Rabbit Milk, Hamster Cells & Singing Quails

The fight for a life-saving drug

Erik van Uden
Maryze Schoneveld van der Linde

Erik van Uden witnessed how patients with a rare disease – Pompe disease – had to fight for years before they gained access to a life-saving medicine. As head of the communications department at the Dutch Muscular Dystrophy Association, he was involved in that struggle. He saw just how much influence patients can have when they organise themselves and take the right action at the right time.

Previously, Erik worked in healthcare, development cooperation and education. He studied Dutch and Cultural Anthropology at Utrecht University.

Maryze Schoneveld van der Linde was diagnosed with Pompe disease, a rare and serious muscular and metabolic disorder, at the age of eight. During her studies, she became dependent on a ventilator and a wheelchair. She did not let that stop her. She created and seized opportunities as soon as they arose. Maryze obtained her Master's degree in cultural anthropology at Leiden University. She held two board positions, including at the International Pompe Association, of which she was a co-founder. In both roles, she was in a position to improve the situation of her fellow sufferers, and she did so wherever she could. In 2007, she started her own business, drawing on the knowledge and expertise she had built up over the years. A large part of her free time and energy was devoted to securing medication, ventilators and wheelchairs for fellow patients worldwide.

For her tireless dedication to people with rare diseases, she was awarded the Dutch royal honour of Knight in the Order of Orange-Nassau, the Rare Angel Award and the Leadership Award from UILDM, the Italian muscular dystrophy association. She passed away on 14 May 2025. The English translation of this book is made in her honor, a year after her passing.

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FOREWORD

In 2013, the first drug for Pompe disease, a hereditary and often fatal muscle disorder, came onto the market. It was the culmination of a long journey that began in the early 1930s with a discovery by the Dutch physician Joannes Pompe. Over time, hundreds of researchers, pharmaceutical scientists, and above all, patients and their parents from around the world contributed to its development.

On October 28, 2024, *Rabbit Milk, Hamster Cells & Singing Quails* was published, a book that provides insight into the course of this extraordinary journey. The first description of the disease, the unraveling of its mechanism, the early, failed attempts to treat the condition, the search for a pharmaceutical company that dared to bring a drug for a rare condition to market, the unique production of an enzyme—including in genetically modified rabbits—and finally the battle for reimbursement of the expensive medication: it's all detailed in the book.

I wrote it together with Maryze Schoneveld van der Linde. She was a Pompe patient and closely involved in the drug's development process. Maryze believed it was important for patients to be aware of their own strength and potential. Her motto was: don't wait around, take action. Joining forces with other patients, researchers, and pharmaceutical companies; encouraging people; and breaking down barriers where necessary. She believed this applied not only to Pompe disease but to all diseases. Especially to rare conditions, which generally languish at the bottom of the priority list for funders, researchers, manufacturers, and healthcare authorities. Not just in the Netherlands, but all over the world.

That is why Maryze felt it was so important for people around the world to learn about the story of the determined Pompe patients. And that is why she was so eager to see an English-language version of our book published. Shortly after the Dutch edition was published, she had already begun working on it, spurred on by the many requests from abroad. She was unable to finish her work. On May 14, 2025, she passed away from the effects of the disease. With this translation, we are fulfilling her heartfelt and final wish.

Thanks to the efforts of Els Wiegant, editor-in-chief of the Dutch edition of the book, and with the help of the DeepL translation program, the translation has been completed. This also highlights the limitations of the English text. As a result, the story is told from a Dutch perspective. English quotations were translated for the Dutch book and then back-translated for this edition, which undoubtedly did not always yield the original English quotation. Furthermore, the text was not reviewed by an experienced medical translator, so errors may have remained uncorrected. However, the text was reviewed by a native speaker, who rated the quality of the translation as very good. This pragmatic approach allows us to offer the English version for free (online, in PDF format).

I am convinced that this translation fills a need: those who contributed to the book can now read it, as can anyone interested in the complex world of drug development or in patient empowerment. I am very happy that we were able to fulfill Maryze's last wish exactly one year after her passing, and I invite you to read the story she wanted to tell.

Erik van Uden

Also on behalf of:
Els Wiegant Frits Poiesz Maryze's family Schoneveld van der Linde

The Dutch edition is published by Poiesz Uitgevers and is available at regular (online) bookstores and via:
https://poieszuitgevers.nl/konijnenmelk-hamstercellen-en-zingende-kwartels/

If you don't hope for the unexpected, you won't find it,
because it will then be untraceable and out of reach.

Heraclitus

CONTENT

PRELUDE

EXCITEMENT IN DIEMEN

On September 21, 2012, the Health Insurance Board in Diemen will hold a public hearing of the Package Advisory Committee. That sounds boring, and normally it is. A handful of committee members, watched by a handful of spectators, will spend two hours discussing medical policy issues. The question is often whether or not a new medicine will be included in the basic insurance package.

This Friday is no different. But unlike previous meetings, the courtroom is now bursting at the seams. A second room has been hastily prepared with a large video screen so that all visitors can follow the deliberations. The large number of wheelchair users is striking. Their faces are tense. Angry posters hang in the room. "I am too expensive and will be sentenced to death," and other such slogans.

The meeting is the culmination of a development that began some eighty years earlier in the dissection room of an Amsterdam hospital by a pathologist: Joannes Pompe. Today is make or break for doctors, researchers, industry, and especially for the more than one hundred people in the Netherlands with Pompe disease. The journalists have their notebooks on their laps, the cameraman from *NOS-Journaal* is looking for the best place for his tripod. The chair nervously sips a glass of water and opens the meeting.

We, the authors of this book, were there and each had our own role: as a Pompe patient, Maryze talked during the session about her experiences with the new drug, while Erik was responsible for communication on

behalf of the patient association. After the meeting, we looked at each other in amazement. "You could write a book about this," we said to each other.
That was it, until we met again ten years later and reminisced. Once again, we said, "What if we wrote a book about it? We know what happened, we have access to archives, we have the phone numbers and email addresses of all the key players. Why not? It's a story that needs to be told."
We thought it would be a piece of cake for us, because we had been right on top of it all that time. Maybe we would interview a few people to flesh it out, we said, and do some more research in the archives... That turned out to be a serious misconception, because what unfolded before our eyes was a complicated history that took place in different parts of the world, with ever-changing key players and great successes, but also serious setbacks. What was striking was the enthusiasm with which the people we spoke to told their stories, sometimes even with a hint of nostalgia for the close collaboration between parties with very different cultures but a shared mission. It was as if it were 'the fellowship of the ring'.
This eventful history shows the barriers to the development of drugs for rare diseases, the ethical dilemmas posed by new biotechnology, and the opportunities patients have to take control of their own destiny.
No specific biological knowledge or familiarity with the world of pharmacy is required to understand the story. There are a few less common words that appear regularly in the text: glycogen, lysosome, M6P. They are all explained. If necessary, consider them characters, because that is more or less what they are. And for those who are afraid of getting lost, the most important concepts are explained in sidebars. Even when we mention a person, we remind you who they are when necessary. At the back of the book, there is a list of names, a list of abbreviations, a timeline, and a bibliography.

In the book, we recount a series of events with wonder, sometimes admiration, without taking sides—except for those of the patients, whose patience was tested to the limit and who therefore regularly took action.

A few comments about the language and the rendering of names. People from all over the world were interviewed. We have translated quotes from interviews, as well as from English articles, into Dutch. Flemish has been left unchanged, unless comprehensibility for Dutch speakers was at stake. Many institutions and organizations have changed their names in the course of the story. To prevent the reader from losing track, we have used the same, most appropriate designation as much as possible. For example, Erasmus MC also stands for the Sophia Children's Hospital, Dijkzigt Hospital, and Academic Hospital Rotterdam, and we use the old name for the Dutch Healthcare Institute: the College for Health Insurance.
That concludes the explanation. We begin the story in Scotland, as the young O'Donnell family is driving to Edinburgh.

Maryze Schoneveld van der Linde
Erik van Uden

1
CALUM
1993

Scottish Kevin O'Donnell and his wife Elaine have a son, Calum, in 1993. He seems to be a healthy baby. He may have colds a little too often, but what do you know about that as new parents? Isn't that just part of being a baby? Not much later, those colds turn out to be a sign of impending doom. Father Kevin kept a blog about the events that followed. An excerpt from it:

"Friday, May 28, 1993, was one of the happiest days of my life. I drove across the border from England to Scotland to a new home in Edinburgh, the city where I had always wanted to live, and to my dream job: running my own microbiology lab. Best of all, I had my wife Elaine and our two-month-old son, Calum, with me in the car. Life was sweet.

The first few months went smoothly. I was busy getting settled in, while Elaine went house hunting with Calum. Calum seemed to be catching colds more and more often. He coughed and sneezed, and it took him longer and longer to recover. But it never occurred to me that anything serious was wrong. Not even when Calum, at six months old, ended up in the hospital with pneumonia. In hindsight, we were incredibly naive, but what do you expect with your first child?

An X-ray showed that his heart was enlarged, but even then we said to each other: He just won't play any rough sports. He'll probably be just as much of a nerd as his father. But in the hospital, the alarm bells went

off. They tested his blood; a routine test, they said, nothing to worry about—and so we didn't. We found a house, close to a park and a school (absolutely perfect), and fixed it up so we could move in.
Then came the news that shattered our world. At the hospital, they told us that the blood test had shown that Calum had Pompe disease. And it was incurable. And fatal. Children with this disease usually don't make it past their first birthday. We couldn't believe it. There had to be some terrible mistake. It couldn't be true that our beautiful child was going to die. And what's more, how could it be an untreatable disease? That was unheard of. Did those doctors even know what was going on in the medical world?
In the weeks that followed, we frantically gathered all the information we could find about this disease, and it didn't look good. Everything confirmed what they had told us at the hospital. There was no hope. Calum's condition deteriorated rapidly and he had to return to Sick Children's Hospital in Edinburgh, where he died on November 18, 1993, just two weeks after his diagnosis.
We had a Buddhist saying engraved on his gravestone: 'The field bindweed that blooms for only an hour is no different in essence from the pine tree that lives for a thousand years.' We still think of him every day."[1]

Calum died of what has come to be known as the classic form of Pompe disease. He had all the symptoms: an enlarged heart, rapidly deteriorating breathing, and weak muscles. Like almost all of his fellow sufferers, he did not live to see his first birthday. It is a fixed, recurring pattern.
Calum's death does not mean that this merciless disease has disappeared from Kevin O'Donnell's life. The grief that has turned his life upside down is looking for an outlet. He wants to know everything about the condition that proved fatal to his son. And whether a cure can be developed, unfortunately not for Calum, but for all those children who will be born with this deadly disease. Although Kevin's daily life is mainly concerned with food crops, as a molecular biologist he is perfectly capable of assessing the value of medical-scientific articles.
In the months that follow, he discovers articles in journals that give him hope. Apparently, there are researchers in the world who have taken on this very rare condition, who are working to unravel the mechanism of the disease, and who have even developed a plausible theory about a possible therapy. These researchers are located in Rotterdam. Kevin picks up the phone. He wants to know more.[2]

2
RARE

This story is about the development of a drug for a very rare and very serious condition: Pompe disease, and especially about the role that patients have played in this. In the Netherlands, there are about 145 people with this condition, and worldwide there may be as many as 5,000.[3] Compared to 'major' diseases, this is an extremely small number, and it is precisely this rarity that brings its own set of problems. There are quite a few misconceptions about rare diseases. That is why we will briefly discuss this before delving into the history of Pompe.

The main misconception is that 'minor' diseases are also a minor problem within healthcare when compared to diabetes, cardiovascular disease, cancer, rheumatism, or lung disease. But that is not true. The Dutch College of General Practitioners has calculated that a general practitioner's practice will see around 100 to 150 patients with a rare condition. In total, this amounts to an estimated one million people in the Netherlands, which is the same number as diabetes patients.[4] And there are 7,000 rare diseases described. Although each disease affects only a small group of patients, together they form a large group; rare diseases are far from rare. The chance that you or someone close to you will be affected is considerable.

As with Pompe disease, these are complex and debilitating diseases, often progressive and usually hereditary. The age at which the first symptoms appear varies from one condition to another. Sometimes it is clear at birth that something is wrong, while with other conditions the first symptoms only appear later in life. In practice, all conceivable variations occur. For example, Pompe disease can manifest itself in infants, but the first symptoms may just as well appear during puberty or in a 60-year-old. Many of these diseases are fatal and, with a few exceptions, there is no treatment available.

The personal and social impact is therefore enormous. As a patient with a rare disorder, you live with the knowledge that there is no cure and that there may never be one. You know that your health—or that of your child—will continue to deteriorate, although it is not clear how quickly. Because these are complex conditions, you will have to deal with a whole host of doctors and care providers: pulmonologists, internists, neurologists, cardiologists, rehabilitation specialists, dieticians, speech therapists, and physical therapists. You will learn what healthcare has to offer, but more importantly, what it does not have to offer. Transportation, school, housing, work: all aspects of social life present challenges. And because your disease is probably hereditary, you may have already passed on the defective gene to your children and grandchildren without knowing it. That makes it even more painful. The diagnosis of a chronic condition is already a blow, but if that condition is also rare, it is double misfortune.

What obstacles does the rarity of a disease entail? It starts with the diagnosis. Especially when the symptoms manifest themselves insidiously, it can take a long time before it becomes clear what disease is involved. We will encounter this many times in this book. Often, an incorrect diagnosis is made or simply no suitable label can be found for the symptoms. In medical jargon, this is called MUS: medically unexplained symptoms. The result: the *patient journey* degenerates into a desperate search for a diagnosis. The journey takes the patient from pulmonologist to neurologist to ENT specialist, and often includes a visit to a psychiatrist's office. The diagnostic delay, the time between the first symptoms and the diagnosis, can easily span years in the case of rare diseases. Pompe disease is no different[5], unless it is the most severe variant, as in Calum's case.

After the diagnosis, the questions arise: what kind of disease is this? Where can I find reliable information? Is it a hereditary condition? Until the mid-1990s, information material on rare diseases was hardly avail-

able. The advent of the internet solved that problem, but it was replaced by another: now there is a flood of information, sometimes of dubious quality.

Before the rise of social media, it was almost impossible to find fellow sufferers. As a diabetes patient, you have a good chance of finding someone in your neighborhood who has the same condition, but with Pompe disease, you will almost certainly find no one in your immediate vicinity. Unless, of course, it is a family member, such as a brother or sister.

Finding the right doctor, or better yet, an experienced team of healthcare providers, is just as big a challenge. Which doctor knows the best way to treat symptoms such as shortness of breath, insomnia, fatigue, swallowing problems, or declining mobility—just to name a few of the possible symptoms? Your family doctor does their best, but they are not familiar with your disease. The same applies to the specialists at your local hospital. Even at the academic hospital, the specialist is sometimes left empty-handed, although it must be said that great progress has been made in the care of rare diseases in recent decades.

What patients want most is a medicine that eliminates the causes or at least slows down the disease. In other words, research into a therapy. There is still a major barrier to this: a lack of research into rare diseases and, as a result, stagnation in the development of therapies. After all, what researcher feels called to a career in rare diseases? For young, ambitious doctors and biologists, a career in cardiology or oncology seems far more preferable than a postdoctoral position in rare disease research. Major diseases confer greater status and, most importantly, much more funding is available for medical research in those areas.

Even if this hurdle is overcome and the researcher emerges triumphantly from the lab after many years of hard work with a blueprint for an effective drug, there is usually no pharmaceutical company willing to get involved. Take Pompe disease, for example. With 145 patients in the Netherlands and a few thousand worldwide, it is not a market. There is no money to be made.

Now imagine that there is a manufacturer willing to get involved, on condition, of course, that it can keep its shareholders happy, because enough money has to be made. Researchers get to work, production facilities are set up, tests are carried out, studies are conducted on test subjects, and after five to ten years, the time has come: the drug can be launched on the market. How much will that cost per person? 100,000, 200,000 euros, or even more? Will the government reimburse that? And suppose a competitor appears on the market offering the same drug? Then the market becomes even smaller. No one is going to take that risk. Medicines for rare diseases? Mission impossible.

3
WITH A CARAVAN TO SWEDEN
1965

A muscle disease. Nothing can be done. Just learn to live with it. That's what Ysbrand Poortman was told in 1965 when a doctor examined his daughter and made this diagnosis. But he's not the type of man to give up. A medicine must be found, a medicine for his daughter's rare muscle disease. He won't rest until he finds it. The quest he embarks on is typical of those with rare conditions.

"I married young," he says, "and we soon had our first child, Simone. Around her first birthday, we became suspicious. She could stand up and even take a few steps, but her legs kept giving way."

Poortman consulted his family doctor, who considered him an 'overprotective parent'. After much insistence, a neurologist examined Simone's muscle tissue and concluded that she had 'a nasty muscle disease'. He did not specify exactly which one. "Otherwise, we would have started searching in libraries and worrying ourselves sick. A professor in Amsterdam finally made the diagnosis: Werdnig-Hoffmann, or SMA type 1. Like Pompe, it is a serious, progressive muscle disease. We didn't have to come back."

Simone was already two years old at the time, and the prognosis was that she had six months to live at most, Ysbrand continues. "But that didn't match her condition. Apart from walking, she was developing well."

Ysbrand continued his search and, after much wandering, ended up with a specialist in Paris. "That's where the crème de la crème of muscle disease research was based. He examined Simone, looked at her muscle tissue, and asked us to come back in three days. Our next meeting was not in a consultation room, but in a lecture hall, an arena, with dozens of curious students' heads above us. There we were told that it was Wohlfart-Kugelberg-Welander, SMA type 3, a disease that had only recently been described for the first time by the three Swedish namesakes."

Poortman decided not to leave it at that. He wanted absolute certainty and called the leading expert, Professor Wohlfart in Sweden. He was invited to visit. "Before the spring break, I bought a second-hand caravan, the smallest model Kip caravan: the Kuiken (the chick). We set off for Lund in Sweden. It was still the middle of winter there. We got caught in a storm and the snow was metres high around our little chick caravan. When we arrived at Dr. Wohlfart's house after a hellish journey, it turned out that he had died a few days earlier. Fortunately, our trip was not in vain, because we were welcomed by the sympathetic Dr. Ingrid Gamstorp, who confirmed the French diagnosis."

With that, the first barrier was overcome: Simone had a definitive diagnosis. But were there other patients like her in the Netherlands, and what was the right treatment for her? No doctor could say. And just as important: where were the researchers, and was there any prospect of a cure? Poortman sought answers.

Not long after, the current affairs program *Brandpunt* aired a segment on mysterious muscle disorders. A mother sat at the table and talked about her son, who was becoming increasingly paralyzed. Poortman responded immediately. "Like many Dutch people, I saw the broadcast with Frieda Huizinga in 1967. That same evening, I wrote her a letter proposing that we meet soon."

A week later, he is sitting across the table from her. For him, research and treatment are the most important things. "Through what I had experienced with Simone, I had seen how little was known about muscle diseases, how little knowledge was exchanged nationally and internationally. Time and again, doctors told you to resign yourself to your fate and accept your lot. Well, you can ask a lot of me, but not that."

Frieda and Ysbrand were at the cradle of the Dutch Muscular Diseases Association (Vereniging Spierziekten Nederland, VSN[6]), which was founded that same year.[7] "I am a biologist. The advantage of that is that I know a little bit about everything that lives. I could understand to some extent what the doctors were talking about, yet initially I was not seen as a discussion partner at all."

Poortman was one of the first to understand that rare diseases require a fundamentally different approach than common diseases. The establishment of the VSN serves several purposes. One of them is to make patients findable for researchers. That is, of course, an absolute prerequisite for research. Hospital registries offer little solace. The extremely scarce patients must be manually tracked down in the filing cabinets of hundreds of administrations.

The membership administration of 'his' VSN should offer a solution. From the very beginning, in addition to members' address details, the following information has also been recorded: the type of muscle disease, the date of birth, location and time of diagnosis and by which doctor, plus all kinds of other information that may be important for scientific research. At that time, there was no legislation to prevent this and patients were eager to participate in research.

In this form, the administration was intended to function as a kind of honey pot for researchers. And that is exactly what it did. Over time, the database has helped countless researchers. And not only researchers. In the years before the internet was invented, patients with the same muscle disease were also able to connect with each other through this membership administration. There was a great need for this as well.

A second part of Poortman's strategy is to seek expansion. Mindful of the saying, "Alone you go faster, together you go further," he builds partnerships between patients. This began in the Netherlands in 1967 with the founding of the VSN, which anyone with any muscle disease—there are an estimated 600—can join. Twelve years later, the VSOP, the national umbrella organization for rare and genetic disorders, was established. An alliance of European patient associations, the European Alliance of Neuromuscular Disorders Associations (EAMDA), and a global alliance, WAMDA, were formed.

The administration was to act as a kind of honeypot for researchers.

And that was just the beginning. Poortman brought together not only patients, but also doctors and researchers in the field of muscular diseases. He established a foundation in the Netherlands to, as he put it, lure researchers 'out of their foxholes'. Of course, this also had to be tackled internationally. This led to the creation of the European Neuromuscular Centre (ENMC), which for decades has been bringing together specialists from all over the world for weekend sessions on specific issues and clinical pictures. They share their research results, present their ideas and insights, and make agreements about follow-up research.

Thanks to these and other initiatives, a global network of patients and researchers has grown over time, maintaining contacts, exchanging information, taking initiatives, and easily finding each other. It is a fruitful strategy, as the example of Pompe will show.

Scientific research requires not only researchers and patients, but also money. A lot of money. The existence of a large fund in the Netherlands for financing research into muscle disease is an indirect consequence of the major outbreak of the polio virus in 1956. That year, there were more than two thousand victims, of whom about two hundred suffered from severe respiratory problems.[8] The need was great. The newspapers published frightening photos of patients who were completely paralyzed and lying in large metal cylinders: ventilators. A fund was set up to assist these patients and their families. Beatrix, the then Crown Princess, was asked to be its patron. That was the start of the Princess Beatrix Fund, which was renamed the Princess Beatrix Muscle Fund a few years ago.[9] Thanks to the introduction of the Salk vaccine, the number of polio infections decreased dramatically from 1956 onwards. The fund's board wondered whether the sharp decline in the number of patients still justified continuing its activities. Instead of dissolving the fund, it was decided to broaden its objective to include all muscle diseases. Pompe research, among others, has benefited greatly from this.

A fourth party is needed to develop a therapy: a pharmaceutical company willing to invest in a so-called orphan drug, a medicine for a rare

disease such as Pompe. No pharmaceutical company in the 1980s and 1990s was interested in this: large investments, high risks, and no money to be made. The pharmaceutical hurdle is the most difficult obstacle to overcome for rare diseases. Poortman also realizes that this will be a difficult task, but nothing will stop him. If necessary, we will set up a pharmaceutical company ourselves, he proclaims. He means it. And he would not be the only one toying with this idea.

Sometimes you simply need luck to make progress in science. This was also the case here. In the 1930s, medical research still focused mainly on common diseases: tuberculosis, for example, and other infectious diseases, heart disease, and mental illness, but also diabetes.[10] It has been known since the 19th century that diabetes is caused by a lack of insulin. In 1921, researchers succeeded in treating patients with insulin prepared from the pancreas of dogs and calves.[11] Everything related to the processing of sugars in the body therefore aroused interest, because exactly how metabolism works in cells remained a mystery. This gave a boost to research into a specific group of rare metabolic diseases. One publication after another appeared with descriptions of new clinical pictures. That was the situation when a young pathologist in training in Amsterdam made a remarkable discovery.

4
THE GIRL WITH THE BIG HEART
1930 - 1945

It is December 27, 1930, a cold, drizzly day in Amsterdam. The white-tiled room is filled with the irritating smell of formalin. The young pathologist-anatomist in training, Joannes Pompe, is bent over the dissection table. On it lies the remains of a seven-month-old baby. The girl died the day before, on Boxing Day, in the clinic of Professor Snapper, one of Pompe's teachers. The baby had been admitted to the emergency room four days earlier. What had started fourteen days earlier with sneezing and coughing developed into a severe cold. She developed a fever and became increasingly short of breath. Initially, the doctors diagnosed pneumonia or, in the terminology of the day, splenopneumonia. Although the girl was blue at birth, probably due to a lack of oxygen, she had started crying immediately and had developed normally. When she was admitted to the hospital, there was no indication of a metabolic disorder. No sugar was found in her urine and her heart appeared to be of normal size.[12]

The latter turned out to be a mistake, because during the autopsy, Pompe found that the heart was no less than five times larger than normal for children of that age. At first, he finds no other abnormalities. The heart valves, vessels, and partitions all look fine. Other organs also show no abnormalities. Examination of the lungs reveals that they are severely inflamed, leaving no doubt as to the immediate cause of death. The initial

conclusion is that this is a case of unexplained, pathological enlargement of the heart.

Pompe could have left it at that. But when he examines the heart tissue under his microscope, he sees 'a network of round to elongated meshes' in which, at first glance, no muscle cells can be detected. Yet those cells are there, but they are pushed to the edges of the network. What is going on? When he tests the muscle tissue, he discovers that it is chock-full of glycogen, a substance that plays an important role in the energy metabolism of cells.

He suspects that there is a connection with the discoveries about which his teachers, Simon van Creveld and Isidore Snapper, wrote an article in 1928.[13] This also mentioned a strong accumulation of glycogen, but mainly in a severely enlarged liver. A year later, in 1929, German researcher Edgar von Gierke published a paper about an eight-year-old girl with a liver weighing 2000 grams, three times the normal weight.[14] Here too, there was a strong accumulation of glycogen.

Pompe sees a clear similarity between what he finds in the girl and the disease described by Von Gierke, with the difference that in her case it is not the liver and kidneys that are enlarged, but the heart. He therefore calls the disease cardiomegalia glycogenica. Or, in plain English, an enlargement of the heart caused by glycogen.

But he wasn't done yet. When he examined the tissue of other organs and muscles, he found large amounts of glycogen there too: the liver, kidneys, thyroid, and spleen—the substance was everywhere. The big difference was that no other organ was as abnormally enlarged as the heart. Joannes Pompe began to suspect that he was onto something special.

A year later, on November 18, 1931, Pompe gave a lecture on his findings to colleagues in Amsterdam. It was published in 1932 in the *Nederlandsch Tijdschrift voor de Geneeskunde*[15] (Dutch Journal of Medicine).

His discovery also becomes the subject of his dissertation, but he immediately encounters a problem. Where can he find other examples to prove that the girl's case is not a random, one-off abnormality, but that there is a pattern, perhaps a separate disease? In the period after his lecture in Amsterdam, only one other case occurs. Fortunately, he was

It's surprising that Pompe has uncovered so many cases yet.

able to find three well-documented older cases that supported his initial ideas about the condition.

With the knowledge we have today, it is understandable that it took so much effort to gather comparable cases. In the Netherlands, an average of one to two babies are born with this specific condition each year. In hindsight, it is rather surprising that Pompe was able to track down so many cases.

On Friday, May 15, 1936, Joannes Pompe obtained his doctorate in medicine from the University of Amsterdam. He concluded his thesis with the remark: "Nevertheless, no one will object to the view that glycogen accumulation in the liver and heart are variations of one and the same metabolic disorder, although much research will still have to be done before the numerous problems are solved."

Unfortunately, that last remark would prove to be all too true. The same cannot be said for Pompe's view that these are two variants of a single disease. That is not correct. Although they do have many parallels, the cause and the course of the disease are very different. Ten other clinical pictures would later be described in which the accumulation of glycogen plays a role[16].

Pompe was the first, but not the only one to publish on this disease at the time. In 1932, articles by German researchers G. Bischoff and W. Putschar were also published describing the same clinical picture.[17]

Pompe also discusses this in his dissertation. An American article suggests that Putschar and Bischoff were ahead of him.[18] "Wrongly so," he argues, "because I presented the story of the case at Snappers clinic at the Society meeting on November 18, 1931, while the report of that presentation appeared in the *Nederlandsch Tijdschrift voor Geneeskunde* on January 16, 1932." Putschar's publication is dated April 5, 1932, "so I beat Putschar by almost three months," Pompe triumphantly adds. The disease would therefore rightly be named after him.

Pompe did not have much time to develop further as a researcher. In 1939, he started working as a doctor at the Onze Lieve Vrouwe Gasthuis

hospital in Amsterdam. When war broke out, he was called up for military service. After the capitulation on May 15, 1940, he was able to resume his work as a doctor, but he refused to comply with the occupying forces' regulations. He arranged shelter for Jewish people in hiding and set up an illegal radio station in the laboratory animal building behind the hospital. The Germans got wind of this and on February 25, 1945, fifty men stormed the building. Radio operator Pierre Antoine Coronel was arrested and executed in the courtyard. An animal keeper and a nurse were taken away. Joannes Pompe had just come out of church at that moment. People warned him that the Germans were looking for him. When he went home to say goodbye to his wife and children, he was met by police officers and arrested.

Three weeks before liberation, on April 14, a resistance group blew up a railway bridge near Sint Pancras in North Holland. Two German soldiers were killed. A day later, the Germans selected twenty random prisoners, whom they shot near the village. Among them are Joannes Pompe and the animal caretaker, Louis Berben. A monument on the site commemorates this cruelty. Joannes Pompe rests in a war grave in the Sint Barbara cemetery in his hometown of Utrecht.[19]

EXPLAINED

ENERGY STORAGE IN CELLS

In order to function, the body needs energy. This also applies to every building block, every individual cell in the body. Each cell has its own metabolism. This is a complex process, a chain of reactions, which we will not discuss here. We will limit ourselves to a single substance in the process: glycogen. This is a form of glucose, i.e., fuel. Glycogen serves to temporarily store excess energy in cells, particularly in those cells that may suddenly need extra energy, such as muscle cells.

When that extra energy is needed, the glycogen is made available in the form of glucose. Tiny cell organs called lysosomes play an important role in this process. You can think of them as recycling factories. There are several hundred of these lysosomes in a cell. Recycling glycogen into glucose requires an enzyme, a protein called alpha-glucosidase. In this book, we refer to this enzyme as alphaGlu for convenience. When it is missing or insufficient, glycogen cannot be broken down. It continues to be produced and therefore accumulates in the cell. The supply becomes larger and larger, eventually destroying the cells. This is what happens in Pompe disease.

In addition to Pompe disease, there are about fifty other lysosomal storage disorders in which similar processes involving other proteins lead to serious health problems. Two of these disorders play a significant supporting role in this story: Gaucher disease, in which the liver and spleen can swell significantly, and Fabry disease, which can manifest itself in a whole range of serious symptoms.

5
STACKS OF SUGAR
1951 - 1973

Although doctors had been able to diagnose Pompe disease since 1936, at least in theory, there was no knowledge of the cause, let alone any treatment. And effective treatment is, after all, what patients and doctors are interested in.

In the 1930s, understanding of energy metabolism within human cells grew rapidly. The discoveries of Pompe, Snapper, Van Creveld, Bischoff, Putschar, and Von Gierke did not come out of the blue. Among other things, it had to do with the suspected link to the common disease of diabetes.

The Cori couple made an important contribution to a better understanding of cell metabolism. Gerty Radnitz[20] was the daughter of a Jewish sugar manufacturer. In 1914, she met Carl Ferdinand Cori at the medical school of the University of Prague, whom she married in 1920. The young couple emigrated to the United States shortly thereafter, fleeing rising anti-Semitism and the scarcity of just about everything in the aftermath of World War I.

The Coris focused their research on sugar metabolism. There is a perhaps apocryphal story that Gerty's father, the sugar director, said to her when she left Prague: "You are now a doctor. Come up with a therapy for this old diabetes patient." Whether true or not, the fact is that she and Carl played an important role in the development of diabetes treatment.

Their research focused on energy metabolism in cells, looking in particular at how the body produces and stores energy.[21] Based on this, in 1951 they produced a clear overview of the seven glycogen storage diseases known at the time. Von Gierke disease was number one, followed by Pompe disease in second place. In third place was the disease they themselves had first described: Cori disease.

From that moment on, the name 'Pompe disease' in scientific articles gave way in the following decades to the term glycogen storage disease type 2, or GSDII for short. This remained the case for a long time, until the 1990s, when the term 'Pompe disease' experienced a revival thanks to a flood of publications by researchers in Rotterdam.[22]

The Cori brothers' clear diagram did not mean that there was also an explanation for the origin of Pompe disease. The major breakthrough came in the 1950s with a discovery by Belgian physician Christian De Duve. He wanted to conduct further research into the effect of insulin on glucose uptake and therefore pursued a second degree in biochemistry. It was a field of study that was developing rapidly in those years. He obtained his doctorate with a thesis entitled *Glucose, Insuline et Diabète*. In 1947, he started two jobs: one at the University of Leuven and one at University College London. He focused his attention on the structure and functioning of cells. One day, while centrifuging cell material, he encountered a remarkable phenomenon. A certain metabolic enzyme seemed to have almost completely disappeared after centrifugation. The material was frozen and thawed again the next day. What happened? The missing enzyme was once again present in the cell. De Duve explained this by assuming that there must be a compartment within the cell, an organelle, in which the enzyme is enclosed by a membrane. Freezing must have damaged the membrane, releasing the enzyme that was thought to be lost. He calls this organelle, which no one has seen yet, a lysosome. The word comes from Greek: soma means body and *luein* means to loosen. That was in 1955.

A year later, Alex Novikoff[23] made these lysosomes visible using a new invention, an electron microscope.[24] This provided the proof: lysosomes were not a figment of De Duve's imagination, but really did exist. In 1974, De Duve received the Nobel Prize in Medicine for his scientific

And the missing substance appeared to be simply available on the market.

work. By then, it had been more than forty years since Joannes Pompe discovered a still unknown disease. Gradually, the mechanism behind it began to become clear.

The obvious culprit is glycogen. The question is why glycogen accumulates in the cells of some people and not in most others. The answer came in 1963 from another Belgian researcher, Henri-Géry Hers.[25] He discovered that Pompe disease is caused by a deficiency of the enzyme 'acid alpha-glucosidase', which we refer to in this book as alphaGlu for the sake of brevity. Without this substance, glycogen cannot be converted into glucose, or sugar. The reverse does happen: glucose is converted into glycogen, causing this substance to accumulate in the cells. Thanks to Hers' discovery, a cure for Pompe disease seems within reach: if you can replicate this alphaGlu and get it to flow into the muscle cells of patients, the problem is solved. But, as is often the case in science, when you solve one puzzle, you get two more in return. That is what happened here, but more on that later.

It is now becoming clear that Pompe disease has many degrees of severity. The most serious form, which manifests itself fairly soon after or even before birth, occurs when the body produces little or no alphaGlu. This is the classic or infantile form. In English: early or infantile onset.

Most Pompe patients do produce alpha-Glu in their cells, but not enough. They develop symptoms as children or even later in life, such as muscle weakness and breathing problems. The heart is not affected. In the Netherlands, five to seven people are diagnosed with this variant of Pompe disease every year, which – unsurprisingly – is referred to as the non-classical or adult variant, or in English: late onset[26]. Regardless of the age at which the diagnosis is made and the severity of the symptoms, the disease mechanism is always the same.[27]

Pompe disease therefore belongs on the list of glycogen storage diseases compiled by the Cori couple. However, there is another list in which Pompe disease appears: that of diseases in which a substance accumulates in the lysosome, known as lysosomal storage diseases. We now know of more than fifty such diseases, including Gaucher disease and Fabry disease, conditions that will appear regularly in the following chapters.

Back to De Duve. In 1964, he suggested administering the missing enzyme via an infusion to people with such a lysosomal storage disorder. This is called Enzyme Replacement Therapy, abbreviated to ERT. Perhaps this would remove the accumulated substance from the cells.

And now, the missing substance in Pompe disease, alphaGlu, is commercially available! It is prepared using yeast. In the same year, a first attempt is made on a five-month-old Pompe patient. Unfortunately, it ends in failure. The child dies within six hours of administration. A second baby showed slightly more favorable results. The heart seemed to function somewhat better and the accumulated glycogen in the liver dissolved. Unfortunately, after a rejection reaction, the child developed kidney inflammation and died six days later. Apparently, working with alfaGlu from yeast is not a good idea.

In the years that followed, attempts were made to extract the enzyme from human material, such as urine and placentas, and even from bull testicles. In 1979, a major symposium was held in the US. There, a selection of researchers gave presentations on the various aspects of enzyme replacement therapy, from purifying the enzyme and administering it to trials with humans and combining it with other forms of therapy.

It turned out to be a dead end. No matter what they tried, the results of enzyme treatment remained disappointing, both for Pompe disease and other lysosomal diseases such as Gaucher and Fabry.[28] In 1976, Belgian researcher Thierry de Barsy listed a whole series of failures with enzyme replacement therapy in his thesis.[29]

Interest in it waned and people began to experiment with a new technique: bone marrow transplantation. British pathologist John Raymond Hobbs did pioneering work in this field. In 1971, he and his team performed the first stem cell transplant on a patient with leukemia, followed by a successful bone marrow transplant in 1973.[30] In the years that followed, this technique became very popular. Experiments were carried out on all kinds of diseases, including Pompe disease. Unfortunately, there were no significant results for this disease. Another setback.

It was not until 1991 that the United States succeeded in developing an enzyme treatment for a lysosomal disease, Gaucher's disease. For patients, this was still a long way off. Nevertheless, researchers at Erasmus University in Rotterdam had already pinned their hopes on enzyme therapy at this time. They were convinced that an infusion with the right alpha-Glu could have a beneficial effect on Pompe disease. That is where the focus of research should lie; that is where the opportunities lie.

EXPLAINED

Pompe disease is a hereditary disorder that is transmitted autosomal recessively. Autosomal means that the disease is not sex-linked: it occurs in both men and women. Recessive means that the disease only manifests itself when a child has inherited the defective alpha-Glu gene from both parents. Someone with one defective and one healthy gene does not show any symptoms of the disease, but as a carrier can pass on the defective alpha-Glu gene to his or her children. In this book, we also use the term 'Pompe gene' to refer to a defective alpha-Glu gene.

