectiveness of a →

drug," says Mewald. At the moment, his main task is to ensure continuity within the process and thus guarantee that product quality is always consistent.

The pharmaceutical industry's demand for PEGs is steadily growing, because more and more active ingredients are now being produced with the help of biotechnology. Therapeutic proteins such as small peptides, enzymes, and antibodies have, in recent years, filled the development pipelines of pharmaceutical and biotech companies. These proteins make up a big part of what are referred to as the "biologicals." In 2001, one out of five candidate active ingredients was such a biological. This figure has now risen to about one out of three.

Biologicals have the advantage that they mostly have a very specific action and are highly effective. In many cases, they are designed to treat severe illnesses such as cancer, infections, and autoimmune disorders.

The one-liter glass reactor at the Evonik lab in Hanau is used for tests

However, the human body tries to make foreign proteins "harmless" as quickly as possible, because they might be a poison or a harmful decomposition product. That's why the immune system often reacts to the therapeutic protein and renders it ineffective. In other cases, the protein is attacked by enzymes that take it apart. Moreover, small proteins are fairly quickly broken down by the kidneys.

As a result, modern pharmaceutical active ingredients of this type require assistance. One means of extending their retention time in the body is called PEGylation. In this process, long PEG chains are attached to the active ingredient. They make the molecule more voluminous as a whole, and thus prevent it from being filtered out of the blood plasma and later broken down in the kidneys. In addition, they shield the protein component against enzymes and the immune system.

This effect can be especially beneficial to patients. In 2000, for example, interferons for the treatment of chronic hepatitis C still had to be injected daily, because half of the administered interferon was broken down by the kidneys within around four hours. Daily injections were the only way to achieve the desired effect—the stimulation of the immune system against the hepatitis virus. The daily visit to the doctor was a big strain for the patients as well as for the healthcare system.

## ESSENTIAL MEDICINES

This changed in 2000 and 2002 when the first PEGylated interferons were launched on the market: peginterferon alfa-2b and peginterferon alfa-2a. Their concentration in the blood drops off ten times slower. Since then, patients have only had to go to the doctor once a week. Peginterferons quickly dominated the market. Since 2013, they have been on the Model List of Essential Medicines published by the World Health Organization (WHO).

Pegfilgrastim, which helps to prevent life-threatening infections from occurring during chemotherapy, was the first PEGylated drug to achieve blockbuster status, generating sales of over US$1 billion. By 2019, sales had already risen to over US$3 billion. This therapeutic agent had also originally existed only in an unPEGylated form that had to be administered daily for ten days after each chemotherapy cycle. Thanks to PEGylation, only a single injection is now needed on the first day after chemotherapy.

Markus Mewald (right) and Michael Reuter, an employee from active ingredient production, check the water content of the reaction solution

According to scientists such as the pharmacologist Dr. Bernd Meibohm, PEG modification is a real breakthrough for transporting active ingredients within the body. "What's special about PEGylation is that it changes the physical-chemical properties of therapeutic molecules without diminishing their effectiveness," says Meibohm, who is a professor at the College of Pharmacy of the University of Tennessee Health Science Center. Meibohm specializes in pharmacokinetics and pharmacodynamics, which study the chronological behavior of active ingredients in the body, and in the development of therapeutic proteins.

Meibohm, a German pharmacologist, is also familiar with other methods for modifying active ingredients, such as by combining them with an albumin protein. However, PEGylation opens up more possibilities for fine tuning. "There's an optimal PEG for every active ingredient," says Meibohm. It's possible to modify the chain length, for example, or the branching of a molecule. "And the careful identification of this PEG pays off," he adds.

Once the right PEG has been determined for a specific active ingredient, a manufacturer has to be found for the product. For supply security, in many cases at least two manufacturers are desired, preferably on different continents. "It would be much too risky if a crucial medication was dependent on a single production site," explains Mewald, the research scientist from Evonik. The coronavirus pandemic has shown how easily global supply chains can be disrupted. →

## "We're one of the top three contract manufacturing organizations in the pharmaceutical sector"

Three questions for Dr. Andreas Meudt, head of the Exclusive Synthesis product line at Evonik