If both parents are carriers of the Pompe gene but do not suffer from the disease themselves, each of their children has a 25 percent chance of developing the disease. Parents usually only discover that they are both carriers of a defective alphaGlu gene when their child is diagnosed with Pompe disease. The 25 percent chance of having a child with Pompe disease does not say anything about how this will play out within a family. Later in this book, we encounter a family with five children, four of whom have Pompe disease; that is 80 percent.

There is a wide variety of defects in the Pompe gene. More than three hundred defects have now been found. These also show regional differences. For example, there are Asian and African variants. And to make matters even more complicated, when someone is diagnosed with two Pompe genes, the course of the disease and the severity of the symptoms are not always predictable. They can be severe, but it is equally possible that someone will only develop mild symptoms later in life.

6

MARYZE

THE YELLOW BICYCLE

Everything went slower for me. It started at birth. My mother had contractions from Friday, but it took until Sunday before I saw the light of day. That was three days of hard work for both of us. I lay blue and exhausted in my mother's arms. Breastfeeding didn't work. Breastfeeding was natural, of course, and better for the child's development, but after a few attempts, I gave up, no matter how hard my mother tried. I didn't have the strength for it. So I had to have a bottle. But even that was too much of a challenge. It was only when my mother cut the hole in the teat bigger with a pair of scissors that I was able to feed and start to grow.

I developed normally. I reached my milestones on time. At fifteen months I could walk, and I could talk even earlier. In the early years, there was no difference between me and other children. Only games like tag, where you had to run, were not for me. I couldn't pick up speed and I kept falling.

When I was six, I got a sunflower-yellow bike with training wheels. I was the happiest kid alive. I paraded around with it on the street, my friends surrounding me, all jealous, of course. But that was as far as it went. I made no attempt to sit on the bike. I kept walking alongside it, much to my mother's surprise. One day, she took me to the schoolyard, lifted me onto the saddle, and gave me a push. I was going to ride a bike. But I kept falling over. Scraped knees, scraped elbows, scraped hands. And crying, of course. My mother was relentless, and after a lot of practice, I finally managed to stay upright. My mother later felt guilty when it became clear what was wrong with me, but thanks to her perseverance, I was able to ride a bike for twelve years.

Swimming was similar. We had lessons with more than twenty children. I did my best and practiced well, but when it came to the final test, I was the only one who failed the A certificate. I didn't hold my hands properly and didn't close my legs enough. Something like that. Nobody fails the A swimming diploma, right? I was very upset. Later, I did get my A. And my B, with some help from the lifeguard.

Meanwhile, my mother regularly visited the family doctor. She was convinced that something was wrong. The doctor saw an overprotective parent and repeatedly reassured her. Some children are just a little faster than others. In third grade, I came home exhausted every day after the morning session. I was rolling around on the floor with terrible stomach pains and had a persistent low-grade fever. Then they finally took a blood sample. I was admitted to the hospital in Doetinchem, where they even thought I might have childhood leukemia, but that turned out not to be the case. Maybe I was just stressed out?

My parents were advised to keep me home for six months. I hated it, because I loved going to school. Fortunately, my friends continued to play with me after class. My mother picked up teaching materials from the teacher every week and taught me at home. But my condition didn't change.

During the Christmas holidays, I spent two weeks in the hospital for further examination. I was seven by then. I have no idea what exactly they were looking for, but the strangest thing I experienced during those weeks was when a young nurse in a white coat put sneakers on me and took me for a run through the center of Doetinchem. He dragged me through the shopping streets while I cried from the pain in my side. I couldn't do it. As soon as we got back, they took a blood sample. Then they suspected that my symptoms were related to my muscles.

Suddenly there were four strong hands that pulled me off the road.

Not long after that, I ended up with Professor Gabreëls at the Radboudumc in Nijmegen. I was wheeled into an operating room full of people. A green cloth prevented me from seeing what was happening around me. Suddenly, there was this terrible, sharp pain. It felt like they were putting a knife in my leg and cutting out a piece of muscle. And that was exactly what they were doing. Next to me, a nurse was reading the fairy tale of Little Red Riding Hood.

Finally, it became clear what was wrong with me: I had Pompe disease. My parents were very upset. They discussed the consequences with the doctor, because it is a hereditary disease. Could my four-year-old brother have it too? And what was the prognosis for children with Pompe disease? It didn't really sink in for me, because I was still the same Maryze. The diagnosis hadn't changed anything, had it? Professor Gabreëls explained clearly what was wrong with me. He used the example of a link bracelet with one link missing. The substance that makes muscles strong cannot pass through the last link. Too much of the substance ends up in the last link, causing it to break. That is exactly what happens with my muscles.

I remained under his care for a long time, even after I had grown up. I went for check-ups once or twice a year. He found it remarkable. Before me, he had never had a patient with Pompe disease in his consulting room. It is a rare disease, after all. When he retired, I switched to Dr. Ans van der Ploeg at Erasmus University Hospital in Rotterdam.

Diagnosis or no diagnosis, my life went on as usual. I finished high school and went on to study cultural anthropology in Leiden. I was eighteen. Like every student, I did everything by bike. One evening, I went to visit a fellow student, Igor. He wanted to show me and my classmates his slides from Jordan.

It happened on Stationsplein. I was waiting at the traffic lights, with a young guy on my left and right, fellow students I think. When the light turned green, I set off, or rather, I tried to set off. My left leg gave way, I swung strangely and ended up in the middle of the intersection under my bike. I couldn't move at all. Time was ticking away and I knew the cars were coming, out of the train tunnel, around the bend and then they would be upon me. Not that I was panicking, I just thought this might be the end. Well, so be it. I could already hear the engines revving, but suddenly there were four strong hands that pulled me off the road and brought me to safety.

Of course, I thanked those guys. “Sorry, my knee gave way,” I said, but by then they were already gone. That was the last time I rode a bike.

EXPLAINED

FORMS OF POMPE DISEASE

The condition originally called Pompe disease was given a different name by the Coris in the 1950s: glycogen storage disease II (type 2 glycogen storage disease), only to be given back its original name after 2000: Pompe disease.
Over the years, various classifications of subgroups have been made based on the symptoms and age of patients, which overlap with each other. Nowadays, we often refer to the infantile, juvenile, and adult forms. The infantile form is the most progressive and severe form, while the adult group is the least progressive. The term 'classic form', the form described by Joannes Pompe, is reserved for babies with a thickened heart muscle and severe paralysis at or shortly after birth. Instead of 'classic form', the terms 'early onset' or 'infantile onset' are also often used, with the most striking symptom being an enlarged heart. The rest fall into the 'late onset' category, including infants who do not have an enlarged heart. All in all, it is a confusing series of terms for laypeople.
It is important to bear in mind that all types of Pompe disease involve the same disease mechanism: due to a defect in the alphaGlu gene, the cells produce insufficient or no alphaGlu. The classification into groups has only relative scientific value. Nevertheless, this classification often plays an important role in the assessment of a therapy.

7
DIETS AND OTHER ATTEMPTS AT TREATMENT
1970 - 1984

The Dutch Muscular Dystrophy Association (VSN), a young, ambitious patient association for people with muscular dystrophy, grew rapidly in the 1970s. Anyone with a disorder of the muscles or motor nerves could become a member, including people with Pompe disease and other storage diseases. The number of members with Pompe disease grew slowly but steadily. From seven or eight members in the early 1980s to twenty in 1987. But how many Pompe patients were there actually in the Netherlands? No one knew. Even the specialists had no idea of the size of the population at that time. In 1994, the total number of patients in the Netherlands was conservatively estimated at around fifty.[31]
As the number of members grew, it also became clear that there were significant differences between Pompe patients, both in terms of age, symptoms, and severity of the disease. Some were in wheelchairs and on ventilators, while others had few limitations but were extremely tired. Over time, parents of Pompe babies also became members of the VSN. But when Maryze's parents, Tanneke van der Linde and Jan Schoneveld, registered as members in 1979, there was no one else with Pompe disease. Shortly afterwards, Robert came into the picture, about whom more will be said later. At eighteen, he was four years older than Maryze. The Pompe group within the VSN acquired two medical advisors,

physician-researcher Christa Loonen from Erasmus MC and John Fernandes, professor and pediatrician at the University Medical Center Groningen. Not only did they play an important role in the development of information material about Pompe disease—at that time, there was nothing available for patients—but they also felt encouraged by the VSN members to set up research. Although the first attempts were a shot in the dark. Wil de Geus, whom we will get to know more extensively later, was the driving force behind the research as a patient during those years. There was a lack of money and waning interest among researchers worldwide, but the patients and their medical advisors were not discouraged.

John Fernandes began his academic career at the Wilhelmina Children's Hospital in Utrecht and moved to Rotterdam in 1969, to the new medical faculty and the Sophia Children's Hospital, now part of Erasmus MC. In 1978, he was appointed professor of pediatrics in Groningen. Fernandes built on the discoveries of De Duve and Hers in his research and sparked interest among his colleagues in Rotterdam in researching Pompe disease and related disorders.[32]

Fernandes focused on special diets. He reasoned that people with glycogen storage disease suffer from fatigue and listlessness, probably caused by a lack of sugar. In 1984, he demonstrated that patients can benefit from regular small meals of slow-release carbohydrates and tube feeding at night.[33] The diet had a beneficial effect on patients with Von Gierke disease, another glycogen storage disease that has already been mentioned, but it had no effect on people with Pompe disease.[34]

Fernandes was not the only one to focus on nutrition. In the same year that he published his research, an article by the young Taiwanese-American researcher Y.T. Chen appeared, in which he explained the therapeutic effect of corn starch in Von Gierke disease.[35] Chen will play a prominent role later in this story.

The other medical advisor to the patient group, Christa Loonen, also tried special diets. She experimented with so-called branched-chain amino acids. The reasoning was that Pompe disease disrupts energy metabolism. Due to the absence of the enzyme, the glycogen stored in the lysosomes cannot be broken down, or at least not sufficiently. Instead,

They were given
a plastic container
at home into which
they had to collect
their morning urine.

proteins are probably used as an energy source. Adding amino acids to the diet increases the production of muscle protein, which can be used as an energy source.

It was a good plan, but it did not work. Twelve patients participated in this study. They were given cans of a type of butter, which they had to use for a year. Some had regular butter, others had butter with the special amino acids. The test subjects were regularly tested for muscle mass, muscle strength, and lung function. After two years, the disappointing results came in: the amino acids had no effect whatsoever.

But patients and researchers persevered. In 1982, the VSN member magazine published an appeal to members with Pompe disease to participate in a urine study. It was conducted by Christa Loonen and Joseph Tager, professor at the University of Amsterdam.

Fifteen subjects participated: six patients, four parents, and five siblings. They were given a plastic container at home in which they had to deposit their morning urine for several days. The aim of the study was to determine how much alphaGlu ended up in the urine. The expectation was that the patients would excrete very little and the parents considerably more, but still significantly less than average because they were carriers of the Pompe gene. It was hoped that the values would vary so widely that a urine sample could be used to determine whether someone was a carrier of the disease. The differences turned out to be significant, but not large enough to distinguish carriers from non-carriers with certainty. Unfortunately, the urine test also proved to be a dead end.

During the same period, researchers in Amsterdam and Rotterdam analyzed the alpha-Glu in the urine of healthy people. They wondered whether alpha-Glu from human urine could be used to treat patients. In 1984, they published their results. Their conclusion: yes, it could. In theory, at least. They administered the purified enzyme to the cells of a Pompe baby, and it worked.[36] It could be a step towards a therapy. Much is still uncertain.

AlfaGlu is a complex protein that varies greatly in composition. The alfaGlu of a cow, rabbit, fungus, or human is not readily interchangeable. Even in humans, there are all kinds of variations in alphaGlu. An infusion of alphaGlu can trigger an immune response because it is seen by the immune system as a foreign substance.
A second uncertain factor is that although alphaGlu can be introduced into the bloodstream via an infusion, how does it get from there into a muscle cell and then into the lysosomes of that muscle cell? No researcher can say for sure. Much work still needs to be done.
But at least this research is not coming to a standstill. For the first time, undeniable progress is being made. Above the 1984 article describing the results of purifying alfaGlu from urine, seven names of researchers with impressive track records are listed, but one stands out in particular: that of Arnold Reuser.

8
TIME FOR CHANGE
1965 - 1984

There are many factors that determine the success of scientific research, but the most important is undoubtedly chance. This is no different in the research into Pompe therapy.
In 1965, physician and cell biologist Hans Galjaard, then just 30 years old, was asked to help set up the Rotterdam medical faculty, a precursor to the current Erasmus MC. Galjaard had a keen interest in genetic research and prenatal diagnostics.[37] This interest arose after the death of his younger brother, years earlier, from a very rare metabolic disease.[38] For the new faculty, he was looking for people who could set up this research.
During the same period, Arnold Reuser began studying chemistry in Amsterdam. He recalls that his motives for choosing this course of study were not very clear. “In high school, I wasn't sure what I wanted to do next. I had a friend who wanted to study chemistry. ‘Come on,’ he said, ‘if you do that too, we can stay together.’”
These were turbulent times, especially in Amsterdam. Demonstrations, protest marches, and sit-ins were the order of the day. In 1969, the university's administrative building, the Maagdenhuis, was occupied. It made front-page news, but for Arnold, his studies were his priority. “I saw friends and former classmates in newspaper photos, but I didn't take part in the turmoil myself. When you have lectures in the morning

and practicals in the afternoon all week long, there's little time left for rebellion."

Reuser became proficient in biochemistry. This was seen as the subject of the future, just like molecular biology later on. In the course of his career, he also became familiar with other specializations. "I see myself as a cell biologist," he explains, "as well as a histologist, tissue scientist, and histological anatomist. I have a broad interest in the structure of cells, the different types of tissue, and the structure of organs. That knowledge is important when you want to make a connection with medicine, even though I never had the ambition to become a doctor." Among others, Reuser studied under Joseph Tager, who—like his predecessors from the time of Joannes Pompe—paid special attention to metabolic diseases.

Reuser describes his move to Rotterdam as a coincidence. "In 1972, two months before I graduated, I got a call from a Professor Hans Galjaard from the medical faculty of Erasmus University in Rotterdam. He said he had placed an ad looking for a biochemist to do research on the background of Pompe disease and who could do a PhD on it. To be honest, I never saw that ad – not even later. 'Would you like to respond?' he asked. 'Well,' I said, 'I'm not looking for a job yet. "Come to Rotterdam, and we can talk about it." So I did. Professor Galjaard turned out to be a friendly man with an enormous drive to propel his department to the highest heights and become famous. The interview lasted over an hour, but I hardly said a word. He ended with, 'Great, just let me know if you want the job.' I returned to Amsterdam, where I informed my supervisor, Professor Tager, about the conversation. He responded with surprise: 'Why would you go to Rotterdam? You can do the same doctoral research with me!' Nevertheless, I made the switch. I was 24 years old, born in Amsterdam, and I felt it was time for a change." Galjaard's phone call turned out to be a defining moment for research into Pompe disease.

Like Amsterdam, Rotterdam also had a tradition in the field of metabolic diseases and Pompe disease in particular. The names of John Fernandes and Christa Loonen, who later became medical advisors to the Pompe group at the Dutch Muscular Diseases Association, have already been mentioned. The Rotterdam medical faculty was in full development. Reuser: "Hans Galjaard was one of the first professors there. I furthered my skills in the technical aspects of the research and after a year I knew pretty much everything there was to know about Pompe disease." On Friday, July 1, 1977, he obtained his PhD with a thesis on clinical, biochemical, and genetic heterogeneity in lysosomal diseases.[39]

Until then, Pompe research had focused almost exclusively on the classic form of the disease: babies born with the most severe form of the disease. These babies produce a maximum of 1 percent of the normal amount of alpha-Glu. Reuser also discovered descriptions of patients with a lesser deficiency of alpha-Glu who reached adulthood without noticeable heart defects. The main symptom in these patients is muscle weakness. At that time, Reuser still believed that the adult form was an exception and that the infant form was the most common. It was only in later years, when diagnoses became more accurate and research was conducted into patient numbers, that it became clear that the opposite was true: the 'adult'[40] form is the most common.

It would take decades before a reliable picture emerged of the size and characteristics of the patient population. This is no different for Pompe than for other rare disorders. There was even a story circulating that Pompe disease was a purely Dutch phenomenon and hardly occurred elsewhere[41].

By the time he obtained his doctorate, Arnold Reuser had become one of the few experts in the world in the field of Pompe disease. This was, of course, entirely due to the fact that it was a rare disease and research into it was just as rare worldwide as the disease itself. Be that as it may, his publications attracted international attention.

Nina Raben, until recently a researcher at the National Institutes of Health (NIH) in Bethesda, USA, remembers their first meeting in the early 1990s. "Arnold Reuser was already an established name in the field at the time, a man with enormous experience. The basic research—the biochemistry, the synthesis of the enzyme, the structure—he had already done it all. We were newcomers to this field, and he rightly viewed us with a certain degree of suspicion."[42]

Research into Pompe disease is already scarce worldwide, but due to the setbacks with the very first enzyme infusions and bone marrow transplants, one researcher after another is dropping out. Only in Rotterdam

are they continuing undeterred.
When Reuser goes to America for a while, his mentor from Amsterdam, Joseph Tager, together with Christa Loonen, temporarily takes over his research into Pompe disease in the Netherlands. Tager remained interested when Reuser returned. Together with a PhD student from Amsterdam, he and Loonen conducted research into alpha-Glu in urine. When the Amsterdam student obtained his PhD, research into Pompe disease came to a standstill in the capital. Reuser was one of the few who remained. He describes how precarious the situation was at the time.
“In the mid-1980s, there were only two research groups left in the world focusing primarily on Pompe disease: Rochelle Hirschhorn's group in New York and our group in Rotterdam. The Americans limited themselves to basic research, while we also continued with applied research into a therapy.”
In short, the research in Rotterdam was the only hope for patients at that time. And it is questionable whether it would have survived if a student had not knocked on Reuser's laboratory door in 1985. This future doctor was looking for an interesting research project. After Reuser's move from Amsterdam to Rotterdam, this was a second coincidence that determined the course of therapy development.

EXPLAINED

THE SUGAR KEY M6P

A specific chemical compound with the ‘code name’ M6P played an important role in the development of a therapy for Pompe disease. It is a simple sugar, just like glucose (grape sugar) and fructose (fruit sugar). M6P stands for mannose-6-phosphate, the P is from ‘phosphorus’. In 1977, the importance of this substance for the functioning of the human enzyme alphaGlu was demonstrated. The M6P molecules are spread across the surface of alphaGlu and look like small bushes. These M6P molecules act as a key for certain receptors, a kind of gate, on a cell wall. Without these pieces of sugar, these keys, the alphaGlu enzyme cannot enter the muscle cell. Researchers in Rotterdam put this to the test. They administered alphaGlu with many M6P molecules to some muscle cells and a variant of the enzyme with virtually no sugars on the surface to others. And indeed, the variant with many M6P sugars easily entered the cells. The other variant was unable to do so, or barely managed it. It lacked the keys to open the locks for the alphaGlu on the cell surface. This also explained why previous treatments with alphaGlu produced with fungi had failed. Fungi do not produce M6P sugars on alphaGlu.

9
IN PRINCIPLE FEASIBLE
1985 - 1989

While Reuser, as a biochemist, ventures into histology and anatomy to find connections with medicine, Ans van der Ploeg is taking the opposite route. As a physician, she wants to delve deeper into laboratory research. And while Reuser was born in the metropolis of Amsterdam, Van der Ploeg saw the light of day in the countryside of Friesland, in the tiny mound village of Tzum. “I grew up in Leeuwarden,” she adds. "In high school, I quickly realized that I wanted to study medicine and become a pediatrician. But there was a hitch, because I was rejected in the lottery. I had to come up with something to bridge the year and ended up studying chemistry in Groningen. Actually, I really enjoyed it; it suited me. I'm a math and numbers kind of person. The following year, in 1979, I was rejected again, so I continued with chemistry. Until, quite unexpectedly, I received a phone call from Rotterdam in December saying that a place in medicine had become available after all. So during the Christmas holidays, I packed my things and moved to Rotterdam."
In retrospect, the U-turn that Van der Ploeg made at the time gave her a new insight, she says. "The medical program has a reputation, and certainly did at the time, for involving a lot of facts and a lot of cramming. The experiments and calculations in Groningen were of a completely different order. I realized that if you want to do relevant research and initiate new medical developments, you have to bring the basic sciences

and clinical practice closer together. You have to translate basic insights into medical applications. In other words, translational research, which everyone is talking about now. And I still believe that: clinical practice and science must work together. Only in this way can we advance medicine. I am therefore very much in favor of clinicians visiting the lab more often and people from the lab connecting more with patients, to see who you are doing it for and what is going on with them."
Her fellow students know Ans as a ‘nerd’ and an enthusiastic researcher. They joke about her when she leaves a party early to add a substance to a cell culture. “We had no idea,” says one of her classmates, “that ten years later she would have become the world's leading specialist in the field of Pompe disease.”
When she finished medical school, Van der Ploeg wanted to work in a lab, doing research in genetics. She inquired about openings and was told that Arnold Reuser was looking for someone for his Pompe research. "That was actually the direction I was looking for. I started with very basic research, and gradually became convinced that we were on the right track. Arnold had done an initial test to see if muscle cells absorb alphaGlu. My task was to investigate this more thoroughly. I extracted enzymes from bovine testicles and human urine and purified them in the lab. It worked, because it was alphaGlu with that special sugar, M6P. Enzymes from placentas lacked those sugars, so they were unsuitable as a source.”
She then investigated why some patients are sicker than others, what the residual activity of the enzyme is, how quickly glycogen accumulates in patients' cells, and how you can administer the enzyme to those cells to see if it ends up in the right place, namely in the lysosome. “Ultimately, we succeeded in all of that. Then we met someone from Biochemistry who had a setup with living, pumping rat hearts. This allowed us to investigate whether the enzyme would actually end up in the rat hearts and then in the lysosomes. We succeeded in doing that. The enzyme also ended up in the muscles of mice.”
Van der Ploeg's research progressed well and she obtained her PhD in 1989.[43] One of the propositions in her thesis was: ‘*Enzyme replacement therapy in Pompe disease is in principle feasible*’. “Hans Galjaard was my

It's too early
to pop
the champagne,
they made a point
of mentioning that.

supervisor, Arnold my co-supervisor. From the moment I obtained my PhD, Arnold and I continued to work together, partly because I really saw the possibilities. That 'in principle feasible' triggered me. I really wanted us to get that enzyme replacement therapy working."
As team members, Reuser and Van der Ploeg complement each other perfectly, one from the laboratory, the other from the clinic. In their environment and among patients, they are mainly known as a duo. Just as you have Suske & Wiske (two Belgian cartoon characters), Fokke & Sukke (two Dutch cartoon figures), Acda & De Munnik (two Dutch singers), in Rotterdam you had Ans & Arnold. They are still referred to collectively in conversations with those involved. In the history of Pompe research, one cannot exist without the other.
On December 4, 1985, a letter from these two young researchers was delivered to the office of the VSN patient association in Baarn. "We have," they write, "been researching the biochemical abnormalities of [...] Pompe disease for the past few years. Recently, our research [...] has also focused on possible treatment options." They had heard from colleagues that there would be a members' meeting on December 14, which they would like to attend. The letter was signed by Dr. Arnold Reuser and Dr. Ans van der Ploeg.[44]
It is still far too early to pop the champagne, they explicitly mention, but they do think it is important to inform patients of their findings. They are both also very aware of the biggest barrier they still have to overcome: producing sufficient quantities of the right alphaGlu to treat hundreds, perhaps even thousands, of patients. They have no idea yet how to go about this. The letter is indicative of the researchers' willingness to collaborate with patients, a feeling that is immediately mutual. The patient who first recognizes the potential of enzyme replacement therapy and becomes the most passionate supporter of both researchers is undoubtedly Wil de Geus.

10

MARYZE

SHORTNESS OF BREATH

Shortly after my diagnosis in 1978, my parents registered as members of the Dutch Muscular Dystrophy Association. My mother immediately became a volunteer in the Pompe working group. She later served as chair for many years.
I always went with my parents to meetings, and I remember a girl of about twelve, Femke, who had a completely different muscle disease than I did, racing through the room in a small, brightly colored wheelchair. I was a little jealous of her. I wanted a wheelchair like that too. But it wasn't possible yet. Later, the memory of Femke helped me to accept my wheelchair: wheel legs instead of normal legs, what does it matter? It's a tool that gives you back your freedom of movement.
There were only a handful of Pompe patients in the association. Robert was the only one my age. Over the years, we always kept in touch, even later when he got married and had a daughter. Robert was eighteen and I was fourteen when we met. We clicked because we were going through the same things. We wrote letters to each other—it was still the era of pens and typewriters—in which we exchanged experiences about our lives with Pompe. He was already on a ventilator at the time. Pompe affects the muscles, including the respiratory muscles, but at the time I didn't realize that Pompe and ventilation go hand in hand. I was sixteen when my mother asked me if I wanted to go to a sympo-

sium in Arnhem about home ventilation. The technology was still in its infancy and some doctors had their doubts: ventilation would only prolong the suffering.
My presence at the meeting had a practical purpose, because there were presentations in English and with my high school English, I could act as an interpreter. I found the presentations extremely fascinating, especially the fact that there were devices that could take over your breathing if your muscles failed. That way, you could just carry on living. Sometimes you only use ventilation at night, sometimes for a few hours during the day, and if necessary, permanently. The possibilities are endless. Ventilation can be provided via a plastic nose or mouth mask or a combination of the two, via a tube that goes directly into your windpipe, via a separate mouthpiece from which you can take breaths, or with a kuras. This is a large cylinder that encloses your chest from neck to waist and creates negative pressure in time with your breathing rhythm, causing your chest to expand and contract. To my knowledge, this latter technique is no longer used.
At that symposium, I learned that the deterioration of breathing occurs gradually. The first symptoms manifest themselves during sleep. Then the respiratory muscles have to compensate for the effect of gravity and therefore work harder.
When I was eighteen, I started suffering from night sweats and nightmares. The disturbed sleep left me exhausted when I woke up. During the day, I couldn't concentrate anymore. I had to read texts for my studies three or four times before I understood anything. I argued with my boyfriend about the most ridiculous things, and if I was startled, for example by a door slamming shut, I burst into tears.
I was admitted to the hospital in Doetinchem for a sleep test, but because there was a man moaning next to me at night, I didn't sleep a wink. The test was a complete failure. They referred me to the Center for Home Ventilation (CTB) in Utrecht. There, they attached sensors all over my body. The results were not good, but I didn't realize what the consequences would be.
That summer, my boyfriend and I took an impressive road trip to Istanbul. I enjoyed it, but it was also difficult. It took more and more effort

I can still remember having strange dreams and a sort of 'high'.

to keep up with everyday life. I did what was expected of me, but I got tired more and more quickly. I developed vague symptoms and began to doubt myself more and more; I no longer recognized myself. I went back to the CTB and was told that I needed to be put on a ventilator. I was relieved, literally. Anything was better than that constant miserable feeling.
The admission, during which the ventilator would be adjusted, could take a while. But when I returned to my student room in Leiden after the holidays, I was completely fed up. I couldn't take it anymore. I called the CTB and said I wanted to come in immediately. After some insistence, I was able to do so.
And there I was, lying in the ICU, waiting for what was to come. In the evening, Rob van Kesteren, a remarkable doctor, came to my bedside. We were a good match: same tone, same sense of humor. He sat down next to me on the bed. “Look,” he said, "this is a standard nasal mask. We'll try that first. Just relax." And I did, I had complete faith in him. I remember it as an intimate moment. There was no rush, no glances at the clock, no other patients waiting. He slid the mask over my nose and I was very aware of how the air flowed into my lungs. It was a wonderful feeling that I hadn't experienced in at least a year. It went well right away.
It was the first night I slept with ventilation. I sank into a deep, invigorating sleep. I remember having strange dreams and feeling kind of “high.” That was because I had too much air blown into my lungs that night. After some fine-tuning, those disappeared.
With the ventilation, I felt a lot fitter. It also changed my life, because wherever I went, I had to drag that device with me. It was a PLV-100, a device so reliable that at the start of the Gulf War, the US Department of Defense bought up all the PLV-100s in the world to be prepared for a possible poison gas attack from Iraq. Fortunately, I already had mine at the time.
A device like that makes you very aware of your vulnerability. You are completely dependent on it and on the availability of electricity. In the

Netherlands, it is fairly certain that power will come out of the socket, and if a disaster occurs, there is a battery for emergency power. I have always been somewhat laconic about it, even when I was abroad, but my mother finds it scary that my life literally hangs by a thread.
There are no guarantees. Home ventilation can go completely wrong, as was the case with Wil de Geus. In the 1980s, Wil was undoubtedly the most passionate Pompe member of the association. I was eighteen when I first met her. Most of the stories about her I heard from my mother.
Within the VSN, there was a lot of emphasis on rehabilitation and physical therapy, but that wasn't enough for Wil. “If you have cancer, you get surgery, radiation, medication,” she said. “But with muscle diseases, there is nothing at all. Why not? Surely there must be another way?” She had a medical background and attended symposiums and conferences to gather information and establish contacts with researchers. This is how she became a great advocate for the research of Christa Loonen, Ans van der Ploeg, and Arnold Reuser. She was convinced that they were on the right track in Rotterdam and deserved all the support they could get. Not a single working group meeting went by without her bringing up the research in Rotterdam. Her strength was her ability to inspire enthusiasm in others. She had a positive vibe.
Wil was on a ventilator, via a kuras. At that time, only the hospital in Groningen was still using it. A kuras is a bulky, difficult-to-handle device, but Wil had been using it for a long time and had become completely familiar with it. When she came home on Friday, May 24, 1991, after a busy day, she became out of breath and fell. She could no longer reach her ventilator. That is how she died.
I went to her funeral. When I offered my condolences to her mother, she looked at me intently. “Maryze,” she said, “you must be as combative as Wil. Don't let yourself be pushed into a corner and take over my daughter's work. You can do it. Take it on.” There I stood, a twenty-year-old, the woman opposite me with her fist clenched, fiery, combative. She was a lioness. I have never forgotten that image.

11
HENRI, YOU'RE CRAZY!
1965 - 1989

While Ans van der Ploeg and Arnold Reuser are searching for ways to produce the right alfaGlu in larger quantities in Rotterdam, on the other side of the ocean, at the National Institutes of Health in Bethesda, Maryland, an important step is being taken in the development of therapy for lysosomal diseases. There, Roscoe Brady[45] began developing a therapy for Gaucher disease, named after a French doctor. As with Pompe disease, Gaucher disease causes a substance to accumulate in the lysosomes due to the absence of an enzyme.
In the US, it is the time of the biotech revolution. New companies are emerging: Genentech in 1976, Biogen in 1978, and Amgen in 1980. Within five years, 155 biotech companies spring up, each of which uses the newly acquired biological knowledge about genetics in production processes for medicines[46] , among other things. It becomes possible to replicate proteins from living organisms and produce them on an industrial scale. Genentech's first approved product is synthetic insulin for the treatment of diabetes, produced by genetically modified bacteria. Unlike the hormone produced from pigs, this insulin does not cause an allergic reaction.
Investors are enthusiastic about the new industry and are investing heavily in it. Everyone is afraid of missing out. The newcomers are growing rapidly. Roscoe Brady will be at the forefront of one of the new

biotech giants. He is not an entrepreneur but a physician and researcher, primarily interested in lysosomal diseases.

Building on the discovery of the lysosome by De Duve in 1955 and of alphaGlu by Hers, he searches for the proteins responsible for storage diseases. He discovers the missing enzyme in Fabry disease and, even more importantly for this story, the enzyme that is absent in Gaucher disease. This disease is characterized by an often extremely enlarged liver and spleen. Accumulation also occurs in the bone marrow, leading to bone problems. The disease is debilitating and sometimes fatal. As with Pompe disease, the severity varies from person to person.

As early as 1965[47] Brady discovered the missing enzyme, which was given the unpronounceable name glucocerebrosidase. That was all for the time being, until he and his colleagues John Barranger and Ed Ginns began working on enzyme replacement therapy in the 1970s. His choice of Gaucher disease for this purpose is understandable. Because some of the affected cells in this disease are located in the blood vessels of the liver, the approach is relatively simple. When he administers an infusion of the missing enzyme to patients, it flows directly into the liver. This is because our blood constantly passes through the liver, liters at a time. With Pompe disease, it is a lot more complicated because you have to make sure you reach every muscle fiber in the body. You don't have that problem with Gaucher disease.

However, as simple as it sounds, the practice of enzyme replacement therapy proves to be difficult. Brady and his team set out to find a suitable source for the enzyme. They ended up with human placentas, but these have the disadvantage that only a very small fraction of the enzyme can be extracted from each placenta. To treat one patient for a year, thousands of placentas are needed, 22,000 to be precise. All hospitals in Maryland are approached and all those placentas together provide just enough enzyme to try out the therapy in practice.

It is a failure. The enzyme appears to hardly enter the cells at all. After the necessary adjustments in the laboratory and tens of thousands of placentas later, a new attempt is made, and again, none of the patients respond to the drug.

Except for one test subject, a four-year-old toddler named Brian Berman. A few months earlier, he had been diagnosed with Gaucher disease. His spleen was already severely damaged, causing his abdomen to swell to the size of a basketball. The prognosis was poor. His doctor recommended that his spleen be removed. Heart failure was imminent. But his mother Robin, a general practitioner, refuses to accept what seems inevitable. She stalks everyone and everything that could help her child and finds out that a trial with a new drug is going to be held. And close to where she lives, too. No one can tell her whether it will be successful, but it is her only hope.

Roscoe Brady is initially reluctant to allow the boy to participate in the trial. According to the rules, a drug must always be tested on adults first. Only when it has been proven safe and effective can children receive it. But Brian's mother refuses to be fobbed off. Rules intended to protect children are now standing in the way of a potentially life-saving treatment. She keeps banging on the door until Brady finally gives in.

But that's not the end of it. If Brian receives the drug, his mother insists that he receive it once a week. Not once a month, as the researchers had planned, given the scarcity of the enzyme. “Why did I argue for that? Just intuition,” she said later. "I said, 'If you don't do it, you'll never prove that the therapy works.[48]

Robin gets her way, and her persistence proves crucial to the further course of the study. Brian is the only one to show positive results, and not just a little. The swelling in his abdomen visibly decreases and the accumulation of fatty substance in his spleen, liver, and bone marrow dissolves. Exactly what the researchers had hoped for.

But there was only a small amount of enzyme available, and when it ran out, Brian's abdomen began to swell again. This continued until a new supply became available and the swelling disappeared again like snow in the sun. It gave him a new life. Brian has completed a study and now heads the American Gaucher Association.[49]

For a layman, this result may be convincing, but a scientist wants to know why it didn't work for the seven other test subjects. Isn't it just a lucky shot? Based on N=1, a positive result in a single test subject, you can't make any reliable statements, can you? And certainly not invest

millions to further develop the therapy for the market. Fortunately, not everyone thinks that way.

At the time, Roscoe Brady was working with a young biotech company, Genzyme, based in Cambridge, Massachusetts. It was headed by Henri Termeer, an economist and the son of a shoemaker from Tilburg. In 1986, Henri made the bold move from a good job at the large American pharmaceutical company Baxter to an uncertain future at this start-up. When he took up his position, he was faced with the question of which direction to take Genzyme. Could he do anything with that Gaucher drug? It was up to him to decide whether there would be any market interest in a drug for a rare disease. Should he take this step?

There were several reasons not to. First of all, the scientific evidence was flimsy. Furthermore, enzyme replacement therapy did not fit into Genzyme's portfolio. In those early years, the emphasis was still on the production of proteins for diagnostics.

Thirdly, according to insiders, the drug would be far too expensive. James Geraghty, now a veteran of the biotech industry, describes in his book *Inside the Orphan Drug Revolution* a discussion he had with Henri Termeer. "I told him that Genzyme would have to charge $250,000 per Gaucher patient per year, and maybe even more, and... that's ridiculous. No one is ever going to pay that much. Henri saw it differently. According to him, the question was whether societies want these terminally ill people to be treated. 'I think they do,' he said. 'And if we explain why therapy for rare diseases has to be so expensive, they will be willing to pay those costs.' But I wasn't convinced. 'Henri, I think you're crazy,' I exclaimed."

12
BUT NOT RIGHT NOW
1988 - 1991

Henri Termeer is not a scientist, but an entrepreneur. He senses his opportunities and persists. He is convinced by the results with Brian and Roscoe Brady's explanation that the other test subjects did not respond because the dosage was too low. The dosage should have been based on the participants' body weight. If the adult patients received more enzyme more often, they too would respond positively. That was enough for Termeer. He took the risk and played a pioneering role in the development of orphan drugs. Incidentally, it would not be the last time there was discussion about the dosage of a drug being too low.

Termeer's first challenge is to conclusively demonstrate to the Food and Drug Administration (FDA) that the enzyme is effective. To do so, he needs enough patients and enough enzyme. A second challenge is to produce enough enzyme for the entire patient population. If the drug proves to be effective, every patient in the world will want it. So he must be able to ramp up production quickly. To do so, he needs money, a lot of money. His goal is to raise $10 million to finance the patient trial. But no matter who he talks to or what he tries, everyone is keeping their wallets closed. No investor has ever heard of Gaucher's disease, no one has any idea what it is, and there is simply no interest in it. In a last-ditch effort, he organizes a meeting for investors, to which he also invites Brian's mother, Robin Berman. Her story makes the difference. Those present

Anyone who's crazy enough to give this a go can have all the placentas for free.

are deeply impressed. Afterwards, they call friends and business associates, and within two weeks, the required amount is raised. For Henri, this is an eye-opener: patients and their parents can make a difference.
Because of her relentless fight for her child, Brian's mother later became known as a 'tiger mom'. Her struggle marks a turning point in the lives of patients, not only those with Gaucher disease, but also those with other rare diseases, such as Pompe disease. She makes a difference three times. First, she manages to secure a place for her son in the study, and then she persuades the researchers to administer the enzyme to Brian on a weekly basis rather than monthly. If Brian had not participated, if he had not been the only one to respond positively and thus provide the 'proof', Termeer would never have taken the gamble.
She also achieves what Termeer fails to do: convince investors that the project deserves their support. That their money will not only yield a sufficient return, but will also radically change the lives of thousands of patients. The voice of the patient, or in this case the mother of a patient, thus changed the course of history.
With the money, Roscoe Brady can return to the lab to perform the necessary biochemical fine-tuning of the enzyme and set up a new trial, this time with twelve Gaucher patients. This brings him up against the next obstacle that repeatedly arises in research into rare diseases: the required number of test subjects. Twelve is actually far too few to provide scientifically solid evidence of a drug's efficacy. The Food and Drug Administration has a strict list of requirements that every trial with patients must meet: a sufficient number, double-blind and placebo-controlled. This means that some of the test subjects receive the real drug and others receive a placebo, and neither the doctors nor the patients know who is receiving what. The results of the drug must speak for themselves. If the results are positive, you have to repeat the trial with other patients to show that it is not a lucky coincidence.
But how do you do that with rare diseases? Where do you find enough patients? And is it ethically responsible to give patients a placebo knowing that they may die during the trial, when they would have lived with

the real drug? Termeer is convinced that different rules are needed for the assessment of drugs for rare diseases. The strict requirements of the FDA are blocking the development of therapies for these conditions. He is certain that, when it comes down to it, he can change the authorities' minds. The discussion and battle with regulatory bodies will also be a recurring theme with Pompe and other rare conditions.
While Brady continues his research, Henri Termeer faces another challenge: finding enough placentas for enzyme production. A simple calculation shows that six tons of placentas are needed to produce enough enzyme for five thousand Gaucher patients. This is an enormous amount, which cannot be collected from neighboring hospitals in a short period of time.
Henri starts searching and, through connections at his previous employer Baxter, he comes into contact with the French family business Pasteur Merieux, which collects about 70 percent of all placentas in the world to extract certain proteins, such as albumin. The surplus, containing the Gaucher enzyme, is dumped as waste. When Termeers requested access to the processed placentas, CEO Alan Merieux must have exclaimed: "Anyone crazy enough to try this can have all the placentas for free."[50]
The results of Roscoe's test with the drug are positive, but according to FDA guidelines, his test group should have consisted of 144 patients, plus a placebo group. This meant he would have had to conduct the study twice. But Henri's optimism that he could change the authorities' minds proved to be justified. He succeeded in convincing the FDA that the severity and rarity of the disease, combined with the convincing results of the test, justified a deviation from the rules.
In 1991, the enzyme was launched on the market under the brand name Ceredase, the first therapy for Gaucher disease. A remarkable milestone celebrated by patients with rare diseases...
...or perhaps not, because there is still a dark cloud on the horizon. The authorities have serious reservations about the raw material used. Doesn't collecting all those placentas from around the world pose too many risks? Contamination, for example? Imagine if a virus got into it...
This caution is also motivated by the fear of a new disease that has been haunting the world for a decade: AIDS. Infection with the AIDS virus

does not only occur through sexual contact and the exchange of injection needles; hemophilia patients—who use medicines prepared from donor blood[51]—are also increasingly becoming infected.
This is a good reason for the FDA to ban drugs produced from placentas from the market. They consider the risks to be too great. The fact that an exception is made for the Gaucher enzyme is due to the fact that there is no alternative drug available for this serious condition. However, the FDA has stipulated that Genzyme must work on an alternative production method that eliminates the risk of contamination. This is in the interests of patients, but also of the company. After all, imagine what a virus contamination would mean for confidence in the drug and in Genzyme!
Genzyme markets Ceredase at a price just under $300,000. The company is not the only one to charge such prices, but the drug for Gaucher disease is one of the most expensive drugs in the US. In practice, the price per patient can vary considerably, depending on the patient's weight and the severity of the condition. A storm of criticism erupts over the high price. There is talk of a bomb under the healthcare system, and words such as 'hostage' and 'abuse' are used. Politicians organize hearings to grill the pharmaceutical companies, but most CEOs fail to show up. Termeer does not. He appears before the Senate committee and explains why he believes the price he is asking for Ceredase is realistic.
Over time, the storm subsides. In 1994, three years after its introduction, 96 percent of Gaucher patients have the drug reimbursed by their insurance companies. This story will be repeated many times elsewhere in the world.
The price is not Genzyme's only challenge with the introduction. Another is the lack of awareness of the disease. That's what you get with rare diseases. Worldwide, there are only a handful of doctors with real knowledge of the condition. There is little medical information available, not for doctors and certainly not for patients. The internet has yet to take off. Patients with Gaucher disease are hard to find. There are no central registries and virtually no patient associations with a membership database. When a patient does come to light, it often turns out to be a misdiagnosis. And before treatment can even begin, the drug must be approved

Henri was really good at
persuading you,
so I said 'yes' and
got started
in my back garden.

and reimbursed in the markets of various countries.
So a huge amount of work had to be done in a short period of time. Henri Termeer called Jan van Heek, a former colleague from his time at Baxter and, coincidentally, also a Dutchman. Would he like to become the pioneer for Europe? "That sounded very interesting," says Van Heek. "Henri was very persuasive, so I said yes and started in my backyard." Van Heek is referring to Genzyme's European headquarters, which was built behind his house in Naarden, so to speak.
Termeer then calls people all over Europe who can help set up the organization, people who know how healthcare works, how reimbursement decisions are made, and where to find the right doctors. And, of course, the patients.
Everything is happening under intense pressure. Genzyme is a small company that incurs large debts. There is no certainty that the Gaucher adventure will be a financial success. Who can guarantee that governments and insurers elsewhere in the world will also be willing to pay these unprecedentedly high prices? Failure will probably kill the company. But in 1994, reimbursements are arranged in Germany, France, and the Netherlands. The concept seems to be working and money is finally being made. In the same year, the enzyme from placentas is replaced in the US by a placenta-free variant, Imiglucerase, and marketed under the name Cerezyme. The enzyme is developed using a then brand-new technique: modified CHO cells, Chinese Hamster Ovary cells. A human gene containing the code for the production of the desired enzyme is inserted into cells from the ovaries of a Chinese hamster. These cells are further cultivated in large bioreactors, after which the enzyme can be harvested over time. We will encounter these hamster cells again later.
In its early years, Genzyme mainly worked with chemical processes. It did not have in-house expertise in genetic modification and biotechnological production methods. That changed when Termeer took over Integrated Genetics in 1989. That company was in financial trouble, while Termeer had visited investors at an opportune moment to raise money. The company was easy prey for him.[52] Integrated Genetics employed

scientists who were able to produce the Gaucher enzyme using hamster cells – cells that can now be ordered online. Incidentally, this was not the only acquisition. Over time, Termeer would go on to acquire dozens of other companies.
When Arnold Reuser runs into Jan van Heek at an international conference, he floats an idea. "Now let's move on to Pompe," he suggests, hoping that a project can be started in parallel with that of Ceredase. Van Heek shakes his head. "Not now. We first need to get Gaucher properly on track." So for the time being, Ans van der Ploeg and he cannot count on Genzyme. But then another, equally interesting option appears.

13
IT'S ALL ABOUT HERMAN
1988 – 1992

Herman de Boer[53] plays a crucial role in the development of the Pompe drug. He grows up in the Frisian village of Nijelamer in a strict Christian farming family. His father owns thirty dairy cows. Before Herman goes to school, he is expected to clean the cows' tails and muck out the barn. He cannot imagine anything other than a future in farming, although it will not be his father's farm. That is reserved for his eldest brother.
At the agricultural college in Leeuwarden, he was introduced to the theory of evolution. It was a revelation. Not that he lost his faith; for him, God and the theory of evolution did not conflict. But his thesis on this subject had the impact of a meteor on his family. The relationship between father and son became strained.
This did not prevent Herman from leaving for Groningen to study genetics. He no longer wanted to be a farmer, but a biologist. Even this academic training did not shake his faith. When people questioned him about this, he referred to the biblical story of creation, which states: 'Fill the earth and subdue it.'[54] In his view, this can be achieved through breeding, improving, and crossbreeding, but also—and even better—by making changes to the genetic structure of living beings. "Because then you know exactly where you are making the changes in the genetic material."
At a conference in Hamburg, De Boer approaches Japanese researcher

Nomura, a renowned biotechnologist at the University of Milwaukee in Wisconsin at the time. He finds a sympathetic ear and, after graduating in 1980, Herman packs his bags and flies to Milwaukee to gain experience. He soon discovers that the epicenter of the biotechnological revolution lies elsewhere. After more than a year, he made the switch to Genentech, the high-profile biotech company in San Francisco.
Initially, Herman planned to stay for one year, but it turned into eight. He saw young biotech entrepreneurs around him setting up one company after another. There were dozens, hundreds of them. Most of them were based around San Francisco Bay or in Boston.
There was no shortage of money. Investors were lining up to get a piece of what was seen as a gold mine: sensational new medicines from the biological design table. But of course, it wasn't that simple. The new industry would experience its own economic cycle, fueled by resounding successes and dramatic failures.
When De Boer returned to the Netherlands in 1988, he was appointed professor of biochemistry at Leiden University. This became the springboard for him to start his own company. In his view, the university was a pleasant setting, but developments were too slow for him. He kept in mind the image of his lab at Genentech. There, he modified the genetic material of bacteria to produce proteins for the treatment of certain diseases.
“I did that first in bacteria and later in yeasts and mammalian cells,” he says, "but we noticed that none of those systems were suitable for the production of a certain type of protein. A different approach was needed. That's when I thought: what if we worked on lactoferrin? That protein is produced in the mammary gland of humans, among others. To start with, we could produce lactoferrin in the mammary gland of cows, which is the same type of tissue.”
De Boer returned to the Netherlands with this plan. “Of course, I didn't broadcast it at the university,“ he says, ”but it was on my mind." He had long conversations about his ambitions with Otto Postma, who at that time was still an industrial liaison officer at Leiden University. Postma became enthusiastic about Herman's project. Together they wrote a business plan. Otto was the ideal partner, De Boer thought. “He wanted

to take care of the administrative and financial side, while I would be responsible for the technical content.”
The Ministry of Economic Affairs also sees the potential of the venture and awards a subsidy.[55] There is sufficient financial basis to start Genfarm, as the company is initially called, in the fall of 1988. It will make history with its genetically modified bull Herman. Genfarm changes its name and structure several times, but for the sake of clarity, we will consistently use the name Pharming in this book.
The young company does not have enough cash for the necessary investments in equipment and personnel. De Boer has to look for more financiers. "Things didn't go very smoothly in the Netherlands. We talked to Rabobank, but they weren't interested. Far too risky. First show us that it works, they said. Biotechnology did not yet exist in the minds of Dutch financiers. So I went back to California, to the big venture capital firms. They were willing to take on large, risky loans. Within a week, we had $4.5 million in our pockets. Once we had that money, the Dutch banks also became interested. We then successfully completed a new round of financing. That's how it worked. Once you have money, they think: hm, those foreigners see something in it, what are we missing? And then they come around."
There was a catch, says his partner Otto Postma. "We simply weren't given the opportunity to experiment with mice for a year or two before making the switch to cows. In the spring of 1989, I was incredibly surprised at how easy it was to raise money to finance the large project. But the generosity of investors always has a downside: they want to see a return as quickly as possible. They are not interested in the scientific results, but in realizing a commercial application. *They are only in it for the money*, that's just the reality. That means that when you start a new company like ours, everyone is under pressure. You can't just work with scientific arguments, you have to take the business side of things into account.”[56]
During his years at Pharming, De Boer would constantly feel the hot breath of the financiers on his neck.
Pharming had another important sponsor: Leiden University. They were very pleased with the new company, which perfectly matched their

ambition to become a major player in the field of *life sciences*. That is why Pharming was given access to a laboratory with support services in the Gorlaeus building. The university promised that no competitor in the field of transgenic animals would be brought in. And Pharming, not the university, would obtain the intellectual property rights to all the knowledge and insights it developed.

Given his background, it was not surprising that De Boer set his sights on cows. He had grown up with these animals and knew their qualities. They had to be able to produce large amounts of protein in their milk. And the choice of lactoferrin as a product also seemed a good one. The substance can inhibit inflammation and could have a wide range of applications, for example in babies, breastfeeding women, and perhaps even people with certain chronic conditions. In short, a very large market for the product. De Boer was already toying with the idea of producing lactoferrin when he was still working in San Francisco. "I spoke to people from Heineken there. We got talking about lactoferrin. They wanted to produce it in bacteria, but that didn't work for technical reasons. This has to do with the fact that lactoferrin is normally produced in mammary gland tissue. I told them my story, and then we said, 'Why don't we try to produce it in the mammary gland of cows?' Cow's milk naturally contains a very small amount of lactoferrin, but the human variant looks slightly different. Our challenge was to get cows to produce human protein."

In hindsight, says De Boer, the combination of those two words – 'cow' and 'human' – was an unfortunate choice. "Because it created the impression that we were trying to humanize cows. We didn't have a PR person or anything, so we just came up with a name, a term, and didn't think about the possible consequences. And so we got the Animal Protection Agency on our backs: large posters at bus stops showing a woman with udders instead of breasts. That was the work of presenter Antoinette Hertsenberg, among others."

Gerard van Beynum[57], Vice President of Research and Development at Pharming in the 1990s, is more emphatic. He believes that De Boer could not have made a worse choice. "The idea was brilliant, but the choice of lactoferrin and then baby food, in collaboration with Nutricia,

The idea was brilliant, but the decision to use lactoferrin was pretty much the worst possible idea you could have come up with.

no less, and on top of that the great sensitivity among consumers: it was just about the worst concept you could think of. It brought Pharming to the brink of ruin."

Yet initially, everything seems fine. With the money that has been raised, a multidisciplinary team of specialists is assembled in Leiden: a protein specialist, two molecular biologists, an expert in bovine embryos (Wil Eyestone from Wisconsin), and a specialist in transgenic mice and microinjection technology (Paul Krimpenfort).

The team set to work enthusiastically. Every Tuesday morning, animal caretaker Herman Ziegler would arrive with buckets full of cow ovaries, which he collected from slaughterhouses in Rotterdam, Zwolle, Leiden, and Bodegraven. It was the same scene as at Genzyme, which in those years collected placentas to prepare the enzyme for Gaucher's disease. Everyone in the lab would sit around a large table sorting through ovaries, recalls Herman de Boer. "An ovary is about the size of a chestnut. It contains follicles, and those follicles contain the eggs. You had to pierce each follicle and then place the egg in a laboratory dish. It was a skill that required a lot of people."

De Boer explains that molecular biologists had by then isolated the human lactoferrin gene. This was placed in a solution and 1 or 2 microliters of it was injected into the cell nucleus of the now fertilized cow egg. "The DNA found its way between the chromosomes and settled somewhere. At that point, it was not yet possible to control exactly where it ended up. After the microinjection, the egg was cultured into a cluster of about 64 cells. After hormone treatment, these eggs had to be implanted into the surrogate cows."

But there is a problem. Pharming does not have any cows of its own. Not even a pasture. De Boer contacts the Dutch Ministry of Agriculture. They have an experimental farm in Lelystad. When asked if they can help, they respond enthusiastically. They are happy to cooperate. The cell clusters are shipped to Lelystad to be implanted in cows. They have done this before, and that is where the experts are. Then it is a matter of waiting to see if there is a transgenic calf among them. And they are in luck: among

the first twenty calves, there are two transgenics. The first is Herman. The bull calf is born on December 16, 1990, on the farm in Lelystad. Incidentally, he is not named after Herman de Boer, as the outside world thinks, but after Herman Ziegler, the animal caretaker. [58]

Bull Herman has one major flaw: he does not produce milk, so it is impossible to determine whether and, if so, how much lactoferrin can be produced per cow. That is ultimately what matters. “But that didn't matter,” says Herman de Boer, "because we now had a prototype. We were also already working on improving the process. The second transgenic calf was a cow named Ineke. At that point, we were able to produce a very small amount of lactoferrin. We hadn't expected more, because the modified genetic material was far from optimal."

However, things are worse than De Boer is willing to admit, because none of Herman's 55 offspring produce a significant amount of lactoferrin in their milk. They all have to be put down. “We immediately started working on a second generation of modified genes,” he continues, “which were supposed to perform much better. That material later ended up in transgenic cows. They performed better. By that time, the cows had been moved to Finland because of all the commotion.”

De Boer is referring to the public debate that erupted after Herman's birth. The press flocked to the story and the bull quickly gained the image of a superstar, or even more: a mythical creature. A minotaur: half human, half bull. Herman evoked not only admiration, but also discomfort. And that discomfort was fueled by actions taken by the Animal Protection Agency, which questioned whether such use of animals was ethically responsible and whether it should not be seen as a form of animal abuse.

Pharming does not handle this debate very well. The company's statements contradict each other. One moment lactoferrin is a remedy for mastitis, the next for udder inflammation, and then it can possibly be used to treat serious conditions. To top it all off, a secret cooperation agreement with Nutricia worth 4 million guilders[59] comes to light.

Paul Krimpenfort, an employee from the very beginning, is critical of the way Pharming communicated at the time. He was hired because of his expertise in the field of transgenic mice. He studied at Radboud

University, where the first Dutch transgenic mouse was born in 1983, and then moved to the Netherlands Cancer Institute, where he further specialized in genetically modifying mice for cancer research. In 1988, he was recruited by Herman de Boer to join Pharming.

In addition to communication, Krimpenfort also criticizes the approach. He witnessed Herman's creation up close. "At Pharming, everything was happening at breakneck speed; there was no time for reflection. The lactoferrin project was immediately started in cattle. That's not how you do it. You first need to acquire basic knowledge before taking such a big step toward a transgenic cow. But those investors at the time—myself included—naturally found it very interesting to start creating cattle. There was too little attention for the public commotion, the feeling of: leave the cows alone for now. First show us that it works."

That didn't happen. The fertilization of the eggs and the injection of the human lactoferrin gene are going well. “We should have paused there,” says Krimpenfort. “You could have waited until the cells started to divide, the first step towards embryo formation, and seen if the human transgene was properly incorporated. We should have tested those modified genes in mice. That was possible, because Pharming had a mouse laboratory. But no, under pressure from investors, it was decided to start creating transgenic cattle immediately.”

In hindsight, Krimpenfort believes that first session was too successful. "We needed much more time to get everything properly set up, and that didn't happen. It's a shame. Nevertheless, the fact that it worked was a sign to many investors that there was something to be gained from this company. We then managed to attract even more money. The disadvantage was that those investors immediately wanted to focus entirely on cattle. In my opinion, molecular biology lagged behind in this respect. There were plans to make other products from cow's milk. I think the mammary gland is a very suitable means of production for this; there is no better protein producer than the mammary gland. I still think it's a very good idea, but you have to execute it correctly."

So bull Herman was initially a resounding success, but then the project ran into trouble. As mentioned, human lactoferrin is hardly traceable in the milk of Herman's offspring. Technically speaking, mistakes were

made and it takes a lot of time to fix them. Nevertheless, Herman de Boer remains enthusiastic. He is brimming with ideas, but that sometimes gets in the way of clear business management. The investors are scratching their heads. De Boer and his Pharming find themselves in dire straits.

14
SUSPICION
1988 - 1992

Both the euphoria and the protests surrounding the transgenic bull result in Herman de Boer receiving invitations from all over the Netherlands to give lectures about his project. From scientific conferences to lunch meetings, from farmers to medical specialists and from animal rights activists to rural women's associations, everyone wants to hear the story of Herman the bull from his own mouth. This is how he ended up at the annual conference for pediatricians in 1992. Afterwards, a young specialist approaches him. She tells him that she and her colleague are looking for a producer of a protein that could potentially save the lives of children with a very serious muscle disease. They are convinced that this specific enzyme, alphaGlu, can only be produced in animal cells. Perhaps they could help each other?

Shortly afterwards, Ans van der Ploeg, Arnold Reuser, and Herman de Boer meet in Leiden. They immediately hit it off, both personally and professionally. If Pharming succeeds in producing a medicine for terminally ill children in milk, it will be a win-win situation. The doctors can save lives and at the same time take the wind out of Pharming's opponents' sails.

Pharming is under attack from animal rights activists and suspicious parliamentarians. The biotechnological revolution is now also gaining momentum in the Netherlands, but society does not understand what

The message is clear: tampering with genetic material will lead to disaster.

is happening in the laboratories and has no idea what to expect from it. This uncertainty leads to questions, criticism, and suspicion.

Tinkering with genes doesn't sound kosher. People are quick to point to the racial theories of the nineteenth century. And for orthodox Christians, it is unacceptable that humans should set themselves up as creators alongside God. This latent aversion is reinforced by ominous films such as *The Boys from Brazil* from 1978, in which neo-Nazis, with the help of the notorious camp doctor Joseph Mengele, create genetic copies of Hitler, and Spielberg's *Jurassic Park* from 1993, in which dinosaurs are brought to life using biotechnology.

The message is clear: playing with genetic material will lead to disaster. It is no coincidence that music from the dinosaur film is used as background music in the 2010 documentary *De gemiste kans* (*The Missed Opportunity*), about the history of Pharming and the restrictions imposed on biotechnology by Dutch lawmakers.[60]

At that time, the public debate was dominated by a wide range of topics: bio-industry, biotechnology, crop breeding, transgenic animals, nuclear transplantation, cloning, and laboratory animals. This confusion was partly due to the lack of clarity that the biotech sector itself allowed to exist. Hans Galjaard, the man who brought Arnold Reuser to Rotterdam, was also highly critical of this. "When a new development is announced suddenly, people are surprised, feel overwhelmed, and put on the brakes." Galjaard said that Pharming's communication during the introduction of the transgenic bull Herman was not particularly smart. "Herman de Boer, who 'created' the bull Herman, is a good scientist. But instead of providing open information about the medical benefits, it turned out that there were commercial agreements about lactoferrin with Nutricia. That arouses resistance."[61]

This dissatisfaction exists in all layers of society. In 1998, activist Lily Eijsten from the Amsterdam neighborhood of De Pijp once again voiced her objections in the magazine De Oogst. She was very old at the time, but when it came to suspicious industries and institutions, she was still full of fighting spirit. "Do you know what bothers me the most? The deception. Those manufacturers only tell half-truths. They present guesswork as scientific research, which shows that genetically modified plants are completely safe. But you're being deceived. It's not true. Studies that claim the opposite are ignored or systematically undermined. That says enough to me. We're being sold a bill of goods." For Eijsten, it's a foregone conclusion. "Genetic manipulation should not be allowed. It is unsafe. And it all smacks of a conspiracy."[62]

This resistance can take extreme forms, as illustrated by the tragic case of English animal rights activist Barry Horne. After a failed school career, he became a street sweeper and garbage collector, but soon began to care about animal welfare. His first major action was an almost tragicomic attempt in 1988, together with four supporters, to free Rocky the dolphin from a dolphinarium in Lancashire. The animal was kept there in appalling conditions. The rescue attempt failed; they couldn't get the 300-kilogram animal onto their stretcher. When the group returned to the car empty-handed with the dripping stretcher, they were picked up and arrested by a police patrol that happened to be passing by.

After a stay in prison, Horne's actions became more aggressive. In southern England, he placed firebombs at shoe stores and shops that collected money for cancer research. After all, laboratory animals are used in this research. He was arrested and sentenced to eighteen years in prison. On January 6, 1997, he began a hunger strike in his cell, demanding an end to the use of laboratory animals. This action was a signal for supporters throughout England to rise up. Laboratory dogs and cats were freed, and in Dover, a McDonald's restaurant was severely damaged in an attack. Another hunger strike in September 1997 led to protests abroad as well. A year later, Barry Horne went on a hunger strike that lasted 68 days, bringing him to the brink of death. But he got what he wanted: the press, both nationally and internationally, focused on the fate of laboratory animals. His actions led to death threats against prominent researchers. Horne died on October 21, 2001, as a result of yet another hunger strike.[63]

In the Netherlands, too, animal rights activists raised their voices in the 1990s. In 1999, *NRC* interviewed two activists, Frank and Erik.[64] Over a period of three years, they carried out 28 attacks on meat processing

companies. Animal rights activists united in groups such as the Animal Liberation Front (ALF) and People for the Ethical Treatment of Animals (Peta). Inevitably, at some point they set their sights on Pharming.
De Boer remembers it well. “One morning, I walked into my office. They had thrown paint bombs at my bookcase, and there was paint everywhere. They did it in the fifteen minutes before I arrived. Back then, you could still walk in anywhere without a badge; you didn't have to identify yourself. I still have things upstairs with green paint on them.”
De Boer was never physically threatened, but he was mentally threatened, he says. "They called me Joseph Mengele. My supervisor from Groningen, Professor Max Gruber, gave me a pep talk. He is Jewish and has been through a lot. He said, 'Herman, it's a good thing you've taken up this new technology.' That was much more important to me than the strange things that were said about me."
The man who succeeded De Boer as CEO of Pharming in February 1993, George Hersbach, also faced threats. These are not pleasant memories. “We disagreed with the Animal Protection Agency,” he says, “but that was still civilized. We had to take them to court, but that wasn't the end of the world. We did have some very unpleasant experiences with the activists from PETA and others.”
Herman de Boer received visits from activists at the university, and they also visited George Hersbach at home. "We had EuroDusnie[65] visit us once, but they were stopped by the police. Those were not pleasant times. They once covered the entire facade of a colleague's house in the center of Voorschoten with paint. It's oppressive when the police warn you to be careful. We had round-the-clock security for months. Our neighbors in Naarden weren't happy with that conspicuously inconspicuous car in front of our door. Neither were my children, for that matter. They're adults now, but they still talk about it sometimes. You don't forget something like that."
The Animal Protection Agency and the Nature and Environment Foundation initially stick to lawsuits against Pharming, but are not very successful. Their lawyer points to the poor treatment of the animals and questions the medical importance of the whole exercise. The legislator has stipulated that the breeding of transgenic animals such as Herman

Committees are being set up to decide on the future of Herman the bull: will he be allowed to breed?

the bull is only permitted when there is a significant medical interest and there are no alternative production options. “But it is entirely possible to produce lactoferrin in other ways,” argues the lawyer. “And it is not plausible that other medicines can be produced in this way.” His plea fails to convince the judge.[66] The lawyer's case is quickly proven wrong when it emerges that Pharming is developing a treatment for Pompe disease in milk. Only this time, not in cow's milk.
Later, the battle moved to parliament, where animal welfare organizations tried to restrict genetic modification of animals through legislation. Committees were set up to decide on the future of bull Herman: should he be allowed to reproduce? Should he even be allowed to live? Ethicists weighed in on the subject.[67] This ultimately led to legislation that restricted genetic modification of living beings and made it subject to a permit.
It is a good thing that the discussion about this new technique is being held, both in court and in parliament. As early as 1975, there was talk in the US about the dangers and risks of transferring genetic traits from one organism to another. If such an organism escaped from a laboratory, could it lead to a plague and a threat to human health? It is a discussion that would later be repeated in all kinds of variations. As recently as 2020, after the outbreak of the coronavirus, a Chinese laboratory came under critical scrutiny.
When it comes to animal welfare, Paul Krimpenfort believes that the criticism of Pharming at the time was certainly justified. "A practical objection was that we were causing animal suffering, and we were. Because the implantation of cultured embryos—whether manipulated or not—often leads to calves that are much larger than normal. This makes calving a problem. Almost all of these animals were born by Caesarean section. This is common in livestock farming today, but it was less so at the time. So yes, you cause discomfort to the surrogate cows, especially if you implant two embryos that both develop into calves. They were right about that. Later, this problem was prevented by implanting only a single embryo and closely monitoring the pregnancy."

The main criticism from activists is that the integrity of an animal is compromised. “But then you first have to define exactly what that integrity is,” Krimpenfort counters. “If you argue that it depends on its genetic makeup, you're on thin ice. Anyway, I can imagine that opponents find it emotionally difficult when you genetically modify an animal. Do I agree with them? I don't think so, but I do think we should have responded better to that criticism.”

You may or may not agree with the fundamental objection that animals are being used at will, he adds. "But of course, humanity has been ‘using at will’ for a very long time. I do think you have to be careful with it.

It was possible to talk about it, but it became so emotional that it was difficult to even engage in conversation with the activists. I think that in hindsight, the Animal Protection Agency will also say: 'Well, maybe we should have handled it differently. That certainly applies to Pharming.”

The fact is that the Animal Protection Agency has continued to ask critical questions about the use of transgenic animals. Michiel Linskens, a long-time opponent of Pharming from the Animal Protection Agency, said in 1998: “In twenty years' time, we don't want to feel that the Animal Protection Agency did nothing to reverse the development of transgenic animals. What we have achieved with our campaign is that Pharming and Numico[68] have become aware of their social responsibility. But I still regret that Pharming has gained a firm foothold.”[69]

After that first meeting between Herman de Boer, Ans van der Ploeg, and Arnold Reuser in 1992, things remained quiet around Pompe for a long time. No publicity was given to the plans for the rare disease. However, a cooperation agreement was established between Pharming, Leiden University Medical Center, and Erasmus MC. Funded by the Princess Beatrix Muscular Dystrophy Fund, young researchers set to work in an attempt to develop a completely new therapy. The result was that in 1996, Herman the bull was replaced by a herd of rabbits. There was hope for Pompe patients, but they didn't know it yet.

15

MARYZE

MY BROTHER IN LEIDEN

I used to challenge my little brother and sister sometimes. I would say to Lee-Anne: “When you grow up, you're going to make sure I can go anywhere in my wheelchair.” And to Leonard: “And you're going to invent a medicine that will make me better.” Of course, it was just a joke, but the fact is that my statements at the time seem to have had a certain predictive power.

I was 23 and living in a student house in Leiden. I had no home care, no help, and my parents lived in Varsseveld, on the other side of the country. I had to fend for myself, and I usually managed just fine. Fortunately, I had Carina, my best friend, who, like me, came from the Achterhoek region and was an anthropology student. I met her in the queue at the university registration desk. We became soul sisters. I could always fall back on her when I needed help. She died in Turkey on July 2, 1993[70], at the age of 22. She was attending a cultural festival in Sivas, where Aziz Nesin, a celebrated Turkish author who had published excerpts from Rushdie's *The Satanic Verses* in Turkish a month earlier, was also present. Despite all the protests, he had announced his intention to have the entire book translated. After Friday afternoon prayers at the mosque, an angry mob of 10,000 people marched towards his hotel – and Carina's. Windows were smashed and Molotov cocktails were thrown inside. Aziz Nesin was rescued by the fire brigade after hours.

Carina died in the smoke, along with 33 others.
My brother enrolled in Leiden to study molecular biology. It was a great program, but he could have done it at other universities. He chose Leiden to be close to me in case I needed help, for example if I fell.
In 1996, Leonard attended a lecture on transgenic animals at the Gorlaeus Laboratory. The lecturer, Martin Verbeet, told the students about the latest developments. He mentioned the bull Herman, whose offspring would produce lactoferrin in their milk. He also reported on another recent development. “At the moment,” he revealed, “we are working on something revolutionary. We can now modify a gene in animals so that they produce the enzyme alpha-Glu in their mammary glands. This enzyme can be used to treat people with a serious condition called Pompe disease.” My brother couldn't believe his ears. He saw an important scientific breakthrough ahead.
It was concrete proof that something was really about to happen. Of course, there were the stories of Ans van der Ploeg and Arnold Reuser at the VSN patient days, but that always remained somewhat abstract. Something like: ‘maybe’ and ‘somewhere’ and ‘someday’. When my brother came home with his story, it suddenly became tangible. In the Netherlands, in a laboratory across the street from me, serious researchers were working on a serious medicine. At the same time, I thought: I have to put this away, store it, not let it get to my head. That's not wise.
Leonard was looking for a scientific internship. Verbeet referred him to Arnold Reuser in Rotterdam. “Why don't you come along to the VSN patient meeting?” my father suggested. “The lectures are always very interesting, lots of biomedicine, lots of microbiology, right up your alley.” At that meeting, I introduced him to Arnold, with the result that he was immediately able to join the laboratory in Rotterdam. There, PhD student Agnes Bijvoet was working with Pompe mice. For Leonard, it was exciting research. If the injected enzyme could indeed remove the accumulated glycogen from the muscle cells, it would be another important step toward a therapy for his eldest sister.
It was exciting for me and my parents too. But if we thought we would now hear first-hand news about the progress being made on Pompe disease, we were mistaken. Leonard kept his lips sealed. On the one hand, it was irritating, but on the other hand, we understood that research results had to remain secret until they were published. That's just how it works. Still, my father managed to get something out of him from time to time. For example, he would ask, “And Leonard, is the sun shining in Rotterdam, yes or no?” When Leonard said yes, we knew enough.
Of course, I would have liked to end the story about my brother with a scientific breakthrough in his Pompe research, but that's not how it turned out. As a researcher, he missed the direct contact with patients and changed course. He is now a rheumatologist. Nevertheless, in my eyes, he has taken up the challenge that I, as a teenage girl, had so carelessly thrown at him.
And my sister, Lee-Anne? She is not only my neighbor, but also the person I can always fall back on. My parents taught us to stand on our own two feet. To be independent in life. And that's what we do. But everyone needs a helping hand, a listening ear, a shoulder to cry on at times. My sister not only makes sure I can get everywhere—she is an architect and designed my wheelchair-accessible home—but also that I always come out on top when it comes to the many hurdles I have to overcome in order to live my life.

16
MILKING MICE
1992 - 1997

Maryze's brother's teacher from the previous chapter, Martin Verbeet, had been working at Leiden University in Herman de Boer's department since 1990. At the same time, he was also working for Pharming. “It wasn't such a big deal back then,” he explains. “I was happy to be able to work on interesting projects.” He comes, as he puts it, from ‘the world of hemophilia’. “With hemophilia, you're dealing with a factor in the blood serum that contains errors and causes damage to patients. I worked on that for a while, because it seemed fairly easy to fix with an IV.”
In 1992, Herman de Boer introduced him to two researchers from Rotterdam, Arnold Reuser and Ans van der Ploeg. They hit it off immediately. “Arnold,” explains Verbeet, “contributed a lot of biochemical knowledge, I was the geneticist, and Ans was the clinician in the team. That resulted in a fruitful collaboration.”
Meanwhile, Pharming was facing setbacks. The most important one was that Herman's offspring were failing. A new, better gene had to be constructed. The whole cycle started all over again, causing a significant delay. After all, cows, like humans, have a gestation period of more than nine months.
But there are other problems, says Verbeet. "Pharming bought a farm in Polsbroek. The farmer traveled to Poland and bought mountain cows there because they were a lot cheaper. That wasn't a good idea. Those

animals have a different physique than Dutch cows, so the hormone treatment and the injection of fertilized eggs had a very different effect. The Polish cows sometimes jumped around like crazy when they were being treated."
It is indicative of the situation at that time. The company still has all the characteristics of a pioneering organization: many enthusiastic scientists and technicians on board, but lacking in business and commercial experience.
Postponements and delays made investors uneasy, including those at Pharming. They could see very clearly that the project was not going according to plan, while Herman de Boer had presented them with a very optimistic agenda with the prospect of substantial revenues. To gain more control over the process, they appoint a second man alongside the director. His task is to ensure a more business-like approach: the aforementioned George Hersbach. In previous years, he had set up the European branch of the American company Cetus, also a biotech company, in Leiden. The outcome is predictable. The two captains got into a fight, with De Boer coming off worse. He left the company he had founded himself.
The internal strife had no consequences for the collaboration between Verbeet, Reuser, and Van der Ploeg. They started their project without any internal or external publicity. They are driven by curiosity, but also by the image of the patients who have placed their hopes in them. Would it indeed be possible to produce alfaGlu in milk? The good alfaGlu, which is not rejected by the body?
A crucial step had already been taken by PhD student Lies Hoefsloot. Together with a team, this Rotterdam-based molecular biologist succeeded in unraveling the code of the gene that contains the recipe for human alphaGlu and then copying that gene. She published her findings in 1990.[71]
“It was a race against time,” admits Arnold Reuser. "At the time, it was a question of who would be first: Rochelle Hirschhorn's group in New York or us. That's how it works in science. We won the battle in 1988 with Lies and her analyst Marianne Hoogeveen-Westerveld, thanks to a grant from the Princess Beatrix Muscle Foundation. Marian Kroos

and I worked on the project as protein specialists, together with Jos van Beeumen. The molecular work was supervised by the expert Ben Oostra. Without him, little would have come of it."[72]

Reuser and Van der Ploeg literally have the gene in their hands, the tiny recipe book that can be used to produce the enzyme alphaGlu. At that moment, they cannot foresee that this gene not only contains the blueprint for the desired protein, but that it will also be the start of a transatlantic battle. But more on that later.

It is during this period that Arnold Reuser receives a phone call from Scotland. The man on the other end of the line introduces himself as Kevin O'Donnell, the father of the deceased boy Calum from chapter 1. Yes, from Pompe disease. He asks Arnold if he can tell him more about his research.

Because Kevin has to be in Amsterdam shortly afterwards for a major conference, he decides to visit Erasmus MC. O'Donnell's respect for Arnold Reuser and his medical counterpart Ans van der Ploeg only increases during the visit. As a result, Ans and Arnold regularly travel to England in the following years to give lectures to Pompe patients. O'Donnell would later emerge as the liaison within the global Pompe community.

But in 1993, there was nothing to communicate yet. The lactoferrin project had made it clear that it was not wise to insert the gene directly into a fertilized cow egg cell. First, they had to find out in the lab and in mice whether enzyme production and replacement would be successful in this way.

Martin Verbeet outlines the major challenge. "I specialized in DNA work: cloning—copying genetic material—with the aim of producing a protein and purifying it. I had joined Leiden University and Pharming to set up precisely this type of project. With hemophilia, it was relatively simple. There, you are dealing with a defective protein in the bloodstream. If you introduce the correct protein into the blood via an infusion, it will simply do its job."

Verbeet explains that it was already known at that time that the principle of enzyme replacement therapy could work. "This had already been demonstrated in Gaucher's disease. But in Gaucher's disease, the affected cells are mainly found in the blood. So it's much simpler. With a muscle disease like Pompe, that's not the case. You just have to wait and see whether the enzyme leaves the bloodstream, ends up in the muscle cells, and then finds its way to the place where it has to do its job: the lysosome. We didn't have any good examples and we just had to see how we could develop a good and reliable production system. That was at the edge of what we could do technically, a process with an uncertain outcome."