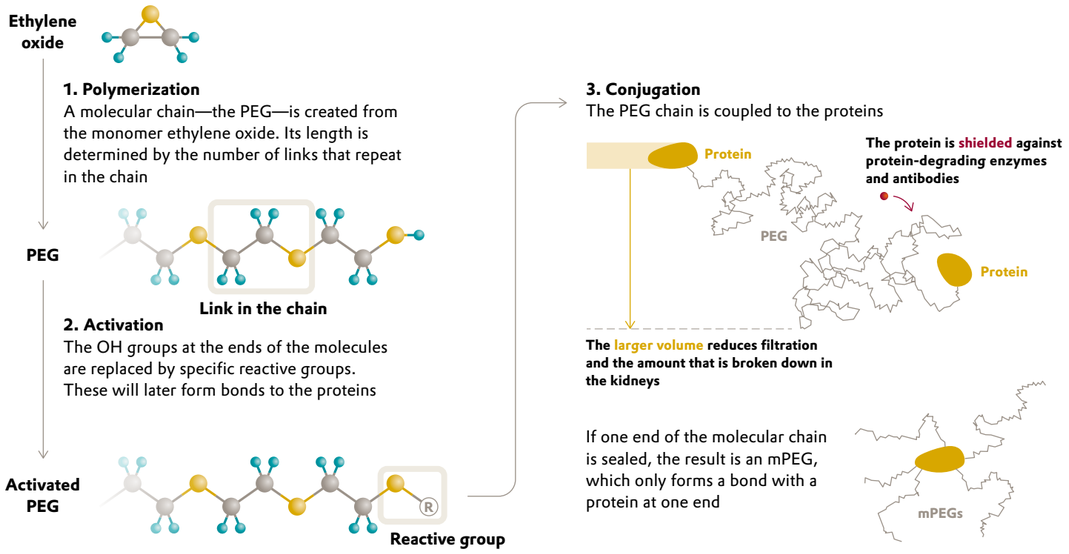
**Why do even big pharmaceutical firms have active ingredients produced by third parties?**
Until around ten years ago, major pharmaceutical firms in particular produced their own active ingredients and drugs. Many are now focusing on their core competencies: the development of new active ingredients and marketing. In addition, more and more specialized technologies are now needed to manufacture these actives and not every company has these capabilities.

**How big is the base of potential customers?**
Worldwide, over 4,000 companies work on the development of new drugs. Many of these companies are university spinoffs that don't have their own production capacities. In terms of value, almost half of the active ingredients produced worldwide are now made by contract manufacturing organizations (CMOs).

**What is Evonik's role in this market?**
We've been a CMO for the pharmaceutical industry for about 25 years and are now among the top three companies in this field worldwide. What differentiates us is our command of very challenging technologies. These include active ingredients known as HPAPIs that have a huge effect in the body, even in small amounts. Many anti-cancer drugs belong to this class. Handling such ingredients requires special safety precautions. We are set up for this work and have the world's biggest production capacity for HPAPIs.

## Supersizing

How PEGylation gives proteins more volume




Evonik began to investigate pharmaceutical PEGs in 2015. Back then, the PEGylation of active ingredients was beginning to turn into an attractive growth market and the company had all of the required skills, although they were distributed among a variety of business units.

The specialty chemicals company had, for decades, been producing PEGs and other polyethers on an industrial scale for a variety of applications. Among other things, they are used as components of foam stabilizers and emulsifiers. That's why Evonik is familiar with the extremely reactive, toxic starting material: ethylene oxide. "Once ten ethylene oxide building blocks are connected into a chain, they are no longer hazardous," says Mewald. However, a manufacturer of PEGs also has to know how to handle the individual molecules of the monomer—and has to make sure that the finished product doesn't contain even the slightest trace of ethylene oxide.