On Saturday, January 4, 1997, an important piece of the puzzle fell into place. Agnes Bijvoet, Reuser's PhD student who had met Maryze's brother during his internship, went to the laboratory early that day. She was going to 'take apart' a mouse, as she herself put it.

In the background, a radio babbles on with reports of the fifteenth and, for the time being, last Elfstedentocht. She is the only one at work. The rest of the country is in the grip of skating fever. Bijvoet began her research with transgenic mice in 1992, not long after the alfaGlu gene was cloned.

"I got in at the right time. For a disease like this, you first need to identify the cause. Often, it's a protein that doesn't work properly or at all. Then you ask yourself: can we do anything about that? Once you've cloned the gene responsible for that protein, you can continue your research."

Bijvoet remembers that when she started, she had two years of funding from the Princess Beatrix Muscular Dystrophy Fund. "Later, money also came in from other funds. I was in the Clinical Genetics department with Martin Verbeet, but I also worked a lot with people from Pharming. When it came down to it, the cows always came first." As Herman de Boer mentioned earlier, Agnes also sat down with colleagues every week to extract suitable egg cells from cow ovaries.

Embedding the human gene for alphaGlu into mouse DNA is not as simple as it seems. It starts with the discovery that the gene is far too large to be transferred into a mouse egg in one go. This problem is solved by injecting the gene into the mouse cell nucleus in three separate parts. The three pieces then have to find each other again in the cell nucleus – a technical feat at the time.

The next challenge is to ensure that alphaGlu is only produced in the

Paul had built little
mouse milk machines
out of pipettes,
small balloons, tubes
and a vacuum pump.

mammary glands and not in other cells. This requires a piece of DNA code. In order for the inserted gene to land properly in the cell nucleus, a starting piece – called the promoter – and an ending piece must also be added. It is a collage of genetic material that is called a gene construct in the world of biotechnology. Bijvoet: "The milk part of this came from Pharming. I created the part that was responsible for the production of alphaGlu in the cell. The outside of it, the promoter and the closure, came from Pharming. That's where the final gene construct was injected into the fertilized eggs of mice."

Martin Verbeet emphasizes that working with animal cells was essential. "With Agnes' gene construct, we were able to produce the enzyme first in mice and later in rabbits. You still have to check whether the proteins have the correct glycosylation with M6P, because only with those sugars on the outside can the enzyme enter the cell. Before that, we thought that you could also make such an enzyme in yeast. I tried it for hemophilia, but it didn't work. So this production system with mice was a very important step in the process."

It is time for the next step: the development of a Pompe mouse, also known as a 'mouse model' or 'knockout mouse'. It is a name that may evoke the wrong associations among laypeople. The mice are not hanging in the ropes like battered boxers; they are just walking around in the mouse enclosure. Agnes Bijvoet will use these mice to demonstrate that enzyme therapy works in living beings.

"For this part of my project, I moved to the protein lab in Rotterdam," she says. "Among others, Marian Kroos, Arnold Reuser's analyst, was there. I found myself in an environment where many more people were working on alfaGlu. This allowed me to learn about other parts of the research. Arnold and Ans are inspiring, driven researchers, which made it even more special for me."

During that period, Agnes and her colleagues created mice with Pompe disease. "Before my time, they had already succeeded in isolating alfaGlu from urine. That alfaGlu turned out to work in a cell system, in a glass dish. But that doesn't prove that it also enters the muscle cells of living creatures. Once we had Pompe mice, we started milking the transgenic mice. That went fairly smoothly. The alfaGlu was isolated from the mouse milk, purified, and then injected into the Pompe mice."

Milking mice sounds almost like a joke, but it really happened at Pharming. Paul Krimpenfort had built mouse milking machines from pipettes, balloons, tubes, and a vacuum pump.

Back to January 4, 1997. For this one day, Friesland is the center of the world, while Agnes Bijvoet performs a section on a white mouse in the Leiden lab. "I sat there with my cutting tools, bent over the little creature. We had already seen that the mouse had the mutated Pompe gene in its DNA. To determine this, it is sufficient to cut off a small piece of the toe or tail of a newborn. But that is no guarantee that the mouse will also develop the symptoms of the disease. While the cheers of the crowd swelled in the background on the radio, I saw the mouse cells filled with glycogen appear under my microscope. And in the Pompe mice that had been treated with the enzyme, I saw the enzyme disappear from the cells. We had succeeded! I too was cheering at that moment."

Agnes' publication[73] on this research was awarded the annual prize of the Neuromuscular Diseases Research Foundation in 1999, in recognition of her excellent research into muscle diseases.

17
WHITE RABBITS
1995 - 1996

In the early days of the collaboration between Erasmus MC Rotterdam and Pharming, little was revealed about the progress being made. The cows and the lactoferrin project were still the top priority, but slowly the tide began to turn. Rein Strijker, an employee from the very beginning and Vice President at Pharming Netherlands in the mid-1990s, says that people were starting to look for alternative products.[74] “That was in '94, '95. It was already clear at that point that the lactoferrin project in cows was even more challenging from a technical standpoint than we had initially thought. So we started looking for other applications: biomedical proteins, for which there was a great need and which were not easy to produce at that time.”

That search yielded a number of candidates, Strijker recalls. “We also had alfaGlu in mind. When you did the math, it turned out that you needed quite a lot of protein, even though it's a rare disease. But it was an option, and we said to each other: this could be something.”

Pharming had its reservations, Strijker continues. "Because we were entering a field we knew nothing about. We even had to look up what kind of disease it was, this Pompe disease, we had never heard of it. We knew little about orphan drugs and rare diseases. Genzyme had just started working on a drug for Gaucher disease, which we found a bit exotic. We came from a completely different angle. For us, it was all about proteins

that were needed in large quantities, in tons, such as lactoferrin. Cows are very suitable for that. The Pompe product is of a different order. We did have our doubts about that. At one point, we said to each other: maybe we shouldn't produce the protein in cows at all. Cows have disadvantages. They are kept in barns where insects fly around and dirty animals run around that can transmit germs. It's not really obvious to produce medicines in such an environment."

But the choice of production animals is not very large. Farm animals have previously been divided among three companies through patents: Pharming has the patent on transgenic cattle, the Scottish company PPL Therapeutics on sheep, and GTC, Genzyme Transgenics Corp[75], on goats.

Sheep and goats are therefore ruled out as alternative milk suppliers.[76]

Gerben Moolhuizen[77] was Director of Business Development at the time and witnessed the developments firsthand. "We were given a small budget to create transgenic mice, and that went well. As the results for alfaGlu improved and the lactoferrin option seemed less promising, our interest in a possible Pompe therapy grew. At the time, it was not yet clear to us that there was substantial market potential for this type of rare disease. But when we saw that Genzyme was becoming increasingly successful with its Gaucher product and that it was financially viable, we decided to focus on Pompe. Instead of lactoferrin, a drug for Pompe became our main product."

It is now clear that alphaGlu should not be produced in mice: they are far too small and the yield is far too low. But how then? At one point, the rabbit came out of the hat, says Gerard van Beynum, Vice President of Research and Development at Pharming. “Rabbits. A cow only has one calf and has a gestation period that is just as long as a human’s. A generation is at least twelve months, and then you get the next calf. I don’t need to explain that to rabbits; they breed very quickly. With each litter, a rabbit has eight to twelve pups, so if you keep breeding, you’ll have a barn full in a few months. What's more, and this was new to me at the time, a rabbit produces a lot of milk if you milk her regularly. So, in addition to the mouse house, we also set up a rabbit house and bred transgenic rabbits at Pharming."

This is done with the gene construct that Lies Hoefsloot had isolated. To get the construct into the right place in the cell nucleus, the help of Professor Louis-Marie Houdebine of the French INRA, the Institut National de la Recherche Agronomique[78], is enlisted. Moolhuizen: "Pharming couldn't do that itself. We did cows and mice, but not rabbits. There were few people in the world who could do that with rabbits. Houdebine was the most successful at it. Pharming sent DNA constructs to Paris. These were injected into fertilized eggs, which produced transgenic offspring. These were sent back to Pharming to be raised further."

The principle is always the same, whether it concerns mice, cows, or rabbits. "An egg cell was fertilized in a glass dish," explains Moolhuizen. "Then you injected the gene construct. You had no control over whether it integrated with the rabbit's genetic material, or where exactly. Nowadays, this can be done much more accurately. Dozens of injected egg cells were put back, a standard technique. But in this case, that happened in France. And then we just had to wait and see if transgenic animals were produced and whether a lot or a little enzyme ended up in the milk. Rabbits have a large number of offspring. There were always a few that scored so well that you could use them as progenitors for further breeding."

Moolhuizen recalls that there was considerable variation in the first generation of transgenic rabbits. "In some animals, the gene construct ended up in a less favorable location in the DNA, resulting in a lower yield. These are all things that the US Food and Drug Administration wants to know precisely. You have to demonstrate that you have a genetically stable composition every time. We have done a lot of research on this." Gradually, the people at Pharming are getting better at mastering the technique.

Van Beynum: "From that moment on, technical developments gained momentum. We had to move quickly. We wanted to have our own buildings and facilities, especially for milking the rabbits. One of our investors suggested talking to VITO, the Flemish Institute for Technological Research, located near Mol in Flanders. 'They have a rabbit colony there,' he said, 'and they do all kinds of things with them, including research into animal models.' Well, those Flemish people didn't need much convinc-

They must proceed carefully, without skipping any steps. They will not be given a second chance.

ing. It was quickly arranged."

As was assumed at the time, the relocation of production to Belgium is not, or not solely, motivated by pressure from animal rights activists or social opposition in the Netherlands. Financial considerations also play a role. The Flemish government is keen to invest in technical innovation, offering attractive subsidies and other financial benefits. Rein Strijker of Pharming confirms this. "In Belgium, there was a lot of money available to support this kind of initiative. The Flemish Investment Company contributed significantly. They had all kinds of schemes in place. That was the main reason for the move." Another reason given by Pharming in 1996 is the knowledge of rabbit breeding available in Belgium.

Pharming's production ended up in Mol, in a small business park. Van Beynum: "We were able to start in office buildings. Maarten van Dongen, our quartermaster, had experience with this. He had previously set up the farm in Finland and the one in Polsbroek." The transgenic rabbits are in their hutches. Technical obstacles are being removed one by one. The moment is approaching when a serious production line for transgenic rabbit milk can be started.

Meanwhile, some friction has arisen between Erasmus MC and Pharming. While the initial contacts between Reuser, Van der Ploeg, Verbeet, and De Boer had been between scientists, now that the company has determined its direction and definitively chosen the rabbit over the bull, business interests are coming to the fore. Since its foundation in 1988, Pharming has only made losses. Investors put their money into the company because they were promised a future of sky-high profits. After eight years of investment, it is time to deliver on those promises.

But university researchers are far removed from the world of venture capital. Neither partner has ever been involved in such a collaboration before, and it is now becoming clear that their interests do not always run parallel. Industry and science simply have different goals and different corporate cultures. Moolhuizen: "The biggest area of tension was that we wanted to bring a product to market as quickly as possible, while Rotterdam wanted it to be as robust as possible. They wanted to inves-

tigate everything in detail. So the question was always: is this a *need-to-have* or a *nice-to-have*? All those wishes cost money, and we didn't have that money. It takes time, and we didn't have that either. The researchers felt that we were moving too quickly to clinical trials. With the risk that it would fail because we hadn't researched everything thoroughly enough. Another factor was that we were also trying to bring other academic centers into the race, but Rotterdam wanted to keep control in order to reap the academic credits. That also caused tension at times."
Ans van der Ploeg and Arnold Reuser, for their part, are aware that they cannot afford to make any mistakes; this process is all or nothing. They have to operate carefully and not skip any steps. They will not be given a second chance. Van der Ploeg: "We saw that it was difficult for Pharming. Later, I learned, also from other industries, that shareholders are often on top of things: guys, you have to make a profit now, don't you have a product yet? That's a conflict, because you have to take your time for such a development process." So there were irritations on both sides, but the relationship between Pharming and Erasmus MC remains good on the whole.
Because Pharming is still under fire from social organizations over the bull Herman and politicians are becoming increasingly suspicious, the management has hired a communications advisor, Rob Meines. Van Beynum: "We now had the rabbits that could produce the enzyme, and we had seen in mice that the principle of enzyme replacement therapy was correct. Meines thought it was high time we went public with it. 'You shouldn't bring Dutch news to the Netherlands,' he explained, 'because the Dutch press isn't excited about it. You have to do it abroad.' He suggested that, as a professor, I organize a symposium on the campus in Geel. We would invite a number of expert speakers, including the renowned physician Désiré Collen from Leuven. And then we would invite the whole of Flanders and send an invitation to the Dutch and Flemish media. 'I bet the entire Dutch press will be there,' said Meines. From then on, everything happened very quickly. The symposium was scheduled for Thursday, November 14, 1996. Rob said, 'Clear your schedule for the weekend, because the media will be all over this.'"
The press release outlined a promising future for the Pompe disease drug: "The biopharmaceutical company Pharming BV in Leiden will collaborate with Erasmus University and the Academic Hospital/Sophia Children's Hospital in Rotterdam on the development of a therapy for Pompe disease, a currently incurable hereditary disease." To make it clear that the company has global aspirations, the press release goes on to mention that the new drug has been granted 'orphan drug' status by the US Food and Drug Administration, meaning it is a drug for a rare disease.
Admittedly, this is old news, as Pharming and Erasmus have been working together for four years, but that shouldn't spoil the fun. The Dutch and Flemish press turned out in force. George Hersbach opened the meeting, Ans van der Ploeg outlined the clinical picture and the principle of the therapy to be developed, and after Pharming's Flemish partners had spoken, the meeting concluded with a forum discussion. There was no shortage of press attention. Gerard van Beynum remembers it vividly. "At around five o'clock, I was driving back from the meeting in Geel when Rob was already on the phone. 'I've had all the Dutch newspapers on the line,' he exclaimed. 'All the talk shows, we can choose. But I'm giving the scoop to *Buitenhof* (a reknown Dutch parliamentary talkshow, ed.). Watch out, everyone is going to write about it.' That was the case on Friday and Saturday. After that, things moved into high gear, which in turn had an effect on our fundraising. It spread around the world. Our shareholders in Europe and America were ecstatic. It was hot, hot, hot."
De Morgen, *De Standaard*, *De Gazet van Antwerpen*, *de Volkskrant*, *NRC Handelsblad*, *Trouw*, *Haagse Courant* and *Het Parool*: they all devoted long articles to this new step by Pharming. The company had been in the news many times before, but the tone of the stories had changed dramatically: from critical to enthusiastic. It was no longer about questionable ingredients in baby milk, but about a medicine for people with the fatal Pompe disease. The newspapers also published statements that were primarily intended for investors. "Hersbach wants to be on the market with this special alpha-glucosidase protein within two to three years," writes *De Financieel-Economische Tijd* on November 15. And *de Volkskrant* reports that the rabbit herd will be expanded to 200 animals in order to

serve all Pompe patients worldwide. Not only financiers, but also patients are following this enthusiastic reporting closely. They will soon realize what such predictions are worth. On the evening after the press conference, Maryze Schoneveld van der Linde is featured extensively on the *NOS news*.

18

MARYZE

THE PRESS ON OUR DOORSTEP

It was Thursday morning, November 14, 1996. I had finished my studies and was living with my parents again. Because I had the day off, I was still in bed, thinking about what job I would take on. The rest of the family had left for school or work. It was a dull, gray November morning. Voices babbled in the background from the radio. Suddenly, my attention was drawn to a word: 'Pharming'. And then I heard 'Geel' and 'rabbits' and 'rare disease'.

I sat frozen in bed. Because of what my brother had told me about the research in Leiden and Rotterdam, the pieces of the puzzle seemed to fall into place. But was it true? Had my imagination run wild with those few words and had I perhaps heard what I wanted to hear? I turned up the radio and waited for the next news bulletin. Yes, I had heard correctly: 'medicine', 'treatment' and 'Pompe disease'. The newsreader left no room for doubt.

I was completely shaken, as if the world had suddenly turned upside down. I called my father. Had he heard? Yes, he had. He spoke calmly, but he certainly thought it was good news. It was important to keep a cool head. Yes, it was undoubtedly another important step, but nothing more than that. And was it a medicine for all patients or only for babies? There were still many questions. He was right. We had to stick to the facts.

A few minutes later, Marg was on the phone. I knew her from the patient association. How wonderful, we said to each other, but would this also be for us? Let's not pin all our hopes on this, otherwise it might be such a disappointment later.
Then I got the VSN director, Ysbrand Poortman, on the line. “You may have already heard the news,” he began. “I'm here at a Pharming press conference in Belgium among a group of journalists who would like a patient's reaction. You're the only Pompe patient I know and whose phone number I have. So?” “Yes, that's fine. When?” I asked. “Right away. They're from the *NOS news* and they'll be with you in two hours.” He hung up. Panic set in. What had I said? The *NOS news* wasn't just any news. What did they want from me? How should I prepare? What should I say? And my room was a mess. I was home alone. I could still walk a little, although it would be more accurate to describe it as ‘moving around’.
Fortunately, my sister had come home early from school, along with a friend. They were sixteen. “You have to help me,” I shouted before they had even entered the house. “The *NOS news* is coming.” Together, they moved all the clutter upstairs. They found it quite exciting.
The crew did indeed arrive two hours later. They were very nice and cooperative. They asked me what it meant to me. “Well,” I said, “I don't know how long I have to live. No doctor wants to stick their neck out on that. But I was certain that I wouldn't grow old. Until now, I've never worried about my retirement, but I think I'll have to start working on that after today.”
Almost no one had ever heard of my disease, but that evening, Pompe was the opening story on the news. It felt almost surreal to see myself walking—or rather, waddling—across the screen. And then there were the interviews with the people from Pharming. It brought the therapy closer than I had ever dared to imagine. There was already speculation about studies involving babies and young adults.
We're talking about a time when most of the Netherlands still watched the *NOS-Journaal* at 8 p.m. As a result, the next day I was suddenly a Dutch celebrity. Not just in my village, but everywhere I went. That was funny.

Since that broadcast, it has never stopped. Every time Pompe or Pharming or Genzyme was in the news, journalists called to hear my story. I kept a list, not complete, of all the interviews and appearances. I met Jos Brink (reknown Dutch presenter, deceased, ed.), Ria Bremer (Dutch presenter and journalist, ed.) with *Vinger aan de Pols*, the VRT, the Bayrische Rundfunk, Teleac, 3Sat, a Finnish magazine, BBC World... Twelve pages in total.
Because of these media appearances, I was increasingly asked to give lectures: in the Netherlands, Brussels, Portugal, London. I hadn't even unpacked my suitcase before I was invited somewhere else. It was fun and educational, but also exhausting. My mother always came with me to take care of me on the road, otherwise I would never have managed. I remember once hanging over the sink in a hotel, retching and completely exhausted. But that was part of it. That was Pompe too.

19
IT STARTS WITH A FUNERAL
1990 - 1992

Johan Van Hove is a Belgian doctor and researcher. Early in his career, he happened to get involved in an academic race around Pompe disease, in the US that is.

He grew up in Mol, Belgium, on the border with the Netherlands. "I also lived close to Geel," he says, "which takes on an ironic twist in the later story about Pompe, because that's where Pharming's rabbits were to be housed. Literally eight kilometers away from me, I cycled past it every week."

He studied medicine at the Catholic University of Leuven, but he looked beyond the border. "I wanted to study metabolic diseases and had the choice between London and Duke University in North Carolina. I chose the latter for one simple reason: Duke paid me, London didn't. I have to make a living, obviously. The program was supposed to last three years. I started there on July 1, 1990, and ended up staying until August 1997."

At Duke, Van Hove joined the team of Yuan-Tsong Chen, who is conveniently referred to by his colleagues by his initials: YT, pronounced Wai-tie. Chen already had a considerable academic career behind him. He completed his medical training in Taiwan, qualified in human genetics at Columbia University, studied pediatrics at Duke, and worked for four years at the prestigious National Institutes of Health, under the supervision of J.B. Sidbury. Together with him, he conducted research into

glycogen storage diseases. Chen's name appeared earlier in Chapter 7 in connection with diets for Von Gierke disease. In 1983, Chen returned to Duke, where he started his own research into glycogen storage diseases types 1, 3, and 4. Pompe disease, type 2, was not included. When Johan Van Hove arrived at Duke in 1990, this was still the case. But that was about to change.

In November 1990, a couple came to see him with their seriously ill baby. The five-month-old child showed severe muscle weakness and developmental delay. The parents had already visited several hospitals, but no doctor knew what to do. Y.T. Chen diagnosed an enlarged heart and an accumulation of glycogen in the muscle tissue. Diagnosis: Pompe disease, untreatable and fatal.

Van Hove followed this episode closely: the examination, the diagnosis, the parents' grief. It was the first time he had seen a child with Pompe disease. He still has vivid memories of it. "There was no treatment yet, but we knew that bone marrow transplantation had a positive effect in some more or less similar conditions. Good results had been achieved in Hurler disease in particular, which meant that this therapy was already considered a possible standard treatment. So we asked ourselves: could we not treat this child with it too?"

Bone marrow transplants had already been tried in Pompe disease.[79] The results were disappointing, but researchers remained interested in the possibilities. More articles appeared, and Arnold Reuser and Ans van der Ploeg from Rotterdam also joined the scientific debate.[80] Chen searched worldwide for specialists and inevitably ended up with Reuser.

It was Friday, January 11, 1991, when the researchers spoke to each other for the first time. During that meeting, Reuser indicated that he did not see much benefit in a bone marrow transplant. Chen shared the same opinion. Enzyme replacement therapy was also discussed. "If it comes to that, I expect more from that," says Reuser. A week later, Chen sends him a letter in which he reiterates his lack of confidence in the results of bone marrow transplantation and that the parents of the sick child are also aware of this. Nevertheless, preparations for the operation continue at the request of the family. In early February, Chen receives permission from the hospital to perform the procedure.

"Those people wanted to seize every opportunity, no matter how small," says Van Hove. "A bone marrow transplant costs a lot of money. They weren't rich, and the insurance company didn't want to cover the treatment. Through their church community, the parents organized a fundraiser and raised $25,000 in two months, half of the cost. During a screening at the hospital, we saw that the girl's heart was already terribly enlarged. We said, 'We're not going to do this; it's pointless.' The child went home and suddenly died the following week."

Van Hove and Chen attended the funeral, which made a deep impression on them. "The pastor said that God must have had a purpose for this child's short life," Chen recalls. "I said to Van Hove, 'The next time we see a Pompe patient, we can't come up empty-handed again.' We went back to the lab with the intention of finding a treatment. That's how it really happened. The parents donated part of the money they had raised to the research."[81]

Of course, you can set your mind to something like that, but you start out empty-handed again, Van Hove continues. "Y.T. Chen had focused on other storage diseases. Pompe disease had long been out of the picture. Since 1990, Duke had been designated as the national reference center for all glycogen storage diseases, including Pompe. Reuser's work then attracted international attention. He showed that the enzyme alpha-Glu is absorbed into the cells when purified from a bull's testicles and then sent through a heart muscle. And that mannose 6-phosphate must be present on that enzyme, otherwise it will not enter the muscle cells. But we did not know how to obtain such an enzyme. In any case, it was clear that it should not be extracted from the testicles of a bull, as this would certainly cause a rejection reaction in humans. There was another publication that stated that very small fractions of a usable form of the enzyme could be found in human urine. That was all we knew, and we had to make do with that."

Van Hove and Chen discuss different approaches to therapy, including gene therapy. Chen: "That was already an option in the early 1990s, but the technology was still under development and the results were uncertain. So it was still too early for that. We also discussed a therapy using so-called small molecules. These are substances that can easily penetrate

Natural sources
such as urine or placentas
were not an option
due to practical
concerns.

a cell and inhibit the production of harmful glycogen there. But the only substance that was suitable for this turned out to be highly toxic. We had difficulty choosing the right direction."

According to Van Hove, an important moment was a meeting in Long Beach. "Our department head, Charles Roe, was a charming and inspiring personality. Every year, he organized a meeting for his senior researchers at his country house in Long Beach, a coastal town in southern North Carolina. The house overlooked the Atlantic Ocean and was just a few steps from the beach. The aim was to exchange knowledge and experiences, develop plans, and come up with new ideas. We called these meetings the Long Beach Institute, or LBI."

From April 4 to 7, 1991, the LBI took place for the ninth time. The theme: the treatment of lysosomal storage diseases such as Gaucher, Fabry, and Pompe. There were also guests from abroad: Arnold Reuser, James Sidbury, and Roscoe Brady. Van Hove: "I was allowed to attend as a rookie, a favor to the young student who was going to do research the following year."

Chen is co-organizer of the LBI. He was delighted with the presence of Roscoe Brady, a former mentor at the National Institutes of Health. Brady, as mentioned, made history with the development of an enzyme replacement therapy for Gaucher disease, which was approved for the market by the Food and Drug Administration that same year.

Brady was no stranger to Reuser either. "I had met him several times through a collaboration on Gaucher disease," he says. "This collaboration had been in place since the early 1980s between the universities of Amsterdam and Rotterdam and the NIH. My graduation professor, Joseph Tager, had taken the initiative. At the NIH, it was mainly John Barranger and Ed Ginns who led the way. They were also the ones who developed the enzyme replacement therapy for Gaucher in practice."

He continues: "During the LBI, there are presentations on a variety of topics. Roscoe Brady talks about the success of the therapy for Gaucher. I reported on our results with enzyme replacement therapy for Pompe

using M6P. We had already published several articles on this in Rotterdam." [82]

After the meeting, the researchers from Duke were certain: they too would continue to develop the option of enzyme replacement therapy. That is where the greatest opportunities lie. Bone marrow transplantation is definitely out of the question, at least for the coming decades.

"After that meeting, the most pressing question was: how are we going to produce that enzyme?" Van Hove continues. "Natural sources such as urine or placentas were not an option due to practical objections. We would have to use recombinant DNA, i.e., insert a piece of genetic material containing information about the Pompe enzyme into cells using other mechanisms. Bacteria seemed the obvious choice, but they cannot produce the Pompe enzyme with M6P sugars. So what could be used?"

The researchers were initially unable to find a solution, and the project was put on hold for a year. In the summer of '92, they picked it up again.

Van Hove: "With the question of which cell type would be suitable in the back of my mind, I searched the literature very extensively. Now it's obvious, but it wasn't then. There was not yet a single enzyme that was produced recombinantly, i.e., with animal cells into which a human gene had been inserted. There was also no commercial enzyme on the market. With the exception of the Gaucher enzyme, but that was still extracted from placentas. So I had no examples. We considered all kinds of cell types: insect cells, monkey kidney cells, everything came up. I searched through a thick stack of articles and ended up with CHO cells, Chinese hamster ovary cells, from the ovaries of Chinese hamsters.[83] Not much was known about them either; I found two articles, but it seemed like a good choice to us. The potential enzyme yield was higher than any other cell type, and CHO cells were known to be very stable. There were no abnormalities, no viruses. That's also important."

Van Hove needs equipment to do more research. There is no money, so he buys as much as possible second-hand. "Everything in the lab was a bargain. Sometimes we were lucky. Y.T. Chen once gave a tour to a couple whose child had recently been diagnosed with Pompe disease. The mother asked if I needed anything for our research. 'A device to purify the protein and a cold box, a very large freezer with a glass wall, so I can see what's happening,' I said. She looked at me and asked, 'How much do you need for that?' I named a figure: $30,000, a fantastic amount of money, more than I earned in a year. The father looked at his wife for a moment and asked, 'May I?' She said yes, and without hesitation, he wrote a check for $30,000. I used that money to buy the equipment, which I worked with for a year to optimize the purification method."

Another important stroke of luck was that Van Hove received a cloned gene from Arnold Reuser. Van Hove: "In Rotterdam, they had succeeded in isolating this piece of genetic material; Lies Hoefsloot had copied it there in 1990. We needed that DNA to make the enzyme. I had started in September 1992, and a few months later, I received the gene from Arnold. Without that gene, we wouldn't have gotten any further."

The fact that Reuser gave the gene away for free to two other researchers, Van Hove and Australian researcher John Hopwood, is one of the most remarkable details in this story. Looking back, it seems rash, perhaps naive, but things were different back then, says Reuser. "Science was much more open at that time. You trusted your colleagues. Everything was for science and the patients. When we couldn't make any further progress in the Netherlands due to a lack of support, I gave the gene to Van Hove and Hopwood."

Before we continue the story of developments at Duke, we must briefly consider the scientific work of John Hopwood. He was a pioneer in research into lysosomal storage diseases, including Pompe disease. Perhaps his biggest drawback was that he worked in Australia. That meant he had to travel far to establish contacts with fellow researchers. Researchers in the US may also have seen him as a threat because of his rapid progress.[84]

Hopwood maintained contacts with the biopharmaceutical company CSL in Victoria, Australia, which later became CSL Behring. He discussed with that company the option of producing drugs for lysosomal storage disorders. That fact prompted Reuser to decide to make the gene for alphaGlu available to Hopwood as well. "This was interesting to us, so I gave it to John because I held him in high regard and trusted him completely."

The 'gift' resulted in an experimental production line using CHO cells.

This does indeed produce the desired enzyme, which also works in the cells of Pompe patients. In 1995, it led to a publication by John Hopwood and colleague Maria Fuller, with Ans van der Ploeg and Arnold Reuser as co-authors.[85] Unfortunately, CSL then made other choices, leaving Hopwood's CHO cells with an uncertain future. For the Rotterdam researchers, this meant the loss of an attractive option for fruitful collaboration.

EXPLAINED

CHO-CELLS

*Chinese hamster ovary (*CHO) cells come from the tissue that covers and protects the ovaries of Chinese hamsters. CHO cells were developed by American geneticist Theodore Thomas Puck in 1955. An important characteristic of these cells is their ability to produce human proteins with complex sugar molecules attached to them, which is exactly what is needed for the manufacture of alfaGlu and similar proteins. Equally remarkable is the fact that they do not die, but live forever.

CHO cells now play an important role in biological and medical research and are frequently used as mammalian hosts for the industrial production of recombinant protein therapies. They grow easily in large bioreactors, which makes them suitable for protein production.

These are exclusively cells; live Chinese hamsters are no longer involved.

CHO cells are now readily available for purchase online, in all kinds of varieties and for a wide range of applications. This new production method began to take off in the early 1990s. Even then, CHO cells came in all shapes and sizes and, depending on the application, had good and bad properties.

20
SINGING QUAILS
1992 - 1997

Research is continuing apace at Duke University. For Y.T. Chen and Johan Van Hove, it is now clear what they need to work on: a bioreactor with CHO cells that produce enough alpha-Glu to treat a small number of patients. How should they go about it? Based on publications, reasoning, intuition, and simply trying things out, Van Hove gets to work. He also finds a fellow researcher who is on the same track.

“That was Emil Kakkis, whom I knew. Emil was working on an enzyme for Hurler syndrome, also known as MPS I. A storage disease, just like Pompe.[86] He also wanted to use CHO cells to produce the missing protein. We emailed each other a few times about the process and so on, but he chose a different method for culturing the cells.”

Van Hove and his fellow researchers went through the same phases as their colleagues in the Netherlands. The first barrier was introducing the alphaGlu gene into the cell nucleus. They just couldn't get it to work. Until a colleague, Jer-Yuan Wu, came to Van Hove's rescue. He manages to get the job done within 24 hours. If Van Hove thought that a stream of protein would now start flowing, he was mistaken. The yield from the cells is minimal; it needs to be much better.

"I carried out a two-and-a-half-year process of improvement. It started with a simple selection. I extracted cells a hundred times, cultured them, tested them one by one to see which ones produced the most enzymes,

and then cultured the best ones again. In the next selection, the cells had to produce more alphaGlu. Again, I had to select the cells one by one. Then I cultured a hundred of those cells, one by one, each clone separately. And so on. We had an installation with affected cells from patients to see whether the enzyme from the cells was properly absorbed. I went through that process about four or five hundred times: each time with a stricter selection, in which the cell had to produce more and more protein in order to survive, followed by a selection from more than a hundred individual cell lines.

Until we finally had a cell that produced a thousand times more than the original cell culture. That should be commercially viable.” Van Hove is highly motivated for the search, but no one knows if anything will come of it. “It could just as easily have failed. We had no example, it was a matter of taking the plunge. I was desperate when nothing seemed to work. Y.T. encouraged me. I wanted to give up when I still hadn't seen any new cells appear after three weeks. Please, please let there be one cell, I thought, peering through my microscope. After two and a half weeks, I wanted to throw everything away. Y.T. said, ‘Wait five more days, three more days...’ And then the new cells appeared."

To be absolutely sure, Van Hove now has to compare the CHO enzyme with alphaGlu from a completely different source. He has chosen human urine for this. "I just had to find enough raw material. The first 60 liters of urine came from Chen and his two sons. Among ourselves, we referred to it as ‘Chen-zyme’, with a nod to the company Genzyme. I obtained another 40 liters from elsewhere. I put those 100 liters in a concentrator in the cold room. Day and night, that machine worked to turn those 100 liters into 10. That allowed me to do an initial purification process. From the hundred liters, I ended up with 1 milligram of Pompe enzyme." But that one milligram is enough to confirm the proper functioning of the CHO protein.

In 1996, the CHO cells finally produced enough alphaGlu to test the enzyme in practice. Animal testing, that is. But where do you find animals with Pompe disease? And apart from that, how do you go about conducting animal testing? Van Hove has no experience with testing drugs in animals. He discovers that a neighboring laboratory at the

university is conducting asthma research with guinea pigs. He is allowed to use them.

"The animals had a cannula, a small tube in their bodies, which made it easy to take blood samples," he explains. "I was able to use that cannula to inject the enzyme. An hour after administration, I euthanized the animals. We did this with three or four guinea pigs. During the research, it turned out that the enzyme mainly went to the liver, lungs, and spleen. Only about 5 percent ended up in the heart and muscles. Still, the absorption was easily measurable. For me, that was an indication that the enzyme I had created could work effectively."

Van Hove's work led to an article in the renowned journal *PNAS*, a month after the aforementioned publication by the Australian Hopwood, Fuller, Reuser, and Van der Ploeg. The researchers were hot on each other's heels.

But they are still a long way off. All Van Hove has demonstrated at this point is that his Pompe enzyme is absorbed into the muscle tissue of healthy Guinean piglets. Whether the enzyme can clear the accumulated glycogen in a diseased cell remains to be seen.

Chen and Van Hove had to search for animals with Pompe disease, with muscle cells full of accumulated glycogen, preferably also with an enlarged heart. Nowadays, such test animals, generally mice, can be 'created' relatively easily in a laboratory, but in the mid-1990s, this was still extremely specialized work. "The technique was developed in the 1990s by Oliver Smithies at the University of Chapel Hill in North Carolina, a neighboring university. He won the Nobel Prize for it," explains Van Hove. "But the technique was still in its infancy." In Rotterdam, Agnes Bijvoet was already working on a Pompe mouse at that time, but this was happening outside the view of Chen and Van Hove.

During the search for a usable animal model, Chen recalls his meeting with Tateki Kikuchi at a conference in Japan some six years earlier. Kikuchi specializes in animal diseases and was working at the National Institute of Health in Japan at the time. It happened to come up that he had a colony of Pompe quails at his disposal.

Quails? Yes, quails. In pre-war Japan, quails, which are slightly smaller than their European counterparts, were very popular. They were kept as pets en masse because of their song. Well, song... it's more like the sound of a squeaky door. They were bred intensively, and a loud squeaking quail could impress friends, family, and certainly rival quail owners. In that sense, the quail was to the Japanese what the canary was to the Dutch. There are still people in Japan and other Asian countries who breed singing quails.

One such quail breeder once turned to Kikuchi with a sick bird. The bird had stopped singing and sat on its belly in the sand all day, without moving a leg. He now had more sick birds in his aviary, which, to make matters worse, were also dying at a relatively young age. The man had already visited several veterinarians, but no one could find an explanation. Kikuchi conducted a few tests and examined the muscle fibers. He saw glycogen accumulation in them. Then it became clear to him: the animals had Pompe disease, but not in a severe form. In terms of symptoms, their condition resembled the adult variant in humans. The animals had no heart defects and lived long enough to reproduce. Kikuchi was fascinated by the phenomenon and used the sick birds to breed a colony of Pompe quails for further study at the Nippon Institute for Biological Science in Kobuchizawa.

For Van Hove and Chen, the Japanese quails are a stroke of luck. The only other animals known to have Pompe disease are a certain breed of cows.[87] But given the enormous amounts of enzyme needed for experiments with cows, they are immediately ruled out. Kikushi's quails are the salvation of Pompe research at Duke.

Because importing sick quails into the US encounters insurmountable barriers, the Duke researchers decide to conduct the tests in Japan. The Pompe enzyme is sent there. Two trials are set up. The first involves six sick and two healthy quails. They receive seven low-dose injections over a period of sixteen days. The results are disappointing.

"We had no idea how to dose," says Chen. "We decided to do a new test: over a longer period of time and with higher doses. To test their muscle strength, the birds were held upside down by their legs, among other things. The healthy animals then began to flap their wings to get up, while the Pompe quails remained helplessly upside down."

The researchers at Duke waited anxiously for six months for the results.

In one case, the quail flew into a lamp; in another, it vanished into the wide world.

Then a phone call came from Japan. "I have good news and bad news," Kikuchi reported. "The bad news: the bird is no longer with us." He paused for a long moment before continuing: "The good news is that it flew away." And he burst out laughing.

The quail anecdote now exists in many variations among the researchers involved at the time. In one version, the quail flew into a lamp; in another, it disappeared into the wide world. In reality, according to the research report in *The Journal of Clinical Investigation*, one quail from the high-dose group spontaneously flew a meter into the air, much to the surprise of the researchers.[88]

The article concludes with a brief reflection on the necessary dosage. The quails were given four to fourteen milligrams per kilogram of body weight, once every two to three days. For various reasons, less might be needed in humans. "All these results suggest," the authors write, "that a lower and less frequent dosage would be effective in humans." Because it takes so much time and effort to produce alphaGlu, this suggestion is noted with enthusiasm.

For the Duke researchers, the quail study is an important milestone, but Chen faces an even greater challenge. He must demonstrate that Van Hove's enzyme also works in humans. This means conducting trials on patients. He quickly realizes that this is no easy task. He has to write a plan of action, stating the conditions that the test subjects must meet, how he can guarantee their safety, how he intends to test the efficacy of the drug, and how he will ensure a pure enzyme of consistent quality. The enzyme used for testing must be produced by a company with a so-called GMP certificate. This abbreviation stands for *good manufacturing practice*. University laboratories almost never meet these requirements. Human trials are subject to strict conditions, and rightly so. As a result, the research will cost a fortune. Chen cannot even estimate how much, but it is certain that he does not have that money. They started the project in 1991 with a donation from the parents of the deceased girl, which was just enough for the first few months. Although larger donations had come in since then, serious money was needed for the next phase.

Chen approached the boss of Genzyme, Henri Termeer. He had demonstrated that the enzyme works in quails, and Genzyme was one of the few biotechnology companies with several years of experience using CHO cells to produce the drug for Gaucher disease. So what more obvious partner could there be?

Termeer was not unresponsive. "He was interested in the results achieved," says Chen, "but for Genzyme, convincing clinical evidence was a prerequisite for collaboration, and we didn't have that yet." Chen was also rebuffed by other pharmaceutical companies. He even appealed to people who had previously supported Duke's research financially, but they were unable to help either. The project is too big and too uncertain.

The savior turns out to be a Taiwanese cement factory. In the corridors of the university, Chen strikes up a conversation with a colleague and fellow countryman, Andrew Huang, a good friend of his. "When I told Andrew about my financing problem, he started talking about a cousin, Leslie Koo. His family owns a wide variety of companies. At the time, Leslie Koo was CEO of the Taiwan Cement Company and a board member of the parent company, China Synthetic Rubber Corporation (CSRC). In addition to the cement factory, they also have companies that produce penicillin. Andrew put in a good word for me with Leslie, and they decided to finance Duke's further clinical Pompe research. To this end, they established a new subsidiary: Synpac NC."

Chen is free to spend the money as he sees fit; the financier only asks for the so-called 'right of first refusal': if the research leads to patentable results, the parent company CSRC will be first in line.

When Chen is asked how much money he needs for his research, he is unable to answer. He has no idea; this is the first time he has had to carry out such research. Chen contacts specialists from CSRC's pharmaceutical division in London. They draw up a plan and a budget. Chen can't remember exactly how much it was, but somewhere between $5 million and $10 million. That's the start.

On the advice of London, the production of the enzyme is outsourced to a large, renowned production company[89], the German Boehringer Ingelheim. They start with a small bioreactor and will later scale up to 100 and 500 liters. Finally, the researchers have enough enzyme to start

their first clinical trial in patients.
“I really wanted to lead this research myself,” says Chen, “because I wanted to be sure that the enzyme worked. If it didn't work, I wanted to be able to find out why. If I wasn't the one in charge, I would never have first-hand knowledge. Fortunately, Synpac and Duke agreed.”
For Johan Van Hove, the Pompe adventure comes to a bitter end. When the money comes in, the atmosphere in the department changes. “We had Synpac come in,” he says. “It was led by two lawyers, and then the only thing that matters is patent protection. I felt very cornered. That firm had no interest in what I had to say. The only person they listened to was Chen.”
Van Hove calls it ‘frustrating’ and ‘a hopeless case’. He leaves Duke in 1997, spends six months in Australia, and returns to Belgium, where he focuses on metabolic diseases. "When I left Duke, the question was: what am I going to do with the rest of my career? I had done nothing but Pompe for five years, so I considered continuing with it. I received a threatening letter from a law firm: if I were to engage in Pompe in any way, they would sue me for industrial espionage. A lawyer I consulted said, ‘They don't have a leg to stand on, but a lawsuit will bankrupt you.’ So I left Pompe behind."

21
KNOCKIN’ ON HEAVEN’S DOOR
1981- 1983

Let's take a step back in time, because there is another important story to tell. The aforementioned American psychologist, lawyer, and author James A. Geraghty begins his book *Inside the Orphan Drug Revolution*[90] with the story of Abbey Meyers, a woman who devoted her entire life to the fight against rare diseases. In previous chapters, we already mentioned a few names: Ysbrand Poortman, who was a driving force behind patient organizations in this field in the Netherlands and Europe, and ‘tiger mom’ Robin Berman, Brian's mother, who played a crucial role in the development of a therapy for Gaucher disease.
Abbey Meyers' contribution to the development of orphan drugs, medicines for rare diseases, can hardly be overestimated. She is the pioneer.[91]
Her son David was born in 1968. At first glance, he was a healthy baby, developing normally, with no problems whatsoever. But when he was two, he started stuttering and making uncontrolled movements with his hands. The pediatrician talks about tics and assures Abbey and her husband Jerry that David will grow out of it. That doesn't happen; on the contrary. He sometimes flails his arms wildly, kicks, shakes his head violently, and cries out. The pediatrician has no idea what is going on. By chance, Meyers reads an article about a rare neurological disorder, Tourette syndrome. The description, the symptoms, it all fits: this is David.

With the magazine in her bag, Abbey goes to the pediatrician and lets him read it. He refers her to a specialist in New York, Dr. Shapiro, who confirms her suspicion.

The only medication available in the US at the time is Haldol, a strong sedative. It reduces the severity of the tics, but it turns David into a zombie. At their own risk, the parents are allowed to try alternative medications, from antidepressants to epilepsy medication. They do not produce the desired results, but they do have many side effects.

Finally, Dr. Shapiro comes up with an experimental drug from McNeil Laboratories, a subsidiary of pharmaceutical giant Johnson & Johnson. The drug, pimozide, is being tested as a treatment for schizophrenia, a condition that is much more common than Tourette's syndrome. Shapiro knows from two other Tourette's patients that they respond well to it and that the side effects are limited.

"When David took pimozide," Meyers writes in her memoir[92], "he did well. His symptoms were barely noticeable, and he didn't fall asleep in school. He was ten, and I was enormously relieved that we had finally found a treatment that was effective and had few side effects. But a year later, when we had an appointment with Dr. Shapiro to pick up a new supply of medication, he handed us the bottle and said, 'Unfortunately, this is the last pimozide I can give you.' The medication had not been effective in treating schizophrenia, so the company had decided not to continue developing it for the US market. But what about the people with Tourette's syndrome who respond well to it, I protested in disbelief. His answer was simple: tough luck. There are far too few people with Tourette's syndrome to constitute an attractive market for a pharmaceutical company. You're talking about an orphan drug. I had never heard the expression before, but it would become the central theme of my life for years to come."

An orphan drug is a treatment for a rare condition. Until the 1990s, pharmaceutical companies mainly focused on large markets where they could sell large quantities of a product: high blood pressure, rheumatism, digestive problems, diabetes, cholesterol. These are markets with tens of millions of consumers, promising high sales and high profits. Investors also like to see blockbusters, which in the pharmaceutical world means

annual sales figures of a billion plus.

For orphan drugs, that is absolutely out of the question in those years. Pharmaceutical companies assume that the development costs of an orphan drug will far exceed the revenues. No one wants to get their fingers burned. Even if a researcher comes up with a ready-made drug, they still won't invest any money in it.

For Abbey Meyers, it is clear where the problem lies. Before she even leaves Shapiro's office, she decides that she is going to rectify this injustice. Not just for Tourette's syndrome, but for all rare diseases. Abbey volunteers at the Tourette's patient association and soon joins the board. She starts gathering supporters around her, people who, like her, want to encourage the development of orphan drugs. Among others, she manages to get Democratic Representative Henry Waxmann on her side.

In June 1980, a rather bizarre hearing on orphan drugs took place in Washington. In addition to representatives of patient organizations, the industry was also invited, but they failed to show up en masse. Meyers still vividly remembers the meeting. "We walked into the hearing room, which was virtually empty, apart from our delegation behind the witness table. [...] The rest of our audience in that hollow space consisted of a sea of empty chairs with an indistinct, silent young man in the back row." Waxman gave an introduction, the delegates told their stories, and that was it. What now, Abbey and her colleagues from the Tourette Association asked. That's up to you, said Waxman. "Get public opinion on your side. Get stories in newspapers and magazines about orphan drugs, and eventually the public will demand that something be done about this."

The silent man at the back of the room turns out to be a journalist from the *Los Angeles Times*. He writes a short report that ends up somewhere in the middle of the newspaper. Coincidentally, that report catches the eye of Jack Klugman, the star of a wildly popular TV series, *Quincy M.E.*[93] His brother Maurice, also a producer on the series, has a rare, fatal form of bone cancer. Maurice calls Abbey and she manages to get him excited about the subject. He says he will do something about it.

In March 1981, the episode *Seldom Silent, Never Heard* airs, in which a teenager with Tourette's syndrome is murdered near a movie theater because he cannot stop shouting and swearing. At the end, Jack Klugman

appears on screen. Although the characters and the story are fictional, the problem of orphan drugs is a bitter reality, he says.

After the broadcast, Meyers receives mailbags full of responses from all over the country. She organizes an army of volunteers to read all the letters and respond to them if necessary, carefully noting the addresses of all the writers. These are the people she will ask to approach their elected representatives in the House of Representatives when a bill on orphan drugs comes up for debate.

Representative Waxman organizes a second hearing at the end of March. He is convinced that the pharmaceutical industry will show up this time. And he is right. Television star Jack Klugman and his brother Maurice are also present. The room is packed with patients and other interested parties. Suddenly, rows of congressmen are sitting behind the tables, not least because the media have turned out en masse for the Klugman brothers. It is this meeting that sets the wheels in motion.

On December 15, 1981, Henry Waxman submits the bill for the Orphan Drug Act (ODA) to the House of Representatives. In 1982, amendments are made in the Senate and later in the House. The final text is adopted on December 17 of that year. On January 4, 1983, after initial hesitation, President Ronald Reagan signs it into law. Europe will have to wait another seventeen years before a similar law comes into force there.

The *Orphan Drug Act* offers pharmaceutical companies a number of advantages when they market an orphan drug. For example, extra patent protection is possible, there are tax breaks and subsidies, and it is even possible to set up a government-led company for research and development. The most important incentive seems to be the seven-year market exclusivity: the guarantee that no competitors offering the same drug will be allowed to enter the market during that period (although what exactly constitutes 'the same drug' will remain a point of contention).

To be eligible for these benefits, a company must obtain a so-called 'orphan drug designation' for its product: the status of orphan drug. An important condition is that the patient group in the US must not exceed 200,000 people.[94] The designation does not automatically grant access to the market. FDA approval is always required for this.

The Orphan Drug Act was not immediately embraced by the large

People thought that it would never be profitable and that there was too much risk involved.

pharmaceutical companies, according to Erik Tambuyzer, who was involved in the creation of the *Orphan Medicinal Products Regulation*, the European version of the ODA, on behalf of Genzyme. "Colleagues in the pharmaceutical industry said to me: 'Those orphan drugs are not interesting, put your time into something useful.' That was the general sentiment at Big Pharma. I never listened to that. I didn't think it was true, and besides, Genzyme was active in that very field. Incidentally, in those first years after the European law was passed, few large companies were involved in the development of orphan drugs. Pfizer and Novartis were the only ones; the others weren't interested. It wasn't until around 2008 that Big Pharma's interest grew."

Nevertheless, according to Tambuyzer[95], the significance of the *Orphan Drug Act* for rare diseases can hardly be overestimated. "I doubt that Henri Termeer would have embarked on the Gaucher enzyme adventure with Genzyme if the ODA hadn't existed. Unfortunately, we can no longer ask him (Termeer died in 2017, ed.). Since it was a drug for a very rare condition, a so-called ultra-orphan drug[96], there was a lot of resistance, even from the board of directors. People thought it would never be profitable and that it involved too much risk. But then there was one ray of hope: supportive legislation. The *Orphan Drug Act* gave Henri the opportunity to approach investors and say, 'Look, here's a law that will give us seven years of market exclusivity.' If the law hadn't been in place, he wasn't even sure he would have had intellectual property or patent protection. Without the ODA, it would have been an impossible case."

Thanks to Abbey Meyers and Henry Waxman. For Abbey, the rest of her working life will be devoted to rare diseases. In 1983, she co-founded the National Organization for Rare Disorders, NORD, where she served as president until 2009.

22
NO ONE IS GOING TO STOP US
1983 - 1998

On January 22, 1983, three weeks after President Reagan signed the Orphan Drug Act, Tiffany House was born in Texas. Apparently, there was nothing wrong with her, but after three months she came down with a bad cold. “I developed slowly,” she writes in her blog, “but not so slowly that the doctors noticed anything was wrong. As a child, I fell a lot. I always had colds. I always had scrapes and bruises. When I was seven, I had pneumonia for the first time. I felt so miserable that I missed a month of school.”

This continued until she was eleven. Then the House family had a visit from a cousin, a pediatrician, who was on his way to a medical conference. Her parents asked him to take a look at Tiffany.

“I remember him asking me to climb the stairs, walk down the hall, and get up from the floor. Within ten minutes, he told my parents that he suspected a muscle disease. I had been seeing doctors for years who told me that nothing was wrong. Ten minutes of observing me was all he needed to make the diagnosis.”

Tiffany received her definitive diagnosis in January 1995. At that point, she weighed only 26 kilograms. Her respiratory function was poor: 40 percent of normal. “The doctors told us that I wouldn't live past the age of twenty. They also said that nothing could be done.”

The latter triggered Tiffany's parents, Marylyn and Randall House. He is an entrepreneur and has never accepted ‘can't’ and ‘won't’ in his work. He was certainly not going to accept a death sentence for his daughter. Randall and Marylyn will play an important role in the coming developments. While Marylyn does a lot of work behind the scenes, Randall is the friendly man who wins people over and brings them together. Like Ysbrand Poortman, parent and director of the Dutch Muscular Dystrophy Association, he and his wife are also searching for a cure for Pompe. They discover that promising research is being conducted in a few places around the world and that a therapy does not have to be a pipe dream. They talk to researchers in New York and at Duke University, and Randall flies to the Netherlands to meet Arnold Reuser and Ans van der Ploeg.

The couple sees possibilities. They decide that this should not be a fight for one patient and one family, but for the entire Pompe community, in the US and the rest of the world. That same year, they founded the Acid Maltase Deficiency Association, AMDA, an association of people with the disease of the same name, another title for Pompe disease. The association aims to raise awareness of the disease among the general public in the US, raise funds, bring patients and doctors together, and stimulate research.

The following year, on March 21 and 22, 1996, the AMDA organized the very first Pompe conference in San Antonio. Most researchers knew each other from publications and other meetings, but never before had all Pompe researchers come together to share knowledge and discuss the best way to develop a therapy for Pompe. Y.T. Chen from Duke University gave an introduction. Frank Martiniuk from New York presented his ideas about a possible gene therapy. Alfred Slonim talked about his experiments with a diet low in carbohydrates and high in protein. Johan Van Hove reported on his attempts to produce alphaGlu with CHO cells. Even Tateki Kikuchi's Pompe quails were discussed. The presentations by Reuser and Van der Ploeg, who outline how far the development of enzyme replacement therapy has progressed, make a big impression.[97] However, the greatest benefit of the meeting was the growing sense of solidarity among the researchers. One of them, Nina Raben[98] of the

National Institutes of Health, whom we already encountered in Chapter 8, puts it this way: "Scientists are always competing with each other. Who will get the research funding? Who will be the first to publish? And in which journal? That's what it's all about. The 1996 meeting changed our focus. I was most impressed by Marylyn. As a mother, she had an eye for the many subtle symptoms of the disease. She described the symptoms in great detail. In this context, scientific competition was irrelevant, frankly ridiculous. What was important was that we worked together, exchanged ideas, and did everything we could to help patients instead of trying to outdo each other."

It is a grueling battle: eighteen lectures in two days. But everyone is wildly enthusiastic. So enthusiastic that more than a year later, in June 1997, a second, larger, and longer conference is held, sponsored by Pharming. The program features 21 speakers who have flown in from different parts of the world. The 'Pompe mouse' from Rotterdam is discussed, and it turns out that Nina Raben now has one too. Gerben Moolhuizen, Pompe project leader at Pharming, explains the production of enzymes in animal milk. Developments are progressing rapidly, and it appears that the first human trials will not be long in coming. According to the participants, the acceleration of research is due to these conferences, initiated by the parents of a Pompe patient.[99]

Another parent, Kevin O'Donnell, who lost his son Calum to Pompe disease, also plays an important role in the process. He joined the English AGSD, the Association for Glycogen Storage Disease, which also has Pompe patients as members. Thanks to his contacts at Erasmus MC, Ans van der Ploeg is a welcome guest at meetings, as is Gerben Moolhuizen from Pharming.

But O'Donnell does much more. An international collaboration between scientists may have been established, but what about patients? How should they organize that collaboration? There is a need for a platform where people can connect with fellow sufferers at home and abroad. The internet is still in its infancy and the term 'social media' has yet to be coined.

Kevin O'Donnell describes in his blog[100] how he brought patients together. "Because I managed the AGSD-UK website, I slowly but surely

They warned
against being too optimistic,
but they themselves
could not hide
their high expectations.

built up contacts with people who had glycogen storage disease, and I wanted to do something with that. I wanted to give those people the opportunity to talk to each other. But how?"

For some time, O'Donnell continues, a mailing list, a kind of digital bulletin board, was the only place where patients could talk to each other about hereditary diseases. The mailing list was called *Gendisease-j* (named after what is now known as Gaucher disease) and was run by a man named Wayne Rosenfeld. O'Donnell signed up and was warmly welcomed. Once he had a good understanding of how the community functioned, he decided to create something similar for people with glycogen storage diseases.

"Wayne helped me understand how to approach it technically. That resulted in GSDNet, which we launched in June 1996. At the time, I thought that fifty subscribers would be a good number and enough to get the conversation going. It turned out to be many more. GSDNet grew rapidly. People from all over the world no longer felt isolated because they were part of a community; a community where successes were shared and setbacks were cushioned. It also gave patients a voice at crucial moments."

At its peak, GSDNet had five hundred participants. Compared to the size of such groups on Facebook and Instagram today, that is marginal, but in those years it was groundbreaking, also because absolutely all information about Pompe was shared. Patients in Taiwan, Peru, India, Australia, the US, or the Netherlands: everyone was aware of the latest developments. People were connected.

This new medium may have provided a global connection, but patients did not yet have an international organization. They were a group of separate individuals. More was needed to have a real impact on the process. In 1997, the next step was taken.

Once again, Randall and Marylyn House are the initiators. Randall quickly realizes that Rotterdam and Pharming are leading the race to develop a Pompe drug, and he flies to the Netherlands several times that

year, for the first time in January.[101] On that occasion, he also visits the Dutch Muscular Dystrophy Association in Baarn, where he meets Ysbrand Poortman. The two men hit it off. Poortman proposes organizing an international conference with the aim of establishing a global patient association. Not only patients, but also doctors and researchers should be present.

The initiators see the global organization of Pompe patients as an important step. At that time, the internet was growing rapidly, especially in the US and the Netherlands, but access to the world wide web and GSDNet was still reserved for a select few. Patient organizations in other countries had to be traced using paper address lists. Phone calls, faxes, and letters were sent. It soon became clear that the VSN, with forty members[102] with Pompe disease, was exceptionally large compared to sister organizations elsewhere.

Through Randall House, Kevin O'Donnell also becomes involved in the initiative. October 1998 is planned as the date for the conference, but it will take until 1999 for the meeting to take place. However, the foundation for the international patient organization is laid at the beginning of spring, on March 21, 1998, in Nijkerk. It is the national patient day for people with Pompe disease. It is no coincidence that foreign guests are also present: Randall and Marylyn House, Kevin O'Donnell, Gerd Hassler from Germany, and Dave Beeckmans from Belgium. In a small committee, the foundations are laid for an international patient organization, the International Pompe Association (IPA). During the large meeting on July 3 and 4, 1999, in Naarden, the IPA becomes a reality. Ten delegations are present, with participants from India and the Philippines, among others. Randall becomes chairman, VSN employee Ria Broekgaarden runs the secretariat, and Kevin coordinates the internet activities. Maryze Schoneveld van der Linde became the contact person for local patient organizations worldwide.

The IPA's objectives are clear: more research, available and affordable medicines, support for national organizations where necessary, access to medication for people who are deprived of it, and reliable online information about important developments. The association will have its hands full realizing these objectives.

Meanwhile, Pharming and Erasmus MC are steadily continuing with the development of enzyme replacement therapy. During the meeting in 1998, Ans van der Ploeg has important news to report. This was also interesting for the foreign visitors, because the time had finally come: Rotterdam was going to start trials on humans. First, safety tests would be conducted on healthy volunteers.[103] If those went well, two small groups would be started: four babies and three older children and young adults. Van der Ploeg emphasized that nothing could be said with certainty, because the effect on humans still had to be proven. Nevertheless, the optimistic mood in the room is almost palpable. “Sometimes,” as the report later states, 'what you see is at least as important as what you hear. And what we saw was a very enthusiastic and very results-oriented team of researchers. They warned us not to be too optimistic, but they failed to hide their own high expectations. Let's consider ourselves lucky that these people chose our disease to put their energy into.”[104]

How this enthusiasm influences expectations is shown in a note by Ysbrand Poortman. On a scrap of paper[105], he writes: "Jan. 1998, safety study in healthy volunteers. Apr./May 1998 application for permission for ‘clinical studies’ to the FDA. July 1998 ‘clinical studies’ in ten babies and ten juveniles. Jan. 1999 ‘clinical studies’ in adults. Jan. 2000 alfaGlu available as a medicine.'

It is a dream timeline, but that dream will not come true.

23
WORKING HARD TOGETHER
1998

At Pharming, the focus has now shifted entirely to the Pompe project. Whereas shortly before, the transgenic cows were supposed to earn big money, the focus is now entirely on the rabbits.
Het Financieele Dagblad of March 17, 1998, outlines the change that has taken place: "In retrospect, you wonder why Pharming started with lactoferrin instead of alpha-glucosidase, which is now at the forefront of the Leiden-based company's development pipeline. Anonymous rabbits, which had a human gene added to their own genetic material, produce this substance that combats the potentially fatal Pompe disease. No opposition can stand up to such a medicinal application. On the contrary, it generates goodwill for Pharming's genetic achievements. A single television documentary about the devastating effects of this rare disease works wonders."
Figures from the Foundation for Scientific Research on Consumer Affairs (SWOKA[106]) also show that the shift in focus to a drug for a deadly disease is indeed a strategically smart choice. The majority of the Dutch population appears to be positive about genetic modification of animals when it comes to drug development.
In Geel, Belgium, the transgenic rabbits are breeding rapidly. In 1998, there were more than a hundred animals producing human alphaGlu in their milk, enough to start a study with a limited number of test subjects.

At the same time, a new large factory is being built in the same town, which will eventually house three thousand rabbits. According to Rein Strijker, initially responsible for Pharming's activities in Belgium, the animals are producing above expectations: about twenty grams of alpha-Glu per rabbit per year.[107]
The construction of the factory in Geel is not without risk. What if the enzyme does not work or does not work sufficiently and is not approved? Wouldn't it be better to wait with such a large investment? *De Volkskrant* put this question to Gerben Moolhuizen, the project leader. "We had to make that investment decision. Otherwise, after successful clinical trials, we would have had to say to Pompe patients: 'Sorry, we can't produce enough enzyme yet.' We don't think we can do that. But it also shows that we have a lot of confidence in our product."[108]
It is a dilemma that is part and parcel of developing a new drug. An untimely investment can spell the death knell for the company. This is even more true for the production of biological agents, where investments can be very high. Scaling up can also cause major problems, as will become apparent.
The rabbit hutch did not go unnoticed by the outside world. Luc Kupers, who has been associated with the factory in Geel since 1999, says that the phenomenon became a topic on the satirical Flemish TV program *Schalkse Ruiters*. "They said: 'There is a company in Geel that milks rabbits. True or false?' Viewers could then vote. Since that broadcast, we have been world famous in Belgium as rabbit milkers. And we still are. When I tell people of my generation that I work at the factory in Geel, they say: 'Oh yes, the rabbit milkers.'"
Caring for and milking rabbits is no easy task. "It was a strange world for me at first. I come from the countryside, so milking a cow, yes. But when you see this for the first time, you think: oh dear, what's going on here. After a while, you get used to it. We had the rabbits in a trailer with about sixty cages, each cage containing a mother rabbit. Before we entered the trailer, we had to take a shower, and the animal caretakers did the same thing again in the afternoon when they came outside. Because if those rabbits contract some kind of disease and you lose them, you also lose your product. It all had to be *specific pathogen free*, SPF."

Breeding rabbits is not without its challenges, says Kupers. "It was difficult to get such a pure and stable line, so that each rabbit produced approximately the same amount of enzyme of the same quality. Milking rabbits required a special technique. A rabbit carries for about a month, after which you can milk it. It took us a while to figure out how to do this, because it was a battle between the pups and us for the milk. A rabbit easily has twelve or thirteen pups. If they suckle every day, all the milk will be gone. If you take all the babies away, the rabbit stops producing milk. Two to three babies turned out to be enough to keep milk production going and still have enough left over. We always had to show the mother her babies first before she got the stimulus to produce milk."

A pulsating vacuum pump is used as a milking machine. A cow has four teats, but a rabbit has no fewer than twelve. All of them have to be connected to tubes. Kupers: "Rabbits can sometimes panic when they are being milked, causing the tubes to come loose. In the beginning, we anesthetized the rabbits, but that's not ideal. One of the animal caretakers then designed a rabbit hammock. It was open at the bottom and they lay on their stomachs in it, so that their teats were accessible. This made them very calm. From that moment on, they no longer needed to be anesthetized."

Nutrition plays a role in the challenge of obtaining roughly the same amount of milk per rabbit. Together with Ghent University, Pharming is conducting experiments in which the rabbits are given specific foods. There must also be enough rabbit sperm stored in liquid nitrogen to rebuild the colony if something goes wrong. “It took quite a bit of effort to come up with a somewhat standardized method of milking. But we succeeded,” Kupers concludes.

News about the production of the Pompe drug in rabbit milk is spreading rapidly around the world, including via the GSDNet. Not a week goes by without a desperate parent calling Geel, having heard about the miracle milk through the grapevine and wanting to register their child to participate in the upcoming trials. These are painful conversations, but the truth is that production of the enzyme is still very modest and that in the coming months there will only be enough for a trial with a few babies and young adults. Moreover, it is not the scientists at Pharming but the doctors in Rotterdam who will determine, according to strict criteria, which children will be the first to receive the enzyme.

Pharming is already used to pleading, begging, and threatening parents, but the father who visited Geel in person in November 1998 is a different story. He introduces himself as John Crowley from the United States. He is the father of two children with Pompe disease. Gerben Moolhuizen shows him around the factory under construction. Later that day, during a meeting with Rein Strijker, Crowley lays his cards on the table. He understands that Pharming wants to start a trial with young children soon. He says, “I run a family foundation and am willing to finance a trial with slightly older children with the non-classical form of the disease.” The family foundation has raised several hundred thousand dollars, and Crowley suggests that amount will quickly rise to a million.[109] Rein Strijker says he was perplexed by the unexpected proposal.

It quickly becomes clear to Crowley that the trial is a dead end for him; his children cannot participate in a Dutch trial. Nevertheless, he does not consider his trip a failure, he says. "Of course, I went to save our children, but I also had another goal, namely to find out what developments there were. It did me a world of good to see that people were working on solving the problem. The idea of creating a drug became a reality. That also motivated me to take action myself. I left there full of optimism. We did have one major opponent: time."[110] Crowley will be in touch again soon.

As the project progresses, the question is increasingly being asked internally at Pharming whether the company has sufficient knowledge and experience to bring a drug to market independently. Although the calculations are based on five thousand to ten thousand patients worldwide, the drug must be available everywhere, from Japan to the US and from Europe to Australia. To make the drug available in all those markets, you need people who know how to go about it. In addition, this is a special drug, an orphan drug, which is also produced in the milk of transgenic rabbits. It is to be expected that the health authorities in various countries and continents will not allow the drug to enter the market without a fight. Management decides to look for a partner who knows the ropes.

When it comes down to it, as the smaller partner, you've got no say in the matter.

In 1998, Pharming has 120 employees spread across four countries. Not everyone on the staff is equally convinced of the need to find a partner. Gerard van Beynum, then Vice President of Product Development, would have preferred otherwise. "We never really had a proper discussion about what kind of partner we needed. If we had, things might have turned out differently. I would have preferred to see if we could develop the product ourselves all the way to market; we were also in talks with distributors. And I was certainly not in favor—because I had learned that during my time at Gist Brocades—of a small company joining forces with a large company. Then you get the story of the elephant and the mouse walking across the bridge, and the mouse says, 'We're stomping along nicely, aren't we, old chap?' When it comes down to it, as a small partner, you don't have a say in anything."

Ans van der Ploeg, who was in frequent contact with Pharming, would also have preferred a different outcome. "I do think that Pharming was not yet very well known in the field, but they should have trusted us more. In hindsight, you know that they had the shareholders breathing down their necks, but I think Pharming didn't realize enough that they had gold in their hands and that they were in a very good position with us."

So the management went in search of a partner. Various discussions were held in the course of 1998. Biogen seemed an attractive prospect. At that time, the company was working closely with Genzyme to make products available on the Asian market.[111] But after a number of exploratory talks, Biogen suddenly pulled out.

A second candidate is the American biotech company Cephalon, which was founded in 1987 and develops drugs for muscle and nerve disorders such as ALS. The company employs about 400 people and has $500 million in the bank. Cephalon is working on all kinds of drugs, but does not yet have any products of its own on the market. They appointed Michael Mellink as General Manager for Scandinavia and the Benelux. His job is to select interesting projects. Mellink: "During my search, I came into contact with Gerben Moolhuizen and Rein Strijker from Pharming, who were responsible for business development. There appeared to be a lot of interest in exploring whether we could develop alfaGlu together. Pharming did not have sufficient funds, but we did, plus access to the US market. We were very interested in substances to treat storage diseases, and Pharming had interesting technology."

The talks went well. Mellink also spoke with George Hersbach, the CEO of Pharming. On Cephalon's side, board member Peter Grebow was involved. In June of that year, all the details were discussed and a letter of intent was drawn up.

Mellink: "I remember it clearly. We were ready for the next step. At the time, I was attending a neurology conference in Juan-les-Pins. That was during the World Cup. Soccer players and officials were coming and going at our hotel. I had such poor reception on my phone that I had to walk back and forth the whole time. I called and called, sent text messages. But no response. Then it turned out that it wasn't going ahead. The deal wasn't set in stone after all. That was quite a setback."

Mellink explains the reason: "The story goes that Frank Baldino, the CEO of Cephalon, was bragging to four other CEOs during drinks after a conference. He claimed to have closed an interesting deal with a small company that could perform genetic modifications. One of those CEO's was said to be Henri Termeer of Genzyme. He must have thought: interesting, and approached Pharming with an attractive proposal.[112] Our letter of intent ended up in the trash. That was also the end of my career at Cephalon, and that of many of my European colleagues. I found that very unfortunate, as I saw a lot of potential in the collaboration."

24
ALFAGLU ACROSS THE BORDER
1998

Genzyme is indeed the third candidate. There are all kinds of stories circulating about how the company managed to remain the last candidate. Whatever the case, Genzyme often operated reactively and liked to respond to opportunities that arose in the market.

For Pharming, Genzyme is by no means an unusual choice. Genzyme has now succeeded in developing and successfully marketing the latest drug for the rare Gaucher disease. The enzyme is produced in large bioreactors in the US.

The company then set its sights on a drug for Fabry disease, which, like Pompe and Gaucher, is a lysosomal storage disorder. Like the drug for Gaucher, this enzyme will be produced in CHO cells, or Chinese hamster ovary cells. The new drug for Pompe fits nicely into the portfolio.

During this period, interest in orphan drugs began to grow, not so much among the large pharmaceutical companies as among the young biotech companies. When Genzyme decided to start producing a drug for the treatment of Gaucher disease, the pharmaceutical world looked on with pity and disbelief. Everyone expected it to fail. But the venture succeeded and the drug turned out to be a blockbuster.

Now that a new candidate is on the horizon, Fabry disease, a competitor suddenly appears on the scene: Transkaryotic Therapies, commonly known as TKT. A fierce battle ensues between the two pharmaceutical companies, both in the laboratories and in the courtroom. In January 1998, Genzyme receives orphan drug status for its Fabry enzyme from the Food and Drug Administration (FDA), followed by TKT five months later.[113] A race against time ensued, and exactly one week before Genzyme, TKT submitted its application for market approval of Fabry enzyme to the FDA and the EMA, the European Medicines Agency.[114] On August 7, 2001, the EMA grants both companies access to the European market and ten years of joint market exclusivity. This is a remarkable decision, because according to the rules, this privilege should have been granted to only one company.[115] And to make the story even more remarkable, the FDA put the brakes on and sent both applications back with a request for more data and better substantiation. This resulted in the approval of Genzyme's Fabrazyme only. Replagal, TKT's drug, was rejected in the US because the FDA considered the presentation of the data to be inadequate.[116]

It was an all-or-nothing race, which meant that in 1998, Genzyme's attention was mainly focused on the development and marketing of the drug for Fabry disease. It was during this period that talks between Pharming and Genzyme got underway. Pharming saw an interesting partner: Genzyme had money, people, and experience with orphan drugs. What more could you ask for in a partner?

Nevertheless, Gerard van Beynum does not have fond memories of that period. "Genzyme proposed making a larger investment in Pharming prior to the planned IPO that year. But we hadn't said we wanted a partner who would also be a shareholder, had we? That pretty much says it all. Quite a few things happened out of naivety and eagerness to get the great Henri Termeer on board. Let me put it cautiously: it didn't go ideally."

George Hersbach, then CEO of Pharming, still believes the choice of Genzyme was defensible. "We were looking for a partner who was familiar with rare diseases, and we found a few and had serious discussions with them. We expected the collaboration to add considerable value to Pharming. We had ambitions, but we also knew that we had to keep our feet on the ground and that we couldn't just set up a sales organization from scratch. We always had the idea that we had to work with distribu-

tors and pharmaceutical companies. In the end, Termeer and Genzyme turned out to be the most enthusiastic."
Incidentally, Genzyme was not initially eager to get involved with Pompe disease as well. The Fabry drug already posed enough risk. Within the management, there was a mistaken belief that the number of people with Pompe disease was much smaller than that with Gaucher disease. It was thought that such a small number of patients would pose too great a risk, even for Genzyme.[117]
Rein Strijker of Pharming therefore did not receive an enthusiastic welcome when he first approached Genzyme. "In hindsight, it turned out that this reserved attitude was based on a miscalculation of the number of patients. It may sound absurd, but someone had actually made a factor of ten error in the calculation. During a meeting in Boston, at Genzyme's office, Jan van Heek, who was in charge at the time, said, 'We are assuming the same number of patients as you, so how can your market be ten times bigger?' We then wrote the figures side by side on a whiteboard and it turned out that a zero was missing somewhere. From that moment on, they became interested."
Genzyme had about 4,500 employees at the time, more than thirty times as many as Pharming – as Van Beynum said: a mouse and an elephant. Another warning sign was that Genzyme already had a track record of more than fifteen acquisitions – and just as many would follow.
But in 1998, Pharming was doing well. Financially, things were going well and all signs were green in terms of research. At the beginning of the year, Pharming raised 48 million guilders, with ABN AMRO and NPM Capital as the largest financiers. In July, Pharming went public on the Brussels technology stock exchange, the EASDAQ. The result exceeded all expectations. They raised no less than 123 million guilders. Their financial worries were over. For the time being, at least.
On July 14, 1998, Genzyme and Pharming announce in a press release that they intend to jointly develop alfaGlu further and market it as a treatment for Pompe disease. Clinical trials in patients will start later that year. Three months later, a second press release follows, announcing that the joint venture is a fact. Genzyme would pay the first $14 million in costs, after which each party would pay half. However, there was some

Newspapers, magazines, radio, TV: when it comes to Pharming, it's in the news.

delay in starting the trials with patients due to a disagreement between Pharming and Erasmus MC about who should pay the additional hospital costs of the trial.
A few months earlier, the phase I study had started: an investigation into the safety and possible side effects of the drug. In August, Pharming announced that the trial had been completed successfully: the drug was well tolerated. On November 9, 1998, Pharming issued a jubilant press release announcing that the Medical Ethics Review Committee of Erasmus MC had given the green light for a phase II trial in patients. This study would begin in January 1999 once satisfactory financial agreements had been made between Pharming and the hospital. The aim of the trial was to test the safety and effectiveness of alfaGlu in a small number of patients. The press release received widespread media coverage. Newspapers, magazines, radio, TV: when it came to Pharming, it was news. The reporting was dominated by optimism. Patients read in the newspaper that the drug is expected to be on the market by the end of 2000 and that it will probably cost 200,000 guilders per patient per year.[118]
In 1998, Pharming celebrates its tenth anniversary. To mark the occasion, a modest booklet[119] is published listing the company's successes. In addition to the alphaGlu enzyme for Pompe disease, the company also has other drugs in the pipeline, such as a drug for the potentially life-threatening and hereditary angioedema, the sudden swelling of blood vessels with sometimes fatal consequences. Until then, this drug was extracted from blood plasma, which still carries the risk of HIV infection. Pharming can now prepare it from the milk of transgenic rabbits. This new drug has not yet been approved for the market either.
The booklet features a parade of good relations who praise the company. Among them is Ysbrand Poortman, director of the Dutch Muscular Disease Association, who is very pleased with the collaboration. "The VSN's interest was piqued in the early 1990s, when the possibilities of Pharming's genetic technology became clear. This led to a formal joint venture

between Pharming, Erasmus University, and the VSN. This is a new form of collaboration, in which a patient organization, university researchers, and the pharmaceutical industry participate effectively." Poortman has always been a passionate advocate of such collaboration, which he considers a necessary condition for the development of orphan drugs.
Former Minister of Agriculture Piet Bukman also contributes to the discussion. He points to the collaboration between the Agricultural Research Service, part of his ministry, and Pharming in the development of a herd of transgenic cows. This was the subject of heated debate in the House of Representatives. Bukman is still angry about the way in which the Animal Protection Agency had opposed the project: "Those protests, which used posters of genetically modified people, went way too far. It was a textbook example of misleading the public."
Meanwhile, the Animal Protection Agency's publicity campaign and political lobbying have prompted legislation on transgenic animals. This could thwart the announced trials with alfaGlu. On November 2, Minister Hayo Apotheker sent a letter to the House of Representatives announcing that a licensing system for the import of genetically modified animals or products thereof will come into force on February 1, 1999. It appears that the enzyme from rabbit milk, which is produced a stone's throw from the Dutch border, will not be allowed to be imported. A setback? No studies with Pompe children in Rotterdam? The patients and researchers are terrified.
Shortly after, two concerned letters arrive at the ministry, one from Pharming and one from the VSN. Both ask for clarity about the licensing requirement, because the trials must, of course, be able to continue. After some insistence, the ministry announces that there are no obstacles to importing the enzyme. The patients breathe a sigh of relief. The studies can begin.