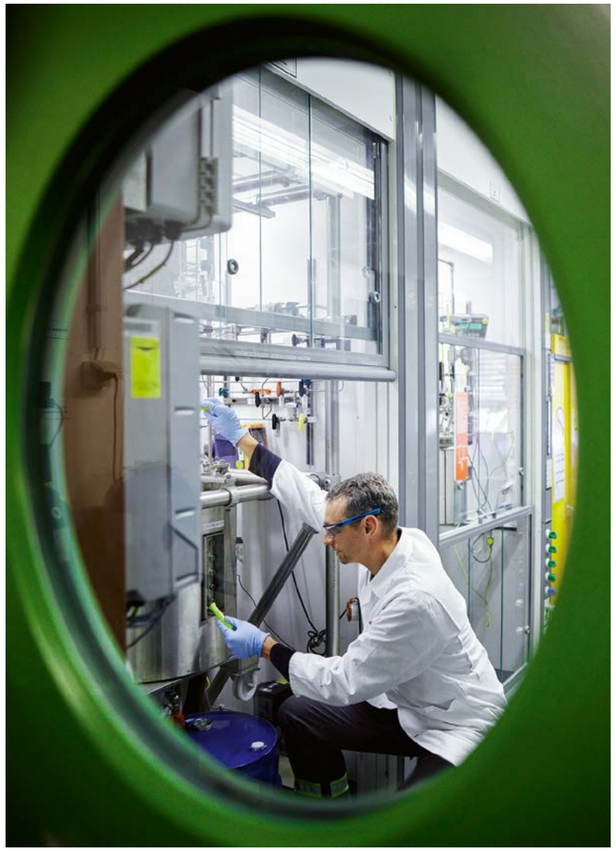
### KNOW-HOW FROM A VARIETY OF AREAS

In addition, Evonik's Exclusive Synthesis product line has long been working successfully as a contract manufacturing organization (CMO) for the pharmaceutical industry and is one of the world's leading suppliers in this field (see the short interview on page 51). Dr. Dietmar Reichert, who is responsible for technical marketing at the Exclusive Synthesis product line of the Health Care business line, says that there are two reasons for this: "We support our customers as a strategic partner and we set ourselves apart with technologies that only a few companies in the world are proficient in."

Some of these technologies require extremely specialized knowledge and experience—sometimes from completely different units. "In the case of PEGs, you have to master the entire chain: the safe handling of ethylene oxide, the development of a specific PEG, and its reproducible production in pharmaceutical quality," says Reichert.

As welcome as the first customer inquiry was, it posed a considerable challenge for Mewald's research team. "It propelled us directly into the champions league," Mewald says. The customer wanted a very big PEG. "However, the longer it is, the more difficult it becomes," says Mewald. That's because the longer a chain is, the greater the possible variability, which is extremely undesirable.

The PEG from Evonik is designed for an active ingredient that will be used against several illnesses that cannot be treated yet. It is still in the clinical development phase. It took the team a number of months to create



The 50-liter reactor is being filled with starting material. Michael Reuter checks the contents

the first acceptable sample, Mewald recalls. Although it wasn't perfect yet, the customer agreed to take part in a joint learning process. The facility was modified several times until the process and the setup were correct.

The second production series is now being manufactured in the pilot plant in Mewald's laboratory. The 50-liter reactor is located in a fume hood. All of the ingredients are automatically measured out through closed lines so that any contact with the ethylene oxide is prevented. Nothing can be seen but stainless steel and lots of sensors. "You're not even allowed to get a marker pen too close to the sensors, because they would react to the solvent," says Mewald. The process developers are now also being supported by colleagues from active ingredient production. This enables production to run in two shifts on six days of the week.

The PEG is subsequently processed further in an active ingredient production facility. This processing is done in accordance with the conditions of good manufacturing practice (GMP) required by the pharmaceutical industry. Finally, an activation step is required so that the molecule can react with the drug's active ingredient. The molecule should bond to a specific place on the active ingredient. To do this, the ends of the PEG molecule are modified. "You can compare the activation step to fitting a trailer coupling to a car," explains Mewald. Other PEGs—called mPEGs (methoxypolyethylene glycols)—are basically sealed at one end and can only be activated at the other end.

The final step, the connection of the PEG to the active ingredient, is carried out in this case by the manufacturer of the active ingredient. The activated PEG can be easily shipped in powder form—to the other side of the world, if necessary. In the future, Evonik may produce not only PEGs and activated PEGs but also PEGylated active ingredients. "We want to extend our product range in this direction," says Reichert.

The company is currently planning a commercial facility in order to expand its PEG production capacity. Once that is done, the reactor and the lab will again be free for what Marius Mewald loves and can only do on the side at the moment—developing processes for other PEG variants, of which there are many.

**Annette Locher** has a degree in biology and has worked for Evonik's communications department since 2012. She mainly writes about healthcare, nutrition, and sustainability