EXPLAINED

PHASES OF SCIENTIFIC RESEARCH

Research into a new drug goes through a number of phases. These determine whether a substance is safe and effective and has the desired effect. Not all phases are always completed. Sometimes steps are skipped or combined.

• **Cells:** a potential drug is tested in diseased cells or tissues to see if it reaches the right place and does its job there.
• Test animals: the potential drug is often tested on 'sick' test animals, usually mice, to see if it has the desired effect in an animal.
• **Phase I study:** safety and optimal dose. A few healthy volunteers or patients are given the potential drug to measure its effect, determine the correct dose, and identify side effects.
• **Phase II study:** administration, dosage, and effect. A larger group of patients is given the potential drug over a longer period of time to investigate its therapeutic effect. The correct administration and side effects are also examined at this stage.
• **Phase III study:** the ultimate test. The study is conducted with more patients. As a rule, it is a double-blind, placebo-controlled study. This means that some of the patients receive the potential drug and others receive a placebo. Neither the researchers nor the patients know who is receiving the placebo and who is receiving the real drug. Although this approach is the gold standard in the research world, there are sometimes ethical objections (for example, in the case of very serious, fatal conditions) and a different approach is chosen.

25
LEAP OF FAITH
1999

On January 1, 1999, the moment finally arrives: the first four babies are administered the alpha-Glu enzyme via an IV. All preparations have been made. Animal testing has been successfully completed, no unpleasant side effects have been observed in healthy test subjects, and now, for the first time, four patients with Pompe disease are being treated with the rabbit enzyme. The start of a study involving several young people and young adults is planned for around the summer.

The parents are holding their breath, and the doctors are no less anxious. They know better than anyone how disappointing previous attempts at enzyme replacement therapy have been. Of course, much more knowledge has been gathered over the past forty years. The explanations for the failure of the treatment in the 1960s are extremely plausible. But no matter how you look at it, you are interfering with a highly complex metabolic process in the body's cells, which you only partially understand. Everyone hopes and expects that it will work, but the worm of doubt continues to gnaw away.

In the study, all four babies are given the active enzyme. A placebo, or fake treatment, is not used, as this would be a death sentence for the children. Babies with Pompe disease almost always die before their first birthday.

The question is how the efficacy of the drug can be determined unequivocally. The answer: with a natural history study (doctors prefer to talk about natural history rather than progression). During such a study, the researcher carefully charts how a disease progresses when no treatment is given: what symptoms occur and how quickly the disease develops. The course study was long neglected in medical research. Counting symptoms, combing through literature, compiling statistics: no one was particularly enthusiastic about it. It was not appealing and was not held in high regard by researchers. However, for the successful development of therapies for rare diseases, it is necessary to start this type of research before a drug becomes available. Precisely because many rare diseases can be unpredictable, with a wide variety of severity and symptoms, it is important to record the course of the disease in a clear and unambiguous manner. Such studies form a basis that can give a boost to the development of therapies for rare diseases.[120]

Hannerieke van den Hout, a young researcher in Rotterdam, ensures that all the necessary data on the course of the disease is available at the start of the trial. In 1998, she was working as a resident and wanted to do doctoral research, preferably clinical and in the field of nutrition and medication. She was interested in metabolism. When she approached her supervisor, Hans Büller, he said he knew of a 'fantastic project' for her. She should talk to Ans van der Ploeg.

Hannerieke recalls: "Of course, it involved reading a lot of literature, but we also visited hospitals in the Netherlands to map out the natural course of the disease. We dug up anonymized data on Pompe patients from archives and mapped it out: was it a boy or a girl, when were they born, what was wrong with them, and what symptoms did they have? We found 133 cases in the literature that we thought were classic infantile, the baby form. We compared those with 20 cases from files. That data was essential. For example, we saw that the heart is enlarged at a young age and becomes thicker over time. And that the children do not start walking. We also found that babies with the classic form, the very seriously ill children, die before their first birthday. That was also clear at the time. In addition, we looked at growth and other things. All in all, these were important findings."[121]

The data can be used for the research design with patients. "After all, you

need to know what you want to measure and on the basis of which data you can draw conclusions about efficacy and effectiveness. We thought long and hard about this with Ans van der Ploeg and Arnold Reuser. We also consulted with Pharming at an early stage. The mouse research conducted by Martin Verbeet and Agnes Bijvoet also yielded useful material. We elaborated on all of this, which led to a research protocol."
Enzyme production at Pharming is improving steadily, and the enzyme supply for the study is now ready. It is time to submit an application to the Medical Ethics Review Committee of Erasmus MC. Approval of the application by the METC is not a foregone conclusion. Research involving children is extremely sensitive, and the standard procedure is to test drugs on adults first. If it works, an application for trials involving children can be submitted. In this case, the test would start with children, very young children in fact, and only later be extended to other age groups.
"That's why it was so special that we got permission," Van der Ploeg emphasizes. "It may have played a role that there was no other treatment for that classic infantile form of Pompe disease; those children were dying. We did have a very strong argument." Studies involving children are still under pressure, Van der Ploeg explains. "There is now more leeway, more awareness of the fact that children are not small adults. But the regulations still stipulate that trials in adults are preferred. Only if you can demonstrate that you cannot obtain the same data in adults are trials in children permitted."
There are also practical considerations for a trial with babies. The first is the limited amount of alfaGlu available. Because the dosage is based on body weight, the trial does not require a large amount of enzyme. Although rabbits are producing increasing amounts of the enzyme, there is still a serious shortage. Economy is therefore the watchword.
The second consideration has to do with competition from overseas, as Professor Y.T. Chen and his colleagues at Duke University have announced that they will also be starting a study soon. And, as mentioned earlier, there is only room for one enzyme on the US market: either the rabbit product from Erasmus MC and Pharming/Genzyme, or the CHO product from Synpac and Duke. From 2000 onwards, this will also apply

We had barely arrived on the ward, when a nurse raised the alarm: the first IV reaction.

to the European market. The first to succeed in getting their product approved by the FDA and its European sister organization, the EMA, will gain market exclusivity. The other will see their efforts go up in smoke. So everyone is in a great hurry. Naturally, patients are following developments closely, with the justified feeling that their lives depend on it.
The METC is less stressed than the researchers and takes its time to reach a balanced decision. This did have consequences for the babies, says Van der Ploeg. "Of the babies, the classic infantile patients, we knew no more than those we had in the study at that time. Before we had gone through the entire procedure, the protocols had been approved, and there was sufficient usable enzyme, some of them were already in much worse condition. The METC also made a different assessment when it came to risk versus benefit. Such a substance from rabbits might not be well tolerated by the children, so we had to start with the patients who were already very badly affected. We argued that we should at least have one patient who was in a less serious condition. We had realized by then that, in order to prove effectiveness, it was important to include someone for whom results could still be achieved, someone who could show progress. In hindsight, that was a wise decision."
For Hannerieke van den Hout, the trial with the babies is the most memorable event in her medical career to date.[122] "We were able to start on January 1, 1999. I will never forget that. We started with the first patient in the ICU. The nurses were there, the staff were walking around. The IV drip was slowly dripping. Ans and I sat next to the bed to see if everything was going well and if the patient would experience any acute problems. It went well, so one patient became two patients, two became three, and eventually there were four. The youngest baby was two and a half months old, the oldest eight months."
Because everything was going so well, it was decided to move the children from the ICU to the regular ward. Hannerieke: "We had barely arrived when a nurse sounded the alarm: the first IV reaction. We had been so careful in the ICU, and then this happened at that very moment.

But we were getting better at dealing with it. What do you do with an IV reaction like that? Because you suspect it's an allergic reaction, you give premedication. Ans saw another solution. She slowed down the IV at the beginning, which worked fine. You also start to recognize the signs of an IV reaction. Oh, this child is not restless and crying because he is cold or lying in the ward, but because he is having an infusion reaction. If you recognize it early, you can pause and the reaction will slowly but surely subside. We got better and better at the therapy."

Hannerieke says that you learn a tremendous amount in such a process. "It's pioneering work, very intensive, personal, emotional. Especially for the parents. They know that they will lose their child if it is not treated, and they also know that it is uncertain whether the medication will work. Just because a drug works in a mouse does not guarantee that it will also work in a human being. How much hope can you have? That was true for the parents, but also for us as scientists and pioneers. Will the drug work? If we run into problems, what will they be? Will we be able to solve them?"

Of course, the question of dosage also plays a role from the start. If you give too much, it increases the risk of an allergic reaction. Too little enzyme can mean that no effect is measurable. The correct dosage for Gaucher was known: 1 milligram per kilogram of body weight. But that is not enough for Pompe patients, because only 5 percent of the administered enzyme ends up in the muscle cells, where it is most needed. The dosage therefore needs to be significantly higher. During the first twelve weeks, the children receive 15 or 20 milligrams per kilogram of body weight every week. There is a significant increase in alfaGlu in the muscles, but the enzyme levels in the cells remain well below normal. The researchers decide to double the doses.

Van der Ploeg: “As scientists, we weren't messing around. Our patients were seriously ill, and we felt they should receive a higher dose. That was difficult for Pharming, because they had to produce it.”

When the trial started, the first patient was already on a ventilator. "In hindsight, you realize that wasn't an ideal situation, but you have to learn all that. You hope for the Lourdes effect: that you can remove the ventilator and the patient gets out of bed. But we also saw that there was damage that could not be repaired. Still, it was remarkable that a patient learned to sit, roll over, and stand, which would never have happened with Pompe otherwise. It is memorable that we experienced that together."

The results in the first months of the trial are undeniably favorable. Although the researchers remain extremely cautious and do not want to celebrate too soon, a press release from Pharming appears on July 1, 1999. This happens on the eve of the first major international IPA conference for Pompe patients in Naarden. The message: the treatment in babies is showing positive results, we are on the right track. Hope among patients continues to grow.

The good results in the babies gave the green light for a study in three older subjects with a milder form of Pompe. Van den Hout: "That trial was necessary because you also have to show that the drug works in patients with a relatively milder form, the *late onset*. In medical research, you have to study every age group if you want to be able to use a drug in those patients. We chose a boy who had recently started walking less well and was partly using a wheelchair. We selected a teenager in a wheelchair who was still in reasonably good condition and a young man who was paralyzed, in a wheelchair, and on a ventilator. That gave us the whole spectrum: a child, a teenager, and an adult."

What was already clear with the babies also applies here: the better the patient's condition at the start of the trial, the more convincing the results. The youngest patient no longer needs a wheelchair, while the oldest and most severely affected patient is stabilizing. His name is Robert. He keeps Maryze informed about the treatment by email. Even he is showing measurable progress: his lung function is improving, his muscle strength is increasing, he is speaking more clearly, and his energy level is improving, so that he no longer needs to take afternoon naps. For the first time in years, he can go out for a whole day with his wife and daughter. Later, he is even able to travel independently by public transport, which makes him less dependent on his carers.

But joy and sorrow go hand in hand. Of the three test subjects, the youngest scores the best. Thanks to the treatment, his breathing and muscle strength are almost at a normal level for a boy his age. A photo

shows him balancing on one leg and kicking a ball away with a bicycle kick. He has a younger brother who also has Pompe disease. Fate has determined that the oldest can participate in the trial. This has unforeseen consequences. The youngest, the stronger of the two, was used to pushing his brother's wheelchair, but as the trial progresses and the oldest becomes stronger, the youngest becomes wheelchair-bound and they switch roles: now the oldest pushes the youngest. In 2004, journalist and presenter Pia Dijkstra draws attention to this distressing situation in the popular television program *Vinger aan de Pols* (Finger on the Pulse). Henri Termeer receives a phone call from his mother in Tilburg. She says she is ashamed of him and urges him to come up with a solution.[123]

26
LEFT OUT IN THE COLD
1999

The drug trials in Rotterdam are in full swing when the founding meeting of the International Pompe Association (IPA) takes place in Naarden from July 2 to 4, 1999. The first day is like a medical update[124], with all eyes on Erasmus MC, of course. You run into the usual suspects: Arnold Reuser, Ans van der Ploeg, Kevin O'Donnell, Randall and Marylyn House, and Ysbrand Poortman, but there's also a new participant: Blythe Devlin from the British-Taiwanese company Synpac Pharmaceuticals. Synpac Inc., as mentioned in chapter 20, is a subsidiary of China Synthetic Rubber Corporation (CSRC), which was founded to house the clinical Pompe research of Y.T. Chen of Duke University.
Devlin's presentation is titled: *The Challenges of rhGAA Manufacture*. The excessive enthusiasm with which she talks about the upscaling of alphaGlu production almost suggests that it is not all going smoothly. She says that Synpac has been financially supporting Pompe research for some time and that contracts have been signed with the German pharmaceutical company Boehringer Ingelheim to produce alphaGlu in CHO cells, the 'hamster cells'.
"The growth of the CHO cells is geared towards large-scale production," says Devlin. "The improvement of culture conditions and the steps in the purification of the enzyme are continuing, while the scale of production is increasing further in order to reach the estimated quantities required

for the market."
A 'master cell bank' of CHO cells has also been established, which has been shown to be free of bacteria, fungi, mycoplasma, and potentially harmful viruses. Devlin concludes her presentation by announcing that a trial began at Duke University a month earlier to treat three babies with the product of the CHO cells.
This is not news to most of those present. Thanks to GSDNet, almost everyone is aware of this. But the announcement once again fuels the expectation that an effective drug will now really come onto the market in the short term and that the long-cherished hope will come true. Whether the drug will come from Duke in North Carolina or from Pharming in Geel remains to be seen.
The trial in the US is led by Y.T. Chen. He is assisted by the young pediatrician Priya Kishnani. She arrived at Duke in 1991, almost simultaneously with Johan Van Hove. "I grew up in Mumbai," she says. "After completing my pediatric studies in India, I went to the US for further training. I ended up in the department of Dr. Chen and Dr. Roe. Glycogen storage diseases were an important field of research. I became increasingly interested in them and they have never left me."
On June 1, 1999, the Food and Drug Administration approved the trial, which—apart from the dosage—broadly follows the design of the Rotterdam experiment. There is great urgency, because Rotterdam is no less than five months ahead and, as everyone knows, at the end of the day there is only room on the market for one producer.
The selection of babies resulted in heartbreaking scenes, even more so than in the Netherlands. The news that an experiment was about to start spread rapidly, and Chen's phone rang day and night. Those moments are etched in his memory. "As soon as a baby is diagnosed with Pompe disease, parents start looking for a treatment. Of course, they soon heard about our test and called to register their child. We were under intense pressure to allow more children to participate. We even received calls from congressmen, senators, and even the White House. But we only had enough enzyme for three babies for two years. That's how much you need, because if the enzyme works, it's difficult to tell the parents, 'The trial was successful, but we've run out of enzyme.'"

Chen receives so many phone calls that it is impossible for him to answer them all. To relieve him, Duke hires an agency to talk to the parents. "It was overwhelming. And then, to make matters worse, the medical journalist from the *New York Times*, Denise Grady, called. She wanted to write an article about the shortage of places in the study. We explained to her how much alfaGlu was available and that we didn't even know if it would work. I thought we had convinced her, but no, she stood her ground. She was going to write the story, but I would have the opportunity to respond. She added that the article might help draw broader attention to this problem."
And so it happened. Under the headline '*In the search for a cure for rare diseases, some are left behind*', she published the sad story of Eric Godek, a boy with Pompe disease who was unable to participate in the trial and therefore did not have long to live.
A week later, Chen's response was published, in which he explained the dilemma he was struggling with. That Eric's participation could lead to a serious shortage of alphaGlu for the other participating babies, that it takes two years to produce even a small amount of recombinant protein, and that the technique has never been used in humans before. He concludes: "We can only hope that this experiment is successful and that in the future children can be saved and their families spared the pain of losing a loved one to this terrible disease."
Denise Grady is right; people understand the difficult decision Chen has to make. According to him, the publication also led to companies such as Genzyme showing more interest in the Pompe enzyme that Duke had developed.
Just as in Rotterdam, Duke also has to solve the puzzle of the dosage. At that point, the researchers were not yet aware of the experiences of Van der Ploeg and Van den Hout. Even if they had had any inkling, they were still dealing with a different product, an enzyme from CHO cells. They were convinced that this was superior to the rabbit product: purer, more concentrated, and with a better structure.
The article[125] published about the quail experiment already suggested that human cells might absorb the Duke enzyme better and that relatively less would therefore need to be administered.

The babies were doing well at first. Then the first one suddenly started to deteriorate.

There is another important factor that seems to have influenced the dosage chosen by the Americans: as in Rotterdam, the availability of the enzyme is a limiting factor. Contrary to Blythe Devlin's comment about scaled-up production, Y.T. Chen's newspaper report shows that the CHO enzyme is only available in limited quantities. It must be used very sparingly. The article about the experiment, published in 2001[126], states that a dosage of 5 milligrams per kilogram, twice a week, was chosen. That is a quarter of what the babies in Rotterdam received.

For two of the three babies, the trial ended tragically. They showed an allergic reaction that could not be controlled with medication. The researchers tried much higher doses, but to no avail. The two babies continued to weaken and died a few years later.

Priya Kishnani witnessed this firsthand. "The three babies were all doing well at first. Then the first one suddenly started to deteriorate. That was worrying. We tried to find out what was causing it, and that led us to an underlying genetic variation. Two babies turned out to be what we now call 'CRIM-negative[127]'. This means that they do not produce any alphaGlu at all. As a result, they can develop a severe allergic reaction. The third patient, number 1-0-3, was doing fine and even learned to walk."

Patient 1-0-3, or Jay, is now well over 20 years old. Despite his illness, you could say he has been lucky. His mother comes from a large family and dreamed of having a large brood of children herself. That plan fell through when her second child was diagnosed with Pompe disease and died shortly before his first birthday. Both parents must have been carriers of the disease, and each subsequent child would have a 25 percent chance of having the disease. The prospect of losing another child led them to abandon their dream.

However, four years later, she unexpectedly became pregnant again. A genetic test revealed that this child also had Pompe disease. As devout Catholics, the parents were opposed to abortion, but they also felt it was unethical to condemn a child to a short life full of suffering and pain. After much deliberation, they decided to keep the child.

At that time, news begins to spread about experiments with a new drug for Pompe disease. The parents are just in time. When they contact Duke, there is still one place available. But their child has yet to be born. These are nerve-wracking months, and on July 16, two weeks before the due date, the baby is delivered by Caesarean section.

Jay weighed seven pounds at birth and looked healthy. He was allowed to participate in the trial. Jay's treatment went much more smoothly than for the other two participants. He was also much less affected at the start. His heart did show slight defects, but to a much lesser extent than the average Pompe baby.

Jay also produced a small amount of alphaGlu himself, which greatly reduced the risk of an allergic reaction, and none occurred. Jay has grown into a young man who now leads a life without limitations, apart from the inevitable infusions.[128]

The article by the Duke research group about the trial caused quite a stir when other researchers realized that the doses for the first two babies had been increased. Because that is not mentioned in the article. Jay's participation also raised eyebrows: how certain was it that he had the classic infant form of Pompe disease? It is possible to test a fetus for Pompe disease, but at that time it was impossible to determine the severity of the disease on that basis. His physical condition at the start of the trial was also much better than that of the other babies. Arnold Reuser and Kevin O'Donnell, in particular, reacted strongly. In an article, O'Donnell writes: "Similar improvements in the hearts of four babies have recently been reported after treatment with the enzyme from rabbit milk. However, the doses required to achieve this therapeutic effect were four times higher than in the current study [by Duke] with enzyme from CHO cells."

One could therefore conclude that the CHO product works much better. But the dosage was already increased in week 20 in patient 1 and in patient 2 as early as week 15.[129] And that, says O'Donnell in his blog, while the Duke researchers report on a period of fourteen to seventeen months. If you don't know that the doses have been increased, it seems as if the CHO product is much more effective than the rabbit product. But that has never been proven.

This discussion took place in 2002. The rapid changes that were taking place at the time turned the discussion into a rearguard action. There is a new kid on the block. Well, not entirely new, because it is John Crowley, the father who showed up in Geel in 1998 to see if he could get his children with Pompe disease into a trial. That did not work out, and he was later turned down by Duke as well. So he decided that he had only one option left: to produce the enzyme with his own company.
And then there is Synpac, the company that has invested millions in Duke's research and now wants to reap the rewards. The confusion among patients is growing.

27

MARYZE

ROBERT OR ME?

I wrote about Robert before. I've known him since I was fourteen through the VSN, the patient association. He was four years older than me, but young enough to be my buddy. We went through the same things and didn't need to explain anything to each other. He was more severely affected than I was: even less muscle strength, even less stamina, and he had invasive ventilation: a tube that goes directly from the ventilator into your windpipe. That's how you get air, every hour, every day, week after week, always.
We wrote to each other regularly, first by handwritten letters, sent in an envelope with a stamp, and from 1997, when the Netherlands embraced the internet, by email. I have kept some of his messages. They date from 1999, the period when drug trials in young adults began. Robert was 34 at the time, married to Heléne. They had a little daughter. We followed the messages with eagle eyes, exchanging information. We were both part of the target group for the second trial with the rabbit product. We could both be selected. Or one of us. Or neither of us, because there were only three places available. His emails convey the tension and uncertainty of that period. With his wife's permission, I am therefore reproducing some excerpts from our correspondence here.

March 4, 1999

Hi Maryze,
Last week (Monday), Dr. Loonen came by to see if I was suitable to participate in the trial. She had to see what my body was still capable of and whether I still had enough muscle tissue to undergo a possible muscle biopsy. You know, for the treatment and then after the treatment.
She also needed to know my height and weight in relation to the amount of enzymes required. The heavier you weigh, the more enzyme you need. In that respect, I have just about everything going against me. My weight, because too much of the liquid gold would have to be used. Too weak, which means there will be little improvement to show. And my age, because cell renewal is slower than in a young person.
That's why I'm pretty sure you'll be chosen, because your weight is a big advantage. The lighter you are, the less you cost. After all, it's all about the money. Tell me what your experiences are when you're doing it. Because I'm incredibly curious. Negative or positive, it doesn't matter. I just want to know how you experience it. And if you don't know when it's going to happen yet, you can say so too. Experience has taught me that it's all going to take a VERY LONG time. I do hope it happens soon, because I'm fed up. Woo, time flies when you're having fun..

March 6, 1999

Hi Maryze,
II got a phone call yesterday afternoon: Dr. Loonen with a few more questions about the study. Whether I realized that I would have to come to the hospital 26 times, spending 48 hours in the ICU each time. And whether I had any objections. No problem, I said. I have nothing else to do but stare at the ceiling anyway. I believe the final decision will be made in May.

Contrary to what Robert thought, no one from the hospital approached me at that time. I don't remember being particularly bothered by that. I

probably took it for granted. I wasn't being treated at Erasmus MC yet, but at Radboud, so maybe I was out of the picture. Although, they did know me there at the time. I had previously participated in a clinical study with Dr. Christa Loonen.
It was only much later that I wondered why I wasn't eligible for selection at the time. I was deteriorating rapidly at the time, having increasing difficulty getting up, for example. I think participating would have made a difference to my condition now. But that's all hindsight. At the time, I was mainly happy for Robert, also because he was in a much worse condition than I was and therefore needed it more.

June 28, 1999

L. was waiting for me at 10 a.m. She told me what to expect over the next three days. Then Dr. P. came to fill out the medical history form and have me sign the informed consent form (the patient's consent for his or her treatment, ed.). After that, I was able to lie down for the neurological examination. I was glad about that, because it was almost noon and my head was already starting to droop. Later, I had to go to the Sophia Children's Hospital to have my muscle function measured. That means you have to lie down on a mat to see if you have enough strength to press a certain meter. Then it was back to the ward for a blood test. A total of about six tubes. Later that day, I saw a dietitian who instructed me to keep a detailed record of everything I ate at home for three days.

June 29, 1999

At a quarter to ten, I had a chest X-ray and then went straight to the intensive care unit for the lung test. Everything went well.
This was followed by a bromine test to determine my fat content. Then I had to go straight downstairs to have the muscle biopsy, which was actually scheduled for yesterday. Well, I thought, I'll just do that. Hmm.

When they started cutting, the anesthesia apparently hadn't taken effect everywhere yet, so I screamed. That, combined with my empty stomach, made me as white as the back of the paper this email is printed on.
After the muscle biopsy, which takes no more than half an hour, I went to my room to recover. It wasn't until a quarter past two, after all the blood tests, that I was able to eat and drink something: apple juice and yogurt. And I must say, that went down very well.
I went straight to the cardiology department for a heart ultrasound and an ECG. You have to lie down for a heart ultrasound, and Heléne had to lift me up and down all the time. You can understand that she was pretty exhausted after those days. The next day, I just had to get a finger prick at the Sophia and then I could lie down again on 4 North. The research nurse K. was able to go through the questionnaire right away. It was a huge list that was actually made for babies. So a lot of the questions didn't really apply to me. Unfortunately, we couldn't finish the list because we had arranged to meet the wheelchair taxi downstairs at 4:30 p.m. We were allowed to finish the rest at home. It was just a shame that the taxi didn't arrive until 5:30 p.m. At home, I immediately got into bed, as you can imagine.

Wednesday, July 7: the moment of truth

I had to be there at eight o'clock sharp. Of course, I had another examination to see if I was in perfect condition—as far as that is possible for me. No inflammation, swollen glands, or anything like that.
Everyone was there. Except for Dr. Reuser and Dr. Van den Hout, I saw everyone. They were prepared for anything, because next to me on a small table was a tray with all kinds of syringes to ensure that if something went wrong, I could be resuscitated.
By the time I finally received the enzymes, it was five past half past ten. You hardly notice anything, because it goes quite slowly at first. The first hour, the speed is 30 cc, the next hour 60 cc, and then 150 cc. At that last speed, if you pay attention, it starts to get a little cold. But you have to pay very close attention. They chose to use about 10 mg per kilo. So that comes to about 680 mg. The only tricky thing is that you have to arrive there sober. But that's only during the test period, so it will be dropped later.
Fortunately, the next two days were pretty boring because I only had to do some blood tests. Every morning at 8:30 a.m., they took a few tubes of blood. You can imagine that I look like a junkie every now and then.

Monday, July 12: is it working?

It was less busy than last time. I did see a lot of doctors, but now they came in one by one. Probably because the novelty has worn off.
Again, I had no problems with the infusion. According to Dr. Ans van de Ploeg, the critical point is the same as with the babies. Something could happen between the fifth and eighth time. Some babies turned slightly red during that phase and had some difficulty breathing. That doesn't mean I will too, because in our case the substance is somewhat familiar to the body, so the chance of an allergic reaction is much smaller. I now also know that the substance does reach the muscles. They recently performed a second muscle biopsy on the babies and were able to see that the muscles had recovered. Of course, I don't know to what extent, but they did increase the amount of enzymes afterwards. They will only be able to see whether this will also happen to me after the second muscle biopsy.

Best regards, Robert

It took a long time for Robert to notice the first effects of the infusion. But those improvements were very important to him. The constant deterioration had made him depressed. Now he could speak clearly again, make phone calls independently, or press a button, which made him much less dependent on help. It also improved his mental health. Now that his energy and muscle strength were gradually returning, he was able to travel independently again and go on day trips with

his family. He still needed a wheelchair and ventilation, but he was completely revitalized.
Eighteen years after the start of treatment, on December 6, 2017, he passed away. The last few years had been difficult for him. He had deteriorated. The depression had returned. My mother and I attended his funeral. Christa Loonen sat next to us.

28
THE WHEEL OF FORTUNE
1998 -2000

On December 16, 1996, Megan is born, the second child of the aforementioned John Crowley and his wife Aileen. Megan appears healthy, but continues to lag behind in her motor development. Meanwhile, her older brother, John Junior, has boundless energy. His problem is that he is having great difficulty learning to talk. John Jr. was diagnosed with ADHD in combination with dyslexia and Asperger's.
“Megan was diagnosed on Friday the 13th,” says John Sr., “Friday, March 13, 1998. It was Pompe. The doctors also told us that there was a one in four chance that our youngest son Patrick, then just seven days old, also had it.”[131] The results of a blood test confirmed this four months later.
How much adversity can a young family take?
John Crowley went in search of information. "We lived in California. I dove into the library and pulled every book off the shelf that could possibly tell me more about the disease. I searched the internet; Google didn't exist yet, so you had to make do with a fairly basic search engine. When you entered the search term ‘Pompe’, two names kept popping up: Y.T. Chen and Arnold Reuser. The first person I called was Reuser. It was a Monday morning. I got up at around three or four o'clock because of the time difference. The secretary put me through and we had a great conversation. It gave me hope that somewhere in the world, talented researchers were working on a solution for the disease. Later, I also spoke

with Chen and his colleague Priya Kishnani."
In his work mailbox—Crowley happens to be a marketing director at a pharmaceutical company, Bristol Myers—he finds a press release announcing the collaboration between Pharming and Genzyme to develop a drug to treat Pompe disease. The press release concludes with the announcement that a trial involving a few patients will start at the end of the year. This leads to his previously described visit to the rabbit factory in Geel, from where Crowley returns empty-handed. His children are also unable to participate in Chen's trial at Duke because they do not meet the criteria.
It is a bitter pill to swallow, but Crowley does not give up. He knows that the disease is progressing in Patrick and Megan and taking its toll. He is not the kind of man to sit idly by and watch his children waste away. He contacts Randall House, but has no intention of joining AMDA, the American Pompe Foundation. He wants to have his hands free. Instead, he establishes his own Children's Pompe Foundation.
During a meeting at the National Institutes of Health, he runs into a remarkable researcher, Bill Canfield. Bill is a headstrong, sometimes hot-tempered man with unconventional ideas about what the molecular composition of a Pompe drug should look like. As explained earlier, alfaGlu must have special sugar bonds, M6P, on the outside to be able to enter a muscle cell. When alfaGlu is produced in animal cells, such as those from rabbits or hamsters, the CHO cells, those sugar compounds are added automatically. Canfield wants to add much more M6P to help the enzyme enter the muscle cells more effectively. He is just looking for a way to achieve this.
John Crowley decides to put his faith in Canfield and resigns from Bristol Myers in April 2000. Crowley has hardly any financial resources; on the contrary, he is facing a substantial student loan debt. Nevertheless, he founds his own biotechnology company, Novazyme, he says with pride. "We took out a large mortgage on our house, maxed out all our credit cards, and collected some money from friends. That was our start-up capital." Within a few months, he managed to raise more than $8 million from investors. "We grew rapidly. We started with four people, and within a year and a half, we had a company with 120 employees."

Pharming and Genzyme have announced that they will be shifting their focus to production using CHO cells.

The time pressure is intense, because the competition, Pharming and Synpac, are already conducting trials. A year later, the first results are already visible. Novazyme's new drug appears to be able to remove all the accumulated glycogen from cells within a few hours of administration. It is astonishing. Cross-sections of muscle cells from Pompe mice show no trace of glycogen. Researchers are overwhelmed, patients are delighted.
In the race between Duke and Rotterdam, a competitor has now unexpectedly joined the fray: Novazyme. Crowley seems to have achieved what no one around him thought possible. Four years after Megan and Patrick were diagnosed, he has a drug in his hands. Well, almost. For patients, this sounds like excellent news. It is clear that, so to speak, a drug is just around the corner. It doesn't matter which one it is, as long as it works.
Geeta Anand, a journalist for *The Wall Street Journal*, tells Crowley's story in the book *The Cure*.[132] The book later forms the basis for the film *Extraordinary Measures* (2010), with Harrison Ford in the role of the quick-tempered researcher Dr. Stonehill, who shares some character traits with Bill Canfield. The book is based on documents and interviews, but in the film, the screenwriters' creative ideas were given free rein. Critics in the US are divided, and the film never made it to Dutch cinemas, but it is certainly to the director's credit that the problem of rare diseases is brought to the fore.
So the new millennium begins with four players in the Pompe field: Pharming, Synpac with Duke, newcomer Novazyme, and Genzyme, which is increasingly charting its own course. It's a crowded field. Never before had companies shown so much interest in the development of an orphan drug. So fireworks were to be expected, because at the end of the race, only one could remain.
And fireworks there will be. In April 2000, something remarkable and, for insiders, disturbing happens: Pharming and Genzyme announce that they are shifting their focus to production with CHO cells. This means that Pharming is moving away from its core business: the production of

medicines in the milk of transgenic animals. In a joint statement[133], the companies say that the decision is not motivated by a difference in safety or effectiveness. The results show that both products are equally effective. The switch is based on production considerations. Pharming and Genzyme believe that the CHO product will reach commercial production levels much sooner and faster than the rabbit enzyme. In addition, trials have shown that much more enzyme is needed per patient than initially estimated, which will cause problems with the rabbits. This does not mean, however, that the same thing could not happen with the production of the CHO enzyme. Only a limited amount of the necessary raw materials is available on the world market. Scaling up to larger bioreactors can also cause problems, because it must be repeatedly demonstrated that the enzymes produced in them are of the same quality as those from the smaller vessels.

However, the two companies add reassuringly that they are working hard on developing large-scale production. This is a remarkable statement, because at that moment there is only one place in the world where alpha-Glu is produced on a larger scale in CHO cells: at Boehringer Ingelheim in Germany, and that is on behalf of competitor Synpac.

Genzyme and Pharming also announce clinical trials for the end of 2000, intended for a limited number of patients with the infantile form of Pompe disease. They will probably be held in European and American centers. Whether the trials can go ahead depends not only on discussions with the Food and Drug Administration, but also on whether sufficient enzyme can be produced.

The future for the rabbits in Geel remains shrouded in uncertainty. Patients and doctors are concerned, and even within Pharming, some are surprised by this announcement. On April 18, 2000, Gerard van Beynum of Pharming said on the Barend and Witteman talk show in the Netherlands that CHO cells are not an alternative to the rabbit product. A day later, the rabbits were sidelined. This did nothing to alleviate the confusion among patients.[134]

29
A SCARY DISEASE
2000

There is another party that is unhappy with the transgenic rabbits: Proefdiervrij (Not Tested on Animals). From April 15, 2000, a radio commercial can be heard with the text: "We all have a hard time sometimes. But laboratory animals have a hard time every day. Rabbit mothers, for example. They are milked. By clever machines. Rabbit milk helps with scary diseases, such as Pompe disease. A small consolation for a rabbit in pain. And it's not necessary. There is an alternative. Made from yeast cells. And there is an association that fights for laboratory animals: Proefdiervrij."

Two days later, full-page advertisements appear in national newspapers, highlighting the plight of animals used in drug production. In the middle of a room full of colorful rabbits stands Dicky, a boy of about six, his arms crossed over his chest, a dark look directed at the viewer. “Dicky wants a rabbit to play with,” reads the headline. An explanatory text explains that Dicky is a fan of all the Flappies and Stampertjes. “He has all the Miffy books. He also has a scary muscle disease: Pompe disease. Milk from specially bred rabbits helps with this. These rabbits are milked by clever machines in immaculate laboratories (a form of genetic manipulation). Milking is no fun for the rabbit mothers. It's a good thing Dicky doesn't know about these things.” Here, too, the text concludes with the assurance that yeast is an alternative.

The campaign is a hangover from the massive resistance from the animal

welfare corner against Pharming and bull Herman in the late 1980s and early 1990s. The advertising text is confusing and the passage about the enzyme from yeast is misleading. There is indeed a company, Biozyme, that cultivates a similar enzyme in yeast cells, but it is intended for the production of beer and can be fatal to humans.

Patients and their parents are not happy with the campaign. One sentence in particular is completely wrong: 'He has a scary muscle disease.' Because who wants to be labeled as scary? Angry letters are sent to the Advertising Code Committee, not only from the Dutch Muscular Disease Association, but also from healthcare workers. A thick stack of responses from hurt and indignant patients also ends up on the committee's desks, from people with Pompe disease and all kinds of other 'scary' conditions. The VSN files a complaint with the committee. On May 12, the ruling is handed down. The plaintiffs are vindicated: Proefdiervrij must discontinue its campaign.

However, there is not only outrage. Proefdiervrij's campaign also fuels unrest and doubt among patients as to whether the therapy will be successful. Imagine if politicians get involved and create new barriers. This has happened before, and now it is happening again. After a series of positive developments, there are now also worrying signs. Such as from Pharming, which, admittedly not under pressure from Proefdiervrij but because of an unclear strategy and production-related motives, has decided to sideline the rabbits – rabbits that were always claimed to be doing so well in the production of alfaGlu.

The confusion is growing. On April 20, almost at the same time that Pharming and Genzyme announced the switch to CHO cells, Genzyme and Synpac made an announcement. Genzyme has acquired the exclusive, worldwide rights from Taiwanese company Synpac to develop and market alfaGlu from the CHO cells that Johan Van Hove had cultivated. Genzyme and Pharming will do this jointly and share the revenues fifty-fifty.

Genzyme pays Synpac $19.5 million, with Pharming covering half of that amount. Because Pharming is short of cash at the time, Genzyme provides the company with a loan of $10 million. Several patents and real estate serve as collateral. The press release makes no mention of the

He said that Genzyme wanted to take over everything from us: the production of the enzyme, the clinical trials and the marketing authorisation.

royalties to be paid to Synpac. That is a concern for later.

The parties involved praise each other in press releases. Henri Termeer of Genzyme assures "that this treatment holds great promise for patients."[135] Leslie Koo, Synpac's CEO, in turn expresses his confidence in Genzyme's qualities. "We believe that their expertise, dedication, and global organization offer the best opportunities to make a treatment available to Pompe patients as quickly as possible."

It was Leslie Koo who decided years earlier to finance the work of Y.T. Chen. Why Synpac is now selling and not marketing the drug itself remains a question. The fact is that neither Synpac nor its parent company CSRC has any experience in the development and marketing of biologically produced orphan drugs. According to Jan van Heek, Senior Vice President of Genzyme, it was mainly a question of money. "Synpac was actually the easiest option. They didn't want anything except money," he says.[136]

Chen says that pharmaceutical companies suddenly became interested when the news about the trial with the babies came out. Termeer also called to offer his help. "He said that Genzyme wanted to take over everything from us: producing the enzyme, conducting the clinical trials, and arranging market approval. They had the experience, we knew they could do it. But I would not be in charge of the follow-up trials myself. Because I had helped develop the enzyme, that could compromise my neutrality as a researcher. When I asked how I could remain involved in the research, they said I could help design the study, write the protocol, and later analyze the data. And, most importantly, Duke would remain in charge of the further research. I then asked Priya Kishnani to take over the clinical trials from me. She was very good at it, better than me."

Meanwhile, relations between the large Genzyme and the much smaller Pharming – the elephant and the mouse – began to sour. As Rein Strijker of Pharming notes in retrospect: "Genzyme was our largest partner, and in addition to being our largest shareholder, it was also our largest creditor. Yes, of course that's not a good situation."

The factory in Geel, which took so long to build and in which more than 40 million guilders had been invested, was virtually empty. The rabbits that were still producing enzymes for the patients who had participated in the trial were located at a different site. No one dared to predict how long that would remain the case. Everything was fluid at that point.
Pharming CEO George Hersbach is still in good spirits. Referring to the deal with Synpac, he says in a press release: "This is a unique opportunity for Pharming to combine our technology with other fascinating developments, both from a scientific and commercial point of view. Ultimately, this will lead to Pompe patients receiving the best possible treatment."[137]
In an interview with *de Volkskrant* on April 29, 2000, he maintains that cheerful tone. He says that the decision to stop using rabbit milk was made in consultation with Genzyme, which paid for a large part of the clinical trials in Rotterdam. Hersbach had access to all the research results, including those from Duke, and in his opinion they were very similar. Both the rabbit enzyme and the CHO enzyme have been recognized by the FDA as potential orphan drugs. This means that the drug that is first approved under the Orphan Drug Act will receive seven years of market exclusivity. And that is where the doubt arises, because Hersbach says: "Approval of drugs made using CHO cells is now a well-established procedure. This is not yet the case for drugs derived from the milk of transgenic animals. So Pharming and Genzyme feared that they might lose out in this race."
Genzyme has long had reservations about production using rabbits. Van Heek, Senior Vice President, is clear about this. "I don't think we put those rabbits on hold so much as it became clear that it would not be a successful production method. Partly because the product was not optimal, partly because production in rabbits was simply not possible. It was more of a research project than a commercial project."
According to Hersbach, the dosages are another bottleneck: in the trials at Erasmus MC, the amounts were doubled to 40 milligrams per kilogram per week. That is forty times the dosage for Gaucher. In addition, the number of patients with Pompe is greater than anticipated.
This means that much more enzyme is needed than was calculated.

Many former Genzyme employees say that this would be an impossible task with rabbits. Erik Tambuyzer of Genzyme calculates that 60,000 animals would have been needed. "The factory, which was already largely in place, was completely unprepared for such numbers.
Moreover, managing such a large number of rabbits for such a project is an impossible task. It was already difficult to do so with 3,000 rabbits. You need all kinds of disease control and lactation support, which is totally impossible in practice. Everyone realized that when they looked into it."
Rein Strijker disagrees. "The amounts of alphaGlu in the milk turned out to be quite high. We don't know how much enzyme the rabbit herd would produce, nor what the correct dosage would be, but we had planned for more than enough capacity. Sixty thousand rabbits would certainly not have been necessary."
Nevertheless, Pharming's management is going along with Genzyme's proposals, because there is much more experience with scaling up CHO cell production than with rabbits. Genzyme already had experience with this when the company started producing the enzyme for Gaucher. The drug for Fabry is also made in this way. According to Hersbach, the switch is therefore a logical and sensible step from a strategic point of view.
The future will show that scaling up CHO cells can also cause problems.

30
GROWING UNEASE
2000

Not everyone has the same level of confidence in George Hersbach's explanation of the switch in business strategy. Doctors, patients, and investors have many questions. On August 12, 2000, the opinion magazine *FEM/De Week* published a six-page critical article with the headline: '*The fable of Pharming*'. It is an unwelcome story, especially since the magazine is read by many investors. Pharming's management is accused of having too many products in the pipeline and not investing enough to successfully bring one of them to market.

However, the author argues that there is now a promising product: alfaGlu. But there are also many problems with this product, not least due to poor communication. "Pharming couldn't resist reporting interim successes with alphaglucosidase. The company had already announced twice that test results in Rotterdam were 'encouraging'. Research leader Ans van der Ploeg was so annoyed by this that she issued her own press release in which she called Pharming's statements premature."

Pharming's predictions are also constantly being overtaken by time. Initially, the drug was to be launched in 2000, then the date was pushed back to 2002, and that too will turn out to be a shot in the dark.

Why is the company now trading in a proven technology for one whose quality has yet to be demonstrated, the authors wonder. Pharming is six months ahead of its competitor Synpac with its rabbit milk. Would the

FDA perhaps raise its eyebrows at a drug derived from rabbit milk? The author doubts it: "According to insiders, it is highly questionable whether this is the real reason for the switch to a different production technology. The FDA's requirements for products from transgenic animals are clear."

No, the author continues, Pharming has been forced to do so by its partner, Genzyme. There are doubts as to whether the quantity and quality of the rabbit milk is stable enough. 'According to one person involved, all it took was for an airplane to fly over the rabbit farm and milk production was disrupted.' Genzyme is said to have given Pharming a choice: either adopt Synpac's technology or go our separate ways.

The article also quotes Kevin O'Donnell, who wrote in the Pompe Bulletin: "We are in great need of information about the new partnership. When will a drug be available? Will there be new clinical trials, with whom and where? What will be the role of the Dutch pioneers? Despite our requests, Genzyme has so far provided no explanation."

"The question is," continues the story in *FEM/De Week*, "what Genzyme still needs its partner for, now that Pharming's technology is no longer being used." At the end, there is still a glimmer of hope: "The value of the Dutch to Genzyme seems to have diminished considerably. Researcher Ans van der Ploeg is not giving up. She is continuing undaunted with the next trial in Rotterdam, this time with older patients. This is also good news for Pharming. The research at the Academic Hospital may well be the last straw to remain involved in the further development of alpha-glucosidase."[138]

Meanwhile, the deal with Synpac means that Erasmus MC loses its leading role in Pompe research to Duke, without anyone in Rotterdam being fully aware of this. The hopeful conclusion of the article is nothing more than wishful thinking.

And then there is another remarkable fact, which is not publicized at the time. Henri Termeer had promised Y.T. Chen that Genzyme would take over everything and take care of the production of the enzyme. But the company does more than that. In early 2000, Genzyme starts developing its own CHO cell line for the production of alfaGlu. A project group was set up under the leadership of Bob Mattaliano. He got the line up and

The government sees no reason to intervene, but it all does feel a bit uncomfortable.

running in record time, and within two years the enzyme was available in a new commercial bioreactor.

Apparently, Genzyme was not very convinced of the quality of the line Synpac was working with. In a small reactor, the production of the enzyme went well, but as soon as they scaled up to larger, commercial bioreactors, things went wrong. The alfaGlu turned out to be contaminated with microorganisms and one enzyme harvest after another had to be destroyed.

The patients are now facing increasing uncertainty. For years, they have lived in the belief that the transgenic rabbits are their salvation. Then an animal welfare organization announces in radio commercials and advertisements that the rabbits must go, because the drug can also be made in yeast cells. This is vehemently denied by Pharming employees, who insist that rabbits are much better medicine producers than any cell culture. Their story is then undermined in a press release from Pharming itself, stating that CHO cells will be used for the production of alfaGlu from now on. The communication leaves much to be desired, to say the least. On the VSN's patient forum *Myocafé*, Pharming is showered with accusations. "We mustn't be fooled, Pharming is interested in patents, but not in patients," one person fulminates. Another responds: "Because of these kinds of practices by pharmaceutical companies, patients who need a (curative) medicine are kept waiting unnecessarily long because of these strange games and because they have to wait a very long time before a medicine is finally available."[139]

The lack of understanding is already so great. The aunt of a boy with Pompe disease writes: "As far as we can tell at this point, it is still unknown whether he will be 'treated' for this very rare disease. [...] It is inconceivable that there is a 'remedy' that is being tried at this stage, and probably with a positive result. Why is it not possible for people with this rare disease to all be treated?"

It is not only patients who are at a loss. Confusion also reigns in the Dutch House of Representatives. On August 16, 2000, Member of Parliament Jan Marijnissen of the SP (Socialist Party) submitted a series of written questions to the Minister of Agriculture, Nature Management, and Fisheries and the Minister of Health, Welfare, and Sport. He wrote: "Are you familiar with the broadcast in which Pharming's research director, Dr. G. van Beynum, stated that he had absolutely no confidence in the Duke University research? Are you aware of Pharming's press release of April 19, 2000, announcing that Pharming is investing millions in this research? In that sense, how do you assess Pharming's credibility and what consequences will this have for the assessment of future applications for permits and subsidies from the company?"

Of course, the minister is aware of the broadcast and the press release, and of course all applications for permits and subsidies are always assessed on their own merits. Public statements about the company's business strategy do not play a role in this, according to the minister's response. The government sees no reason to intervene, but it all feels uncomfortable.

On September 9, the annual meeting for English Pompe patients will take place in Oxford.[140] Genzyme and Pharming are present with a delegation of four people[141], who have their hands full answering questions from patients. Is there a difference between the CHO and rabbit enzymes? Why not continue with large-scale production of the rabbit product? We know it works, don't we? Why do more trials need to be done? Are they only being held in the US?

The speakers assure those asking the questions that the CHO cells will produce results the fastest because they can be scaled up more quickly. Scaling up does present some problems, but every effort is being made to solve them. And the quality of both products is not very different. Arnold Reuser, a welcome guest at the English meetings, nuances that statement somewhat. He points out that there is still insufficient data on which to base such a conclusion. The industry representatives return to the confusion that arose in the previous months surrounding the acquisition of Synpac and the switch to a different production method. They promise that communication with the patient community will be clearer from now on. Modern means of communication clearly place different demands on this.

Erasmus MC is represented in Oxford by a delegation of four researchers. In addition to Arnold Reuser and Ans van der Ploeg, Hannerieke van den Hout and Marian Kroos are also present. Over the years, the latter has contributed to virtually every Pompe research project in Rotterdam as an analyst.

The time has come for the good news: the results of the Enzyme Replacement Therapy (ERT) have been published in the July issue of *The Lancet*, and they look promising.[142] Ans van der Ploeg reports on the research involving four babies with the classic form of Pompe disease, and those present listen breathlessly. At the start of the test, the participants were between two and a half and eight months old. Two of them were already quite affected: their muscle strength had deteriorated significantly and they needed oxygen. After twelve weeks, the alphaGlu in each of them was at the level of a healthy baby. Muscle biopsies showed that the accumulation of glycogen in the muscles had decreased significantly. The heart also looked much better. In summary: the treatment is well tolerated and prolongs life. The function of the heart and skeletal muscles improves. An important lesson here, too, is that it is better to prevent damage than to cure it and that it is therefore advisable to start treatment as early as possible. What Van der Ploeg is keeping to himself for the time being during this meeting, out of caution, is that one of the patients, Bartje, has now started walking. Since the start of the trial, he has shown fewer and fewer symptoms and is making the most progress. Of course, those present also want to know about patients in whom the disease manifests itself later after birth and who do not have an enlarged heart. Van der Ploeg does not reveal her hand. “It's too early to say anything about that,” she says. “We started the trial with older patients, but we need more time than with the babies to be sure that the improvements measured are the result of the treatment. To do that, we first need reliable data and statistics. But the course of the treatment offers hope for all Pompe patients.”

The patients return home with mixed feelings. The results in Rotterdam are encouraging, but the presentations by Genzyme and Pharming also make it clear that it will all take much longer than expected. Much more research is needed before the drug can be approved for the US and European markets. And those trials will not start overnight because, as the Genzyme speakers hinted, there are problems with the production of the enzyme. Those problems must first be solved. How much time will that take? No one dares to venture a prediction.

31
THE MAGIC TRIANGLE
1996 - 1999

On January 22, 2000, seventeen years after the United States, a regulation for orphan drugs comes into force in Europe. Its history is a fine demonstration of how things work in Brussels: an eternal tango between parliamentarians, civil servants, and lobbyists. For Genzyme and Pharming, it was a milestone because the new drug for Pompe disease could now also obtain exclusive status on the European market. Not only the industry, but also the patients in particular had lobbied hard for this.

The idea that Europe is decades behind the US with this regulation is distorted. Before the European Medicines Agency (EMA) was established in 1995, there was no central European organization that could implement such a law. Erik Tambuyzer, European Vice President of Corporate Affairs at Genzyme, was closely involved in the creation of the law. In his view, there was no lack of drive in Europe either. "In America, the Orphan Drug Act was approved by Ronald Reagan in 1983, but America is one country and the European Union consisted of fifteen countries at the time. Before 1994, there was no regulator at the European level. People had to wait for the establishment of the EMA[143] to be able to implement such legislation. In that year, discussions about the first draft began immediately. When you consider that, it went fairly quickly."

Internist Harrie Seeverens from the Netherlands was involved in the process. He worked at the Ministry of Health, Welfare and Sport in the Directorate for Medicines and Medical Technology (GMT). In that position, he dealt with all kinds of aspects related to medicines: funding, availability, and stimulating scientific research, especially in a European context, but also in the Netherlands. “At a certain point, rare diseases emerged as an important topic, along with legislation in Europe. I was asked to answer the question of how we were going to implement this in the Netherlands.”

When the European Orphan Medicinal Products Act was being drafted, examples from elsewhere were also considered, Seeverens explains. “This is even mentioned in the regulation: the American law of '83 and the Japanese law of '93. They were not copied verbatim, but let's say that as a framework, as an architectural structure, they were an important source of inspiration.”

In the mid-1990s, the legislative carousel surrounding rare diseases in Europe really got into full swing. Conferences and workshops were organized everywhere. The same trio of Americans regularly appeared at these events: Abbey Meyers, director of the US National Organization for Rare Disorders (NORD) and driving force behind the Orphan Disease Act; Marlene Haffner, head of the FDA's Office of Rare Diseases; and Stephen Groft, who began his professional career as a village pharmacist. He moved to the National Institutes of Health to emerge as a tireless advocate for research into rare diseases. Their stories and experiences have been reflected in the text of the law.

In Brussels, researchers, patients, and industry easily find common ground. Tambuyzer: "I started at Genzyme in 1992 as Vice President of Diagnostics and Genetics Europe. In 1996, Henri Termeer asked me to set up a Corporate Affairs department. I was responsible for Europe and other areas outside the US. In the same year, official discussions began on orphan drug regulations in Europe. I felt that Genzyme should participate in this, because we were marketing a drug for Gaucher disease and had other orphan drugs in the research phase."

Tambuyzer held talks with the pharmaceutical industry to reach a common position. He believes that corporate affairs involves more than just contacts with governments. “In my opinion, researchers, the media, and

patient organizations are also part of it."
In his previous position at Genzyme, Tambuyzer had already established contacts with patient organizations and researchers. For example, the renowned geneticist Jean Jacques Cassiman introduced him to Ysbrand Poortman of the Dutch Muscular Diseases Association. He became acquainted with the European Alliance of Genetic Support Groups (EAGS) and the Genetics Interest Group in England. Alastair Kent of the latter is an important discussion partner for him, as is Cees Smit of the Dutch Hemophilia Association.
"Ysbrand, Cees, and Alastair founded the European Platform for Patient Organizations, Industry, and Science (EPPOSI) in 1994. Ysbrand asked me to be one of the first board members, and I accepted. At the time, it was still fairly unclear what EPPOSI would actually mean, but that changed later."
At the same time, another important umbrella organization for patients was established: EURORDIS, the European Organization for Rare Diseases. EURORDIS was inspired by the success of Abbey Meyers' NORD. The French Telethon, which organizes a large annual fundraising event for muscular diseases, played an important pioneering role in this. They also provided funding, says Seeverens.
He believes that patient organizations certainly contributed to the draft texts for the orphan drugs law. Although it is difficult to determine in retrospect how great their influence has been. "As a member state, you are presented with a draft text. You don't know who contributed what. That is confidential and is not mentioned anywhere. But whatever the law, there is always lobbying. Whether it's about cars or agriculture or whatever, there are always interest groups and a lot of consultation. You can be invited to provide input or lobby yourself. That was no different with the Orphan Drug Act."
Tambuyzer made his first contacts with the European Commission in 1996. A first draft of the law had already been published by then. He was advised by Lisa Raines, head of Government Relations at Genzyme US, who had worked extensively with the Orphan Drug Act in her position at the biotech organization BIO. "She advised me to hire a specialist lawyer. That turned out to be Peter Bogaert from the law firm Covington

and Burling." Lisa would die a few years later in the 9/11 attacks. She was on the plane that crashed into the Pentagon.
Tambuyzer and Bogaert made amendments to the first draft of the legislation. "We took it to European Commissioner Marie Donnelly, who was responsible for this area. 'Interesting,' she said, 'but this isn't for the industry, it's for the patients. We're not changing anything in the draft.' There I was. Yet I hadn't proposed anything to the detriment of patients. On the contrary, they were pragmatic suggestions that would improve the draft in practice. What now? I then decided to set up an orphan drugs working group within the European biotech industry association: EuropaBio."
A while later, Tambuyzer knocked on Marie Donnelly's door again, but she closed it in his face once more. "So I changed tack and went to talk to my friends at EPPOSI: Cees Smit, Alastair Kent, Ysbrand Poortman, Jean Jacques Cassiman, and other people from the academic world. And with EURORDIS, which was led by Steven Korsia. Together we went to the European Commission."
Marie Donnelly had just moved to another position, and Patrick Deboyser had taken her place. "He said, 'Ah, so you all agree with the proposals you are making here?' Everyone nodded. The proposals were pretty much the same as the ones I had made earlier, but with a few additions. For patients, the most important one was patient representation in the future Committee for Orphan Medicinal Products, COMP. This committee advises on the granting of orphan drug status."
For Deboyser, that was the end of the matter; he promised to adopt the proposals. "I had taken Peter Bogaert with me to the meeting, and we rewrote part of the draft, I think about 15 percent, on the spot. The result was a better and more pragmatic text. Those changes remained in the final version."
Tambuyzer recalls that some parts of the draft text were also deleted. "The Commission wanted to set a ceiling on the profits that companies could make. If profits exceeded that ceiling, orphan drug status could be revoked. The term 'sufficient profitability' was used. But even during the subsequent discussion in the European Parliament, no one was able to adequately define that term because it means something different for

every company." Despite that inability, sufficient profitability is precisely the theme that often recurs in discussions about drug prices.
On December 16, 1999, the Orphan Drug Act was passed, with an official effective date of January 1, 2000. In the same year, the COMP was established to assess whether a drug is eligible for orphan drug status. Harrie Seeverens was one of the Dutch representatives from the beginning until 2006. “We met eleven times a year to discuss dossiers submitted by companies. The discussions focused on patient numbers, the potential of the drug, and, of course, the nature and severity of the disease.”
For the Ministry of Health, Welfare and Sport, the new law is a reason to demand more attention for rare diseases within healthcare and research. There is now a law to stimulate the development of orphan drugs, but it is important that industry and researchers make use of it. With this goal in mind, the ministry is setting up the Orphan Drugs Steering Group. This group also includes the parties that are dependent on each other for the development of new medicines: patients, researchers, doctors, and pharmacists. The steering group includes representatives from patient organizations, the pharmaceutical industry, health insurers, the Medicines Evaluation Board, the Health Insurance Board, a hospital pharmacist, and researchers. Among them, coincidentally, was Fons Gabreëls, the doctor who had diagnosed Maryze with Pompe disease in 1978. Harrie Seeverens attends the meetings as an observer on behalf of the ministry. The steering group has two secretaries: sociologist Jolanda Huizer and biochemist Sonja van Weely.
According to Van Weely, the meetings often focused on the cost of medicines and the criteria used, such as when a disease can be considered rare. "Some people disagreed with the threshold used in Europe: fewer than five patients per 10,000 inhabitants. For one disease, that means a maximum of 225,000 patients in the EU. They thought that was too generous. In Japan, the threshold is less than four in ten thousand. They consider one to two in ten thousand to be more realistic. That discussion is ongoing: when do you consider a disease to be rare?"
Another point of discussion was the length of market exclusivity. In Europe, they opted for ten years, in the US seven. Van Weely: “The regulation also states that after five years, you can review whether the exclusivity is still justified. Nothing has ever been done with this, even though there may have been reason to do so. But there are many uncertainties: who takes the lead in this, who has the final responsibility? Was there a lack of courage?”

You don’t want to block market access for a medicine that demonstrably performs better.

Moreover, market exclusivity is not absolute. A competing product can still be approved if it offers a ‘significant benefit’. For example: a product with the same composition but greater effectiveness. Or: a simpler or safer form of administration, a pill instead of an infusion, for example. Van Weely: "You don't want to block market access for a drug that demonstrably performs better than a previously approved drug. But there has been a lot of discussion about what that criterion of ‘significant benefit’ actually means. Whenever the Orphan Drug Act is up for discussion, the same old arguments resurface. It's exactly the same as what I heard twenty years ago. Apparently, people are still hung up on that. At the time, opinions were also divided on the question of under what conditions someone could apply for orphan drug status for a second drug."
Approval alone is not enough to gain access to the European market. Seeverens explains: “The EMA is primarily concerned with ‘efficacy’, the quality and effectiveness of a product. But the costs, price, and reimbursement that member states are willing to give to patients or hospitals fall outside the scope of European regulations.”
Meanwhile, orphan drug laws in Europe and the US appear to be having a clear effect. Between 1983 and 2020, approximately 800 drugs with orphan drug designation were approved for the US market. In the EU, 170 drugs were approved between 2000 and 2020. The emphasis is on drugs for cancer, neurological disorders, and infectious diseases.[144] Considering that there are some 6,000 to 7,000 rare diseases, there is still a long way to go.
The European law was therefore established thanks to close cooperation between patients, researchers, and industry, the ‘magic triangle’. In an article[145], the pioneers even refer to ‘the Pompe model’, in which patients abandon their wait-and-see attitude, seek allies, and thus take fate into

their own hands. The creation of American and European orphan drug legislation is a striking example of this.

32

MARYZE

CONCERNS ABOUT SOPHIE

Of course, I loved hearing stories about the miraculous recovery of Pompe patients after receiving the infusion, or at least the effect of increased energy and muscle strength. However, I tried to remain realistic and not get carried away, because I knew that the enzyme works differently for everyone. During the IPA conference in Heidelberg in 2003—more on that later—we saw a video of a patient who participated in a study with young adults. After four years of treatment, she had more muscle strength and more energy.

But there are also other stories. Sometimes there are serious allergic reactions. Several babies did not survive despite the infusions and died. Sophie is a girl with Pompe disease who was nominated by Belgian pediatrician Johan Van Hove in 1998 for the study with the rabbit enzyme in Rotterdam. She received her first infusion when she was eight months old, which was quite late. She is the third child in a Flemish family. In Heidelberg, her father Arno tells their story. The room is completely silent. I am reproducing it here in a slightly abridged version with the parents' permission.

"Sophie is now 4,5 years old. According to the normal course of the disease, she should already have died, probably even before her first birthday. Since she was eight months old, she has been undergoing experimental treatment that is still keeping her alive. The treatment

consists of administering the enzyme that her body lacks via an IV every two weeks. For this, we took her to the Sophia Children's Hospital in Rotterdam, 180 kilometers from where we live. When she was six months old and had just been diagnosed, this was the only place in the world where she could be treated, and then only as part of a research study. She underwent extensive testing to see if she met the inclusion criteria. After that, it still took two months before she could be admitted. By then, she was critically ill. Her heart was severely enlarged, functioning very poorly, and her breathing was becoming problematic. She was already dependent on tube feeding."

"When Sophie was admitted, it was not yet known whether the therapy would have any effect. We only knew that the drug had been well tolerated by three other patients who had started treatment a few months earlier. And that promising results had been achieved in a study with mice. We felt we had no choice: not participating would have meant Sophie's death, while participating at least gave her a chance."

"Initially, the plan was to drive her back and forth every week for the infusions. But immediately after admission, she fell from one infection into another, requiring her to remain in the hospital. After twelve weeks of treatment, she was transferred to the intensive care unit during a critical respiratory infection. After some hesitation, the decision was made to put her on a ventilator. Again, it was a choice that was not really a choice, given the uncertainty about the outcome of the therapy at that time. Shortly thereafter, she received a tracheal cannula, an opening in the windpipe to which the ventilator is connected."

"As results were not forthcoming, it was decided to double the dose of the enzyme for all patients participating in the trial. Four weeks later, Sophie began to show visible signs of improvement. First, her heart function improved. Then she began to breathe better on her own and gained more strength in her upper body (head, arms, shoulders). At one point, she was able to breathe without the help of the machine for five days in a row. She could sit upright without support for a full minute. There was even talk of removing her cannula. She would then be able to go home soon."

"Unfortunately, she suffered further infections, both from the Port-a-cath, the IV connection, and from her airways. This weakened her again and she needed more ventilation. Sadly, she has gradually deteriorated since then to where she is now."

"In the end, Sophie spent almost two years in the Sophia Children's Hospital, including twenty months in the intensive care unit. At first, she was too weak to be transferred to a treatment center closer to home. After that, other issues came into play: the practical arrangements for the IVs in Belgium, choosing and setting up the right home ventilator. It all had to be figured out. Everything was new to everyone. In the end, there was even an unfortunate leg fracture."

"During that time, we as a family lived almost continuously apart. We had a second residence at the Ronald McDonald House, close to the hospital. Ellen, my wife, who is a nurse herself, interrupted her career and stayed with Sophie during the week. I worked partly in Belgium and partly in Rotterdam and took care of the other two children. At the weekend, we were usually together in Rotterdam. We divided our time as best we could between Sophie and activities with the other children."

"Since the transfer to Belgium, everything has gradually evolved into what the situation is now. During the week, Sophie is admitted to a rehabilitation center for children, in a department specializing in respiratory disorders. She is admitted to a living group, undergoes daily therapies (physiotherapy, speech therapy, occupational therapy), goes to school, and also stays there at night."

"For the time being, she comes home every other weekend. During that weekend, we take over her intensive care completely. We have both been trained for this at the Sophia Children's Hospital. She still receives daily physical therapy, alternately from us and from a neighbor who is a physical therapist. And we regularly invite someone to come and play with Sophie."

"The whole home care routine is physically and mentally very demanding. Providing 24/7 care and supervision for someone who is totally dependent, in addition to running a normal household with two children, is no mean feat. We have to get up regularly during the night

to respond to alarms from the equipment, to provide care or to change Sophie's position. After a weekend like that, we are exhausted."
“Transportation also has special requirements. For this, we usually call on a Red Cross ambulance with a permanent team of attendants. Until now, my wife has accompanied every transport. When Sophie is at the rehabilitation center, we visit her regularly, even though it is located 110 kilometers from where we live. We also regularly ask family members who live closer to visit her."
"When Sophie is seriously ill, usually due to an infection, or needs to undergo tests, she is admitted to the Gasthuisberg University Hospital in Leuven, always to the intensive care unit because of her ventilator. This has happened about a dozen times in the last two years. During those periods, we are extra vigilant and our family life is disrupted even more.”
“The heart problems she used to have have practically disappeared. Unfortunately, the therapy does not have the same effect on the other muscles in her body. They are slowly but surely becoming weaker or cannot keep up with her growth, making her increasingly dependent on medical support and aids. She is still ventilated by a machine and receives nutrition via a gastrostomy, a passage in the abdominal wall to her stomach. She is confined to a wheelchair with a custom seat shell. In this, she can sit upright and play for a few hours a day. The strength in her arms has been decreasing more and more lately, which also limits her in this respect. She has a curvature in her spine and contractures in her hips and ankle and knee joints, for which she wears splints for a few hours a day. She also has a mild form of hearing loss. She wore hearing aids for a while, but they are no longer necessary."
"The infusions are given every two weeks. They usually start around noon and are finished by evening. During that time, Sophie has to process a lot of fluid. That is why she regularly receives extra diuretic medication on the day of the infusions. The infusion rate is very slow at first, to allow the body to become familiar with the foreign enzyme. The speed is then gradually increased.”
“Sophie has had a few reactions. She becomes restless, feels uncomfortable, develops a high fever, has irregular heartbeats, and sometimes her skin changes color. Fortunately, this happens only rarely, when she is already weakened by illness prior to the infusions."
“We have been walking on eggshells for several years now. Always vigilant, always under stress, always uncertain about what the future will bring. Usually tired too. When Sophie is ill, the tension increases even more. We have to constantly fight for our daughter's quality of life. And for our own and that of our two other children. We regularly come up against institutions, administrations, and people who are not well adapted to the needs of a child in need of care. In the past, there has also been uncertainty about the continued availability of the medication on a few occasions. This causes extra stress and uncertainty every time.”
“Our other two children are doing reasonably well, considering the circumstances. They sometimes have difficult periods, just like us, in fact. They have also had a lot to endure. First, the news that their sister was going to die, then the news that the doctors were going to try to ‘cure’ her after all. Then the long period of weekly trips to Rotterdam. Confronting seriously ill and sometimes dying children in an intensive care unit. Regularly missing their mom or dad. The uncertainties about Sophie's future. They experience and process it all in their own way.”
“For our part, we try to always be open and honest with them and to answer the difficult questions they sometimes ask in understandable language. For them, Sophie is a sister with whom they play games, sing songs, read books, and make jokes. They are a fantastic duo of play therapists for her."
"Despite her many physical limitations, Sophie is developing mentally quite normally. She reads books, does crafts, and plays games on her tablet from her chair, such as coloring, puzzles, catching fish, and memory. She even plays on the computer, using a special mouse. Despite the cannula, she has also been developing her voice lately: she is making more and more intelligible sounds and trying to sing along to songs. We are even able to have a ‘conversation’ with her over the phone.”
“We have a very good relationship with Sophie and believe that she is still happy. Our main concern is that, despite the treatment, she will

continue to weaken, that she will become increasingly aware of her limitations, and that one day she will no longer be happy. We regularly ask ourselves whether we can give her a good enough quality of life, whether we are doing the right thing by continuing this treatment. We live with constant uncertainty about her and therefore our future. After all, there is no prognosis. We are concerned about the effect of all this on ourselves and our other children. Sometimes we wonder whether we can keep this up."

33
SEVERE TURBULENCE
2001-2002

From the beginning of 2001, the eyes of Pompe patients and researchers increasingly turned to John Crowley and biologist William Canfield of Novazyme. In their rapidly growing company, they were developing a drug that, as they themselves claimed, was superior to those of Synpac, Genzyme, and Pharming; the best the market had to offer.
The secret of the Novazyme enzyme lies in the number and quality of the M6P sugar keys on the surface of the alphaGlu. For the time being, this special enzyme exists mainly in Canfield's head; he has yet to see that he can get those sugars in the right place.
Crowley feels that things are not moving fast enough. He sees his children's condition deteriorating, while there are still so many barriers to overcome. The announced trials at Duke University are also being postponed. Are they going to lose the race against time?
Meanwhile, most of the Pompe community's attention is focused on the development of the CHO enzyme that Genzyme and Pharming are going to market. Patients want to know how long they will have to wait. Their muscles are weakening while somewhere, in large vats, a drug is being prepared that could halt their decline. In March 2001, Kevin O'Donnell conducted an extensive interview with Paul Kaplan, who was in charge of the Pompe operation at Genzyme at the time. Of course, the rabbits were also discussed. Kaplan said: "We don't think we can produce

enough enzyme with rabbits. Considerations regarding FDA and EMA approval also played a role. […] I know there was a lot of excitement and frustration among patients who wondered why we decided to give up an apparently successful product in favor of a still unproven product. […] But I am confident that we made the right decision and that this will make the drug available to all patients as soon as possible."

O'Donnell asks whether the rabbit enzyme will continue to be produced. Kaplan is clear on this point. "It will be produced for as long as necessary. New patients will receive the CHO drug. If it turns out that some patients cannot be switched to the CHO drug for some reason, we will continue to produce the rabbit enzyme. [...] We have an ethical duty to do so, despite the fact that it is not profitable."

Regarding the trials, Kaplan says: "We will start the new baby trial [with Genzyme's alfaGlu] within a few days. It will be conducted in several locations, one in the US and two in Europe. This is for logistical reasons. They are accessible to everyone, anywhere in the world."

When asked why the development of the drug is taking so much longer than anticipated, he replies: "Partly because things have not gone as well as predicted. In the past, unrealistic expectations may have been raised. I have now done my utmost not to do that. I don't think anyone doubts the value of the therapy, but it is clear that it is more difficult than we originally thought."

Regarding the time it takes to submit an application for approval to the authorities, he says: "Because a higher dosage of the drug is needed than was expected a few years ago, production facilities need to be developed to produce large quantities of the drug." And Genzyme is not yet working on that? "No, from a business perspective, it would be too risky to do so before the approval decision has been granted. A production facility costs several hundred million dollars, and there is always a risk that approval will be denied."

Based on Kaplan's answer and a simple calculation, the conclusion is that the drug will be available by early 2004 at the latest. Noted. What about patients who are at risk of dying, O'Donnell asks. Is the limited availability of the drug also a problem for them? Kaplan: "At the moment, yes. There is enough enzyme for the planned trials, but beyond

He also knows that
he can't use
his children's health
as a bargaining chip
with his lenders.

that, there will be no more available until next year at the earliest. There have been some problems with development. A large quantity of the drug had to be rejected." The interview does not go into detail about what these problems are, but it is clear that they must concern the Duke/Synpac enzyme.[146]

John Crowley has since concluded that it would be better to sell Novazyme. He is certain that he will not be able to make the enzyme available in time for his children within his company. Apart from that, he admits that he did not have enough money. "There came a point when I realized that I needed a lot more money for the trials, clinical expertise, and production facilities."

This would require him to invest tens of millions of euros, while the enthusiasm of potential new financiers was waning. "I had two options: Genentech, then the largest biotech company, and Genzyme, at that time the largest in rare diseases and with knowledge of Pompe. I advised our investors to go with Genzyme. With Genentech, we would have become a small part of a very large company. If the product flopped with them, too bad. Genzyme had the most experience with lysosomal diseases, and Pompe would become their most important program. And the most expensive. They couldn't afford to fail."[147]

Henri Termeer of Genzyme has already floated the idea of a takeover of Novazyme during a biotech conference in California. It sounds attractive, but Crowley foresees a financial barrier. Genzyme paid around $20 million for Synpac and invested around $17 million in Pharming. Novazyme's investors estimate the value of 'their' company at around $50 million. Given that they have high expectations for the results and are assuming a return of two or three times their investment, Genzyme would have to pay between $100 million and $150 million. Crowley does not expect Termeer to agree to this.

He also knows that he does not need to appeal to his financiers with the health of his children; their lives play no role in this arena. Crowley devises a ruse to persuade Genzyme. He wants to make Termeer believe

that Novazyme is developing a competitive drug for Genzyme's golden goose: the drug for Gaucher disease. That generates about $540 million a year. Crowley's story is not entirely fabricated: Novazyme's plans state that the company wants to bring a new enzyme to market every 18 months.[148]

Biologist Canfield initiates the development of a Gaucher enzyme, and Crowley registers the trademark Ceravance for a therapy that will never see the light of day. On April 2, 2001, Novazyme issues a jubilant press release: '*Unprecedented response to enzyme therapy for Pompe disease in a mouse model.*'

The company reports that it has developed a method to produce an enzyme that is identical in every respect to the human enzyme. In Pompe mice, all the accumulated glycogen disappears from the cells, the size of the heart returns to normal, and muscle function is restored.

The press release also quotes Crowley. "If we can replicate these results in Pompe patients, we expect to see a dramatic improvement in their muscle function, which will hopefully halt or even reverse the progression of the disease. [....] Novazyme will move quickly to test the drug in clinical trials later this year."

Two days later, Crowley and Canfield meet with Genzyme's Vice President Jan van Heek and a delegation of ten scientists. They give a short presentation in which they show—as the press release triumphantly reported—muscle cells from which the glycogen accumulation has completely disappeared within a few hours. Conclusion: the Novazyme drug is indisputably superior to those of Pharming and Synpac. To conclude, Crowley shows a few more slides about their latest product: Ceravance, a third-generation drug for the treatment of Gaucher disease. The registration symbol, the small circled R after the name, does not escape anyone's attention. There is unrest at Genzyme.

On May 21, Kevin O'Donnell and Randall House visit Novazyme's headquarters in Oklahoma City on behalf of the International Pompe Association. They meet with Novazyme's top management, including Crowley and Canfield. O'Donnell takes notes. Crowley and Canfield explain to the patient representatives that the Novazyme enzyme is better than the other products because it is virtually identical to human alphaGlu. This

is due to the addition of extra M6P, which makes it much more effective. From O'Donnell's notes: "Animal studies have been conducted that indicate that normal enzyme activity can be restored with just one injection of our enzyme. Large amounts of glycogen are cleared from muscle cells in just six hours. We have been able to demonstrate this result repeatedly. Because the enzyme is so highly active, we can probably achieve this with a much lower dosage than Duke's CHO product or the transgenic product from Rotterdam. Once enzyme activity is restored, the glycogen in the muscle cells is cleared and muscle strength is restored. […] The big question now, of course, is whether these results can also be achieved in humans."

O'Donnell and House would also like to know: what is the status of the trials? "We plan to start a clinical trial at the end of 2001. Children will participate in this trial, which will take place at three different centers in the US: Florida, Bethesda, and Philadelphia. The trial will be set up in such a way that we can quickly expand to other international centers in order to move on to the decisive phase III. Twelve to eighteen children will participate. Our criteria differ from those of the other trials, because we will also allow seriously ill children to participate to see if we can make them better."

How independent is Novazyme, the IPA representatives ask. Is there a chance that Novazyme will enter into an agreement with another company, as Genzyme did with Synpac? The answer seems to be intended more for Genzyme's top management than for the patient representatives. "We will do whatever is necessary to make the treatment available to as many patients as possible as quickly as possible. At this point, we have investigated whether that would be best as part of a partnership and have concluded that it is best to remain independent. But that is a decision that can be reconsidered in light of our patient-centered philosophy. Although 95 percent of our activities are focused on the Pompe drug, we also have plans for other products. We are also developing drugs for other lysosomal storage diseases, such as MPS I, Fabry disease, and Gaucher disease. […] The decision was not made to compete with Genzyme. We believe we have a product that is an improvement over Genzyme's Gaucher product and that it can help patients who do not

benefit from it."[149]

Kevin O'Donnell adds a personal impression to the report he publishes on GSDNet on May 28. He is wildly enthusiastic. "The main impression I have of Novazyme is 'movement'. Have you ever seen a time-lapse film of a flower bursting out of its bud? That's exactly what it's like. It's a place where it's all happening. […] I've never seen so many people all working on Pompe. […] Of course, what we saw was a company presentation. […]. So take my word for it. But I think it's unlikely that we were being hoodwinked, for two reasons: first of all, they were incredibly open. We were shown all kinds of confidential information. And secondly, and most importantly, John Crowley is one of us, don't forget that. He's certainly not motivated by money. So there are interesting times ahead."[150]

Discussions with Genzyme about a takeover have been going on for a month and a half now.

34
HIGH STAKES
2001-2002

The big question for John Crowley in the spring of 2001 is how far Genzyme is willing to go. It's a game of poker. Genzyme's opening bid is $48 million. Crowley shakes his head. Even a bid of $100 million would not get approved by his board of directors. He and Canfield return home empty-handed.

Meanwhile, not everyone at Genzyme is impressed with the Novazyme enzyme. Scientists point out that the effects in mice have never been confirmed in new trials. The researchers do not think an acquisition is wise. Looking back, a former Genzyme employee comments: "The data provided by Novazyme was not falsified, but it was more, as we say today, 'sales support information'. John was an excellent salesman. The fact that he sold Novazyme to Genzyme was questionable. It was partly marketing."

But that is with the benefit of hindsight. At the time, Henri Termeer and Jan van Heek had a difficult decision to make. If Novazyme's product did indeed have the qualities it claimed, was it still worthwhile to invest in their own product? The FDA and the EMA would most likely consider the superior qualities of the Novazyme product to be a 'significant benefit', which would virtually guarantee its approval for the market. And Genzyme is certainly not keen on a competing product for its cash cow, the Gaucher enzyme. What's more, its market exclusivity is about to expire.

After much deliberation and back-and-forth phone calls, they finally settle on an offer of $137.5 million. Some Novazyme shareholders still protest, but eventually they too come around. Novazyme changes ownership and Crowley changes employers. He moves with his company and takes charge of Genzyme's entire Pompe program. It is almost a rhetorical question whether you should give such responsibility to a father of two children with the disease, but it happened.

Jan van Heek still sees the acquisition of Novazyme as an almost inevitable step. "John Crowley was, of course, highly motivated to push through the acquisition as quickly as possible. John and I communicated a lot and eventually convinced each other that it was better to work together than to compete. From the outset, it was clear that the orphan legislation would protect one, maybe two, but certainly not three or four companies. So it was a practical decision to buy Novazyme and continue working with John to see how we could make the best product."

On August 7, 2001, Genzyme announced in a press release that it had acquired Novazyme. Genzyme said it had every confidence in the potential of the new drug. The acquisition of Novazyme, Termeer explained in the press release, was in line with Genzyme's commitment to developing the best possible product for patients. Not only Pompe patients could benefit from Novazyme's innovative approach. The same was true for patients with Gaucher disease, for example. Good news, then?

The Federal Trade Commission (FTC), the watchdog of the free market in the US, takes a slightly different view. Anything that could hinder innovation and competition and smacks of monopoly arouses suspicion here. The question is whether Genzyme's acquisition of Novazyme has nipped a promising and innovative, but also competitive, company in the bud. The commission decides to investigate the matter. The main players are interviewed, including representatives of the International Pompe Association (IPA).

One of the five FTC members[151] is convinced that Genzyme has broken the rules. "The evidence shows," he argues, "that between 1998 and 2001, Genzyme gained control of three other companies that were trying to develop an enzyme replacement therapy for Pompe. [...] If Novazyme had been acquired by a biotech company other than Genzyme, this

could have resulted in either a win for Novazyme in the race for market approval or the breaking of Genzyme's market exclusivity even if Genzyme had won the race."[152]

The rest of the commission took a different view and, with three votes against and one abstention, decided not to prosecute Genzyme. The case was closed in January 2004.[153] Not all experts agree that this decision was justified.[154]

Be that as it may, for two years a dark FTC cloud hung over enzyme development, causing considerable stress for patients and other parties involved.

The announcement of the takeover also has repercussions overseas. Alarm bells are now ringing for Pharming's shareholders. The takeover of Synpac already raised questions, but the announcement that Genzyme wants to market Novazyme's product spells the end for the company. No one has any confidence left in Pharming's future.

Yet the company started the year full of optimism. In January, CEO George Hersbach made a prediction in *Beursplein 5*, the magazine for investors, that would turn out to be more accurate than he would have liked. "Let there be no misunderstanding. This year will be a costly one for Pharming." He cheerfully added: "According to our calculations, we will break even in the course of 2003. We hope to make a profit in 2004. This is based on the expectation that the first product [for Pompe] will be launched in 2002."[155] In February, when the annual figures were presented, that expectation was repeated.[156]

But financially, things were not going well. In the first half of 2001, a loss of 35.6 million guilders was recorded, 14 million more than a year earlier. Pharming announced on July 23 that it hoped to raise additional funds in the third quarter.[157] By then, investors had little confidence left. '*Pharming in free fall*', headlined the NRC on July 28. "The share price collapsed and lost more than 16 percent after the figures were announced. In total, the fund lost half its value last week."

After the announcement of the takeover, there is no saving the company. Hersbach receives a phone call from Genzyme the day before, informing him of the news. He is in the US at the time to raise additional funds. Hersbach is nowhere near having enough money to pay half of the

Novazyme takeover costs, as he is contractually obliged to do. Three days later, in a last-ditch effort, he visits Genzyme to request additional financial support. His request is denied. Hersbach has no choice: Pharming requests a deferment of payment. An administrator is appointed, and within a week, four interested parties come forward, the most important of which is Genzyme.

And yet, despite its dire financial situation, Pharming will manage to make a fresh start. To do so, however, it will have to sell its crown jewel, the Pompe enzyme. From now on, Pharming will be sidelined in the further development of the drug. At least, that is how it appears.

The relationship between Genzyme and Pharming soured as a result of these events. Jan van Heek, who witnessed the discussions firsthand, says: "It was painful, because we would have preferred to continue the collaboration. It was a moment when it became personal. And that was very unpleasant. I have to admit that at a certain point, I was done with it."

George Hersbach blames the debacle primarily on Pharming's financial management. "What I learned from this is that in drug development, you have to constantly look for funding. You never have enough money. You always have to make sure you have enough cash on hand for at least a year to be able to absorb setbacks."[158]

The developments surrounding Pharming are causing complete confusion among patients. In fact, no one can say how things will proceed from here, and in particular whether the rabbits will continue to produce the enzyme on which nine patients now depend: four toddlers and three slightly older patients in Rotterdam, plus two babies participating in a mini-trial that started a year earlier in Essen, Germany. '*Lives of toddlers possibly threatened by Pharming's suspension*', headlines *de Volkskrant* on August 15. "Pharming did promise that the children who participated in the trial [in 1999] and who will need to use alpha-glucosidase for the rest of their lives would continue to receive the drug from rabbit milk until an alternative was found. Now that the company is in trouble, the AZR [Erasmus MC] is concerned about the promised supply of the drug. According to a spokesperson, this concern has been communicated to the Health Care Inspectorate. Today, AZR wants to receive

further assurances from Pharming's administrator."[159]

At that point, there would still be several months' worth of stock. These are worrying signs. Even though Pharming and Genzyme are issuing reassuring statements, patients and doctors are not confident that enzyme production will continue without disruption.

Pharming's former partner and shareholder has now become its largest creditor. Thanks to the collaboration, Genzyme knows Pharming inside and out. Henri Termeer is known as a tough negotiator[160] who has little compassion for companies in distress. On the contrary, he sees them as easy prey. When Pharming rejects Genzyme's bid for the entire company because it is too low, a discussion arises about how the company intends to repay its debt to its partner. The most important asset is the factory in Geel, Belgium, where the rabbit enzyme is produced. The new building, nicknamed 'the blue box', had cost around 45 million guilders up to that point. Genzyme made an offer of 22 million for the complex and the existing buildings and – in a very clever strategic move – linked this to a job guarantee for all employees.

There is a second candidate: Genzyme's old acquaintance and rival in the development of the Fabry drug, Transkaryiotic Therapies. TKT offers no less than 50 percent more for the new factory: 33 million guilders. For Pharming, the choice seems simple, but there is a catch. The factory is housed in a separate Belgian legal entity, which means that it is not the owner but the court that has the final say.

Luc Kupers, who joined Pharming in 1999 as Managing Scientist, experienced this firsthand. "I was on vacation when I received a call from a colleague who told me that Pharming had applied for a court settlement, or deferment of payment, in the Netherlands. Philip van Holle, our boss, then played the Belgian card. Because we were a separate Belgian entity, we had to apply for a separate judicial settlement. Pharming wanted us to go to TKT, not Genzyme. So the dispute came before the commercial court. There, a number of staff members said they supported Genzyme's bid. Pharming Holding was particularly keen to prevent us from joining Genzyme and made many accusations against Genzyme, but in the meantime, Genzyme had convinced us, the staff, to play their card and choose Genzyme. There were about a hundred people who earned their

Of the four companies
that wanted to bring
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living here in Geel. Genzyme promised that no one would be laid off, that everyone could stay for at least a year, that salaries would continue to be paid, and that in the meantime they would consider what to do with the factory. Genzyme kept that promise. Of the people who were there at the time, I think sixty are still working there now. The judge ruled in Genzyme's favor. He said: I had to, otherwise we would have gone from a rabbit hole into a wasps' nest.

From the moment Pharming applied for a moratorium on payments until the Belgian court's ruling, it remained uncertain who would take care of the production of the rabbit enzyme. The Dutch Muscular Dystrophy Association was so concerned about continuity that it prepared for summary proceedings. But on the day of the court ruling, Genzyme issued a press release with the reassuring message: "Important to this acquisition is that we can ensure that the nine patients suffering from Pompe disease who are currently participating in clinical trials can continue to be treated with alpha-glucosidase from rabbit milk. This brings an end to a period of great uncertainty for a number of patients and their families."[161]

However, this does not mean that the supply of the rabbit enzyme is guaranteed indefinitely, even though Paul Kaplan had promised this six months earlier. The supply is finite. Kupers: "I think we continued to produce rabbit enzyme for another six months. Until we had enough on the shelf and enough inventory to give patients enough time to be transferred to the CHO cell material."[162] The assumption seems to have been that there would be enough of this in early 2003 to continue treating the patients who participated in the studies, as well as the patients in trials that were yet to begin.

Of the four companies that wanted to market the Pompe enzyme, only one remains at this point: Genzyme. And now they have to decide which enzyme to go with: the one from Synpac/Duke, Novazyme, or the enzyme they have been developing themselves for the past year.

35
A NEW START
2001-2002

In September 2001, John Crowley joined Genzyme as head of the Pompe program.[163] His task was to bring the Pompe drug to market. But which drug? Genzyme now had four options: the alfaGlu from the – now written off – transgenic rabbits, the enzyme from Duke and Synpac (which had caused problems during upscaling), Novazyme's alfaGlu (which would perform many times better than the other products, but was still in an experimental stage), and finally Genzyme's homemade enzyme. As mentioned earlier, this had been developed under intense pressure by Bob Mattaliano's group over the past year and a half, but was not yet in production.[164] However, six months earlier, on February 14, it received orphan drug designation from the EMA.[165]

In order to make the choice as objective as possible, it was decided to subject all four enzymes to a series of 'blind' tests. The results had to be fully verifiable for all parties involved. It was an intensive operation, given the somewhat corny name 'Mother of all experiments', which took about two months to complete.

On January 31, 2002, the results were announced internally. They can be read in a report that the researchers published years later, in 2008.[166] Four enzymes were compared: the rabbit enzyme, the Novazyme enzyme, the homemade Genzyme enzyme, and enzymes from human placentas. The latter served as a benchmark. Perhaps unsurprisingly,

Genzyme's own enzyme was chosen.
The article does not mention the Duke enzyme at all. This is undoubtedly due to the manufacturability of the product. Attempts had already been made for two years to produce the Duke enzyme on a larger scale, but without success.
Scalability is of the utmost importance because the purity and composition of the product must always be virtually identical, regardless of whether it is produced in a 10-liter or 10,000-liter bioreactor. This is a greater challenge than it might seem at first glance. Compare it to preparing a pot of vegetable soup for five thousand people, where each bowl of soup must contain exactly the same amount of broth, meatballs, carrots, peas, celery, and vermicelli. It is no different with biological medicines. It is impossible to achieve this completely. In practice, there will always be differences between enzymes from a large and a small kettle, but also between batches. A half-degree difference in temperature during production already yields a different result. The controls on a biologically prepared medicine are therefore strict, especially when the medicine—such as the Pompe enzyme—will enter the bloodstream directly.
Erik Tambuyzer[167], Senior Vice President Europe at Genzyme, explains why the production of the Duke enzyme cannot be made stable and pure: “It was in the cells. They only produced a good run one in three or four times. The other times, the production was full of mycoplasma, a certain type of bacteria.” Research has shown that it was not just a bacterium, but also a specific virus. This would later cause Genzyme major problems.
It is no less surprising that Pharming's drug is being evaluated in this large experiment. Almost two years earlier, Genzyme had decided, with Pharming's reluctant consent, to discontinue the production of alfaGlu in rabbits. The number of rabbits that would be needed for enzyme production would be unmanageably large. Here too, there was in fact a problem with poor manufacturability.
According to pharmacologist Henk Schuring of Genzyme, there was a good reason to include the transgenic enzyme in the test after all. This made it possible to demonstrate that the concept of enzyme replacement therapy (ERT) works. "Among other things, we were able to show that this method is successful in removing glycogen from muscle cells. Otherwise, we would probably have had to collect other toxicological data in animals before we could continue."
Finally, according to the publication, the Novazyme enzyme showed good results until it was tested in Pompe mice. There, the results were disappointing. It was decided to shelve the drug: perhaps something for later. For now, there were too many uncertainties surrounding the product. And the global Pompe community was eagerly awaiting the moment when the enzyme would become available.
The ‘Mother of All Experiments’ took a lot of time and was extremely costly. Not everyone at Genzyme was convinced of the usefulness and necessity of the exercise. Looking back on the process, Carlo Incerti, Senior Vice President, cautiously expresses his doubts. “We spent a lot of money and learned from it—I want to hold on to the good memories. I want to believe that we did it with a clear goal in mind, to leave no stone unturned. But when you look at it from an economic and management perspective, there is room for criticism.”[168]
Be that as it may, the choice fell on Genzyme's own enzyme. That brought them back to square one. The trials that had taken place at Duke and Erasmus up to that point were of only marginal value for the market approval of Genzyme's own enzyme, because a differently produced alphaGlu had been tested. What the experiments did show, however, was that enzyme replacement therapy has a clear effect in babies and young adults.
Genzyme also has obligations from the past. All patients who have ever participated in a trial must continue to receive the same enzyme afterwards. They are entitled to this. As mentioned, the production of the Duke enzyme faced a number of setbacks and only a limited quantity of the rabbit product was still available in 2003, frozen in glass vials. After that, this group of patients would have to switch to the new product made from CHO cells. And, of course, enzymes were needed for trials to convince the FDA and EMA of the therapy's effectiveness.
So, the production of the Genzyme enzyme had to be accelerated, but this was going much less smoothly than expected. In order to start the

trials, a year's supply of enzyme was needed, in case problems arose in the production process. Three older bioreactors are used for production. The very first run immediately yields much less enzyme than expected. The yields from the following runs are also disappointing, which means that the number of children in the trial has to be limited.[169]

To make matters worse, in April 2002 it became apparent that the vials containing the rabbit product were not resistant to the very low temperatures in the freezers. The glass broke and the enzyme became contaminated with tiny glass splinters. A third of the stock is unusable. This makes it impossible to provide patients who have participated in trials with sufficient alfaGlu in the longer term. Feverish consultations are held with the doctors involved and the international patient organization IPA about limiting the number of enzyme treatments.

In July 2002, Genzyme explains this setback in a press release: "The production of the drug from rabbit milk is very complicated, which has often led to production problems in this experimental phase. This is not unusual for biotechnological products in this phase. Due to the production problems, the yield of the drug is lower than planned. This shortage was anticipated several months ago, and Genzyme immediately consulted with the treating physicians at that time to find a possible solution. […] Six of the nine patients have now been switched from the transgenic product to the CHO product. The intention is to continue supplying the drug from rabbit milk until spring 2003. In the coming period, Genzyme will consult with the doctors at Erasmus Hospital with a view to eventually switching all patients to the CHO product."

The production problems have dramatic effects. Even though Genzyme is doing its utmost to limit the damage, the impact on patients is significant. Later that year, Genzyme sets up its first 160-liter bioreactor to produce alfaGlu for trials with its own drug. In the meantime, patients have to make do with Duke's CHO product or the leftover rabbit product. Meanwhile, the disagreement between the pharmaceutical company and practitioners about the correct dosage continues.

The newspapers published harrowing stories of patients who feared they would be left without the enzyme. Henri Termeer's mother called from Tilburg, distraught. "At my age, do I still have to be ashamed of my

That was a very difficult time, because suddenly there was no enzyme left in stock.

son?"[170] It was not the first and certainly not the last time she called Boston; she was Henri's conscience from afar.

At the end of September, John Crowley flies to Rotterdam with a large Genzyme delegation to explain the problems and the proposed solution to the patients. The patients are not convinced and continue to ask critical questions. The meeting ends on a sour note. That same day, the Genzyme mission meets with the staff of the Sophia Children's Hospital to discuss cooperation and finances. That conversation also goes poorly. Frustrations have been building up over the past few years, partly because of how Pharming's debts to Genzyme were settled, and partly because of the high fees that went to Duke University and Synpac. The prevailing feeling is that most of the scientific work was done in Rotterdam and that others are now reaping the rewards (and the profits).

The relationship between Genzyme and Duke on the one hand and Rotterdam on the other became seriously disrupted. Ans van der Ploeg says: "We were kept out of the loop for a while, but they couldn't ignore us. They realized that too."

Hans Büller, then head of the Pediatrics Department at Sophia Children's Hospital, blames the debacle on amateurism. [171] "We had a potential drug; we had even shown that it could be effective. We didn't know the long-term effects yet; we had to learn how it worked, for whom, and in what dosage as we went along. We were unfamiliar with the world of the other side, where it's all about patents, ownership, and investors. I think I was also quite naive in the beginning. I wanted to be left alone, to administer the drug to patients and see what the effect was. That's the best thing you can imagine as a pediatrician: having a potential cure for what is essentially a deadly disease. That was the world Ans and I lived in. For us, there were additional issues of legal constructions and purchasing and buyouts."

Nowadays, every university has a Valorization department. It ensures that the ownership rights to the results of scientific work are legally secured in patents. In early 2000, this was still pioneering work in the

Netherlands and things sometimes went wrong. Büller: "Those guys at Genzyme just knew how strong their position was. They had an attitude of 'take it or leave it'. We had a legal advisor, a very naive man, who thought he understood the pharmaceutical industry very well. But he was easily misled."

Perhaps most poignant is that part of Rotterdam's misery can be traced back to the gift that Arnold Reuser gave to Duke University in good faith at the time: a copy of the human gene with the code for alphaGlu.

It is not just financial malaise. Patients are experiencing the consequences of the shortages firsthand. Physician-researcher Johan Van Hove returned from Duke to Leuven via Australia as a doctor. He registered a patient for the first trial with infants in Rotterdam.[172] "That was a very difficult time, because suddenly there was no more enzyme available. Genzyme then said: we are going to halve the dose. Within a week, our Belgian patient had lost a lot of strength; the switch did not go well for her at all. Genzyme kept trying to convince me that the half dose was just as good, but I could see that child deteriorating. Shortly afterwards, the dose was increased after all, but by then it was too late. It's clear: if you're too late and a cell switches from receptive to non-receptive, you can't get it back."

Van der Ploeg also fought many battles.[173] "We always had to be on the barricades. Nothing came easily, especially in the early days. Actually, they wanted to switch patients from the rabbit enzyme to the CHO product. They also said: just don't give those patients anything for a while and see how it goes. Or treat them with a lower dose. That was unacceptable to us. Especially in the early stages, there was nothing right about that dosage. We thought the patients were important. We said, we're not just going to do something that could harm them. Go back from 40 to a dose of 10 or 20 milligrams? There was no evidence for that at all. That's why we continued to use the rabbit enzyme until 2002. In the beginning, we had seven patients on enzyme therapy: four classic infantile patients and three older patients. Those older patients had not been receiving alfaGlu for some time, or had been receiving less. But in the end, we made our point that you need more enzyme for it to get into the muscles."

36
DEALING WITH A PRINCESS
2001-2002

Most patients have no idea how precarious the situation is. However, they do notice that the planning for the trials keeps getting pushed back, which fuels their anxiety and impatience. The drug is available, it works, so what are we waiting for? Time is a scarce commodity for a patient with Pompe disease—and that is especially true for babies and children. Patience can be deadly. And so many parents choose to take the elephant path. A popular route is via politicians or well-known actors, singers, or athletes. In America, Y. T. Chen had to deal with this, but it happened in Europe as well.

Erik Tambuyzer[174] in Belgium, for example, has a tricky problem on his hands. "Around 2000, the possibility of treating Pompe became more widely known. Many people asked their country's Minister of Health to arrange this medicine for their sick child. They sometimes went to great lengths to do so."

Tambuyzer tells the story of the mother of a girl with Pompe, Rossella Passero, who chained herself to the gates of the ministry in Italy and declared that she would not leave until Genzyme had delivered the drug. She was successful. Newspapers published photos of the minister handing her the enzyme.

For Tambuyzer, it is clear that he must proceed with caution in similar cases. So he contacts Joseph Torrent i Farnell, the chairman of the Com-

mittee for Orphan Medicinal Products, a committee of the European Medicines Agency (EMA). "I asked him: is Genzyme morally obliged to give the product to these patients in dire need, or should the limited supply be reserved for clinical trials, so that hopefully many more patients can be helped in the future? The answer was clear: the priority must be clinical trials. I think that makes sense, but at the time it was a delicate and difficult situation for the company to say no to an individual patient. To be able to do so with conviction, we needed the support of the government."

The parents of a Flemish baby with Pompe disease wrote a letter to the Belgian royal family. Princess Astrid, the sister of the current King Philippe, was concerned about the girl's well-being and had the best of intentions. The Minister of Health, Magda Aelvoet, also approached Genzyme. She believed there were good reasons to give the girl priority. Wasn't Genzyme's factory located on Flemish territory and wasn't it built with substantial subsidies from the Flemish government?

Together with Philippe van Holle, then Vice President of Genzyme Northern Europe, Tambuyzer visited the minister's office on a Sunday morning in May. "I explained the situation and promised that we would make the product available to the patient as soon as there was enough of it."

The child was supposed to receive treatment that fall, but the product arrived too late. Tambuyzer: "You have to treat children[175] before they are six months old. Otherwise, the disease has affected their hearts and muscles too much to have a have a beneficial effect. This child was seven or eight months old at the time and subsequently died. Later, Princess Astrid accepted our invitation to open the factory in Geel."

This took place in the second half of 2002. A few months earlier, on October 30, 2001, the Dutch Muscular Disease Association (VSN) issued a press release with the headline: "*VSN: compassionate use for people with Pompe disease within six months.*" The VSN wants alfaGlu to be available to patients within six months, even before all the formalities surrounding approval and reimbursement have been completed. "It will [...] certainly take several more years before the drug is officially registered and becomes available to patients," argues the VSN. "In the meantime, babies,

young people, and adults [...] will die from Pompe disease knowing that an effective drug exists. The industry has also indicated that this drug can be produced in larger quantities."

On December 13, a similar letter was sent to the Dutch Minister of Health, Welfare and Sport, Els Borst. People are drowning in sight of the harbor, argues VSN chairman Klaas van der Ham. They are becoming increasingly disabled and dying, even though an effective drug exists. Why wait to dispense it until the EMA and FDA have given their approval? The researchers no longer have any doubts, the industry wants to produce more, so make sure that arrangements are made for seriously ill patients. Only laws and practical objections stand in the way. You can remove those. Minister, what are you waiting for?

The letter expresses a feeling that regularly arises in such processes. Patients, parents of terminally ill children; they spring into action whenever there is hopeful news, whenever reports appear that a new therapy may offer relief. That therapy is shielded by walls of laws and regulations, once created to protect citizens from unscrupulous providers, false health claims, or even deadly side effects. But patients are living with the prospect of death, and for them, agencies such as the EMA and FDA—as well as national institutions and commissions—are bureaucratic juggernauts that are blind to their needs. It is a devilish dilemma between time and care.

With its appeal to the minister, the patient association also wants to combat arbitrariness in the provision of alfaGlu. Without clear regulations, parents with the best connections and the most popular advocates will be able to obtain the medicine for their child, while other children may need it more urgently. This requires proper regulations. And that already exists. It is called 'compassionate use'[176], to which the VSN refers in its press release. This regulation offers the possibility of providing a medicine if the formal assessment has not yet been completed. Compassionate use is usually requested by the treating physician. Permission must be granted by the competent national authorities.[177]

On November 17, 2001, a major article appeared in *de Volkskrant*[178] under the headline "*Medicines out of compassion*". "The idea of the VSN [for *compassionate use*] is not new. When the AIDS epidemic was growing,

the American AIDS lobby managed to force through such emergency provision for the first AIDS inhibitors, which were not yet officially on the market: so-called compassionate use. This has since become a familiar phenomenon in the US. In the Netherlands, too, this option was offered at the time. During the European registration period, a procedure that takes about three months, the Health Care Insurance Board (College voor zorgverzekeringen, CVZ) created a subsidy scheme at the request of the Ministry of Health to bridge the gap. […] For the time being, the CvZ is not considering financing the provision of alpha-glucosidase (estimated at several tons per patient per year). Only registered medicines are eligible for this, according to a spokesperson."

Despite the CvZ's negative stance, the VSN is continuing its crusade undeterred. In January, there will be a meeting with the organization that must grant permission for the import and admission of alfaGlu, the Chief Inspectorate for Public Health.[179] Contact is also being sought with members of the House of Representatives. One condition has already been met: doctors support the initiative. This is important because, if it comes to that, they will have to sign a statement that they take responsibility for administering the experimental drug.

Of course, the VSN is also talking to Genzyme. They need to scale up production and medically monitor the patients who will receive the drug. In a meeting on January 28, 2002, Genzyme states that humanitarian use, another term for compassionate use, is only structurally possible if there is enough left over from the production of the drug for the current trials. It is not clear when that will be. The patient organizations want more clarity on this.[180]

That clarity comes, but it is not the outcome that patients had hoped for. In mid-2002, there is not enough enzyme to treat the patients who previously participated in the trials. At the same time, a supply must be built up for the babies who will participate in the trials with the Genzyme enzyme.

It is a catch-22 situation: on the one hand, there are the seriously affected patients who will die if they do not receive the drug; on the other hand, the trials must be conducted as quickly as possible in order to make the drug available to all patients.

There are days you never forget. This was the day we'd been working towards.

The enzyme shortage also puts John Crowley in a difficult position. He had hoped that the sale of his company to Genzyme and his move to his former competitor would mean that his two sick children could be helped sooner. The opposite turns out to be true, because any suspicion of abuse of his position and favoritism toward his children would be severely punished. As a result, his children move further back in the queue rather than forward. What makes it even more poignant for him is that, on the one hand, he is forced to ship the drug to countries where, thanks to persistent lobbying by ministers and ambassadors, a few patients receive preferential treatment, while at home he sees his children's health deteriorating.

It's an untenable situation. The solution is found in a simple deal: his children Megan and Patrick can participate in a small trial if Crowley resigns from Genzyme. He does so on December 19, 2002. Three weeks later, on January 9, 2003, his children receive their first infusion.[181]

Crowley: "There are days in your life that you will never forget. This was the day we had been working towards. The children had been diagnosed five years earlier. Pressing the infusion button meant that our hopes had become reality. And we saw it happen that very night: the energy the children had. The infusion saved their lives. Their hearts returned to their normal size, and by summer, Megan was sitting up and playing with weights."[182]

It is the moment when production problems have been overcome and space is slowly being created for the treatment of patients outside the trials, even if this is still only happening on a small scale.

37
HEIDELBERG
2003

A plan needs to be made for treating seriously ill patients, and thanks to the efforts of the IPA, the international Pompe patient association, one is coming together. There are intense talks with Genzyme CEO Henri Termeer.[183] It's not just about little kids, but also adults who are deteriorating fast.

In the fall, the wind finally begins to blow from a more favorable direction. On September 16, 2003, Genzyme announces in a press release that the available quantity of alfaGlu is increasing and production capacity is growing steadily. The tone is extremely optimistic. There are plans to set up clinical trials with older children and adults, although these will be limited in scope. In addition, a special program will be launched to ensure that patients who are unable to participate in the studies also have access to alfaGlu.[184]

Just a quick explanation to avoid confusion: the version of alpha-glucosidase, alfaGlu, developed by Genzyme is called alglucosidase alfa. That is the name of the active ingredient. The Genzyme enzyme has since been given the brand name Myozyme,[185] which means 'enzyme for the muscles'. By way of comparison: acetylsalicylic acid is the name of the active ingredient in certain painkillers, while Aspirin is a brand name. From this point onwards in the text, the substance name will generally be used rather than the brand name, except in quotations and where it is clear that the brand is being referred to.

That special program for rapid access will start that same year, albeit on a limited scale at first. The IPA is pleased with the development. Secretary Ria Broekgaarden welcomes the start of the program in the press release. But we are not there yet, she warns. "Further steps are necessary, because not everyone has access to the therapy, while the disease continues to affect everyone."

Genzyme's announcement comes on the eve of the IPA annual meeting, which takes place in Heidelberg from October 31 to November 2. Patients, parents, doctors, researchers, a delegation from Genzyme: everyone is there again. Visitors come from thirteen countries, including Japan, New Zealand, and the US. The association now reaches 650 Pompe patients in 32 countries.[186]

Optimism prevails among the visitors: the studies in Rotterdam and the US have so far shown mainly favorable results, although the effects vary from patient to patient. Some stabilize and show improved condition, others show a clear increase in muscle strength.

It is disappointing, however, that it may take years before the drug comes onto the market. Genzyme has announced that it will submit an application for approval to the European authorities at the end of 2004. This means that the drug will not be available on the European market until the end of 2005 at the earliest. Due to different regulations, it will probably take even longer in the US. "Why does so much have to be done before it's ready?" sighs one patient.

During a forum discussion on the first day of the meeting, Genzyme is asked whether it is already clear how much enzyme they will ultimately need to produce. The answer, in short, is no. As mentioned above, scaling up a biological product is a balancing act, partly because there are so many uncertain factors. Frank Ollington, who succeeded John Crowley as leader of the Pompe program, sums them up. One: we don't know exactly how many patients there are worldwide. Two: we do not yet know what the correct dosage is. And this also depends on the patient's body weight. And three, not unimportantly: we do not know if, where, and when the drug will be approved.

The company also explains a planned, larger study with older patients,

which is due to start in 2004. This is a 12-month observational study involving around 60 patients in the mild to moderate stage of the disease. The patients will not be treated with the enzyme, but their data will be used to set up a clinical study. If they meet the criteria, some of them will probably be allowed to participate in that study. Half will receive the real drug, the other half a placebo. The studies will take place at three centers in the US and two in Europe: Paris and Utrecht. The Erasmus MC's place has apparently been taken by the UMC Utrecht. This seems to be a consequence of the tensions that arose when Pharming had to drop out.
Later that day, during a question and answer session, Kevin O'Donnell takes the opportunity to solve a puzzle that has been on his mind for some time. It concerns the images of mouse muscle cells that he and Randall House were shown during their visit to Novazyme at the time and about which he had reported so enthusiastically. The muscle cells of untreated Pompe mice were packed with glycogen, while the cells treated with the Novazyme enzyme were completely clean after just a few hours.
"How is it possible," he asks Bill Canfield, Crowley's former partner, "that the convincing success you showed everyone could never be reproduced afterwards?" Canfield replies that there was probably an 'artifact', an error in the staining process, which meant that the glycogen in the treated cells was not visible. Over the years, other explanations have been suggested for the disappearance of the glycogen. Whatever the case, the error misled many people. More than twenty years later, O'Donnell is still angry about it. "On the one hand, it matters, but on the other hand, it doesn't. It has no direct impact on the development of the therapy, but I find it incredible that no one ended up behind bars."[187]
The mistake does not detract from the fact that Canfield had an interesting approach to developing a better enzyme, but in 2003 that was still a mirage. The Novazyme enzyme has been shelved for the time being.
Of course, the future price of Myozyme is also discussed during the meeting. Everyone knows that high prices are charged for comparable drugs for Gaucher's and Fabry's diseases. "Will this drug be very expensive? And do you think it will be reimbursed by insurance companies once it has been approved by the authorities?" someone in the audience asks.

For Bakker,
the compensation
is an ethical issue,
a matter
of civilisation.

The vague answer is: "The price of our drugs must be seen in the context of the costs and complexity involved in developing and manufacturing innovative products for patients with complex, rare, serious diseases."
For those who understand, this means it's going to be a hefty price tag. This is where the next obstacle on the road to therapy looms. What if the authorities refuse to reimburse the drug? Then it will all have been a waste of energy, as no patient will be able to afford it. These are also the thoughts of Johan Bakker, director of the Rivierenland Water Authority in his daily life and, for some time now, a Pompe patient. He only developed muscle weakness later in life, which, as it turned out, was caused by the disease.
Bakker sees how Minister of Health Hans Hoogervorst is moving towards a separate scheme for expensive orphan drugs that threatens to have an unfavorable impact on hospitals and ultimately on patients. In practice, this would mean that a treating physician would have to negotiate with the hospital pharmacy and management about whether or not to purchase a drug, while the patient is, so to speak, waiting in the waiting room for treatment.[188] This would put the physician and the hospital in a strange position vis-à-vis their patients. Bakker sends a letter to a party colleague of VVD member Hoogervorst, who will be in charge of the Ministry of Health, Welfare and Sport at a crucial moment in the reimbursement process: Edith Schippers.
He writes: "It is common knowledge both within and outside this water board that I do this work, even though I have to sleep on a ventilator at night and I can hardly use a number of muscle groups anymore. Unfortunately, my decline is rapidly progressive, but not hopeless. Mentally, I am still unbroken... With the medication, I will be able to continue working normally and remain relatively healthy, and I will not have to go through the disability benefits process and then be dependent on nursing care for the rest of my life. Speaking of costs: that also costs a lot of money. Even more money than providing the medication, and that is not difficult to calculate."

For Bakker, reimbursement is much more than a financial issue; it is an ethical issue, a matter of civilization. He will continue to draw attention to this in various ways in the coming years. "The fundamental question I struggle with is why I am being excluded—let's be honest, that's what it boils down to—because I have a rare condition, whereas that would not happen if I had a rare accident and needed intensive nursing and treatment for the rest of my life. Draw the parallel. A sentence to a secure psychiatric hospital is not linked to the budget of the prison in question in criminal law, is it? Surely a comatose patient is not disconnected because the costs of care are too high in a multi-year perspective? Or is a trend being set and are orphan drugs leading the way? Does the coalition agreement only offer guidelines for economical accounting, or are we in the Netherlands capable of something more?"[189]
Johan was right: the discussion about costs would flare up again. He is a good friend of Maryze's and will have more to say on the subject.

38
THE 1602 AND 1702
2003 – 2004

Genzyme is now making every effort to start trials with alglucosidase alfa, its own alfaGlu enzyme, in babies. As in the Erasmus MC study, they are looking for an ethically responsible alternative to a placebo-controlled study. After all, treating babies with a fake drug would mean signing their death warrant. The solution chosen is very similar to the approach used by Ans van der Ploeg and Hannerieke van den Hout in 1998.
Pharmacologist Henk Schuring is jointly responsible at Genzyme for guiding the drug through the EMA and FDA approval process. He explains: "In 2002, we visited around 50 to 70 hospitals that had treated babies with Pompe disease over the previous 15 years. We reviewed all the medical records, I think around 350 to 370, and from those we selected the patients who met the inclusion criteria for our study. They were used as a comparison for our trial."[190]
The main difference between the earlier study in Rotterdam and this one is in the numbers. The results of both file studies show the same picture: babies with Pompe deteriorate rapidly, develop heart and respiratory problems, and almost always die within their first year of life.
When Genzyme's study begins, the results of the Rotterdam study have yet to be published. They appear in August 2003 in *The Journal of Pediatrics*.[191] In May 2006, three years later, the publication on Genzyme's study follows.[192]

This clinical study is also limited to babies. There are three good reasons for this: an ethical one (babies cannot wait), a practical one (there is not enough enzyme for a study with adults, who need much more enzyme) and a research-related one (because the course of the disease in adults is so diverse, it takes much longer to demonstrate a positive effect of the therapy).

This approach presents a huge dilemma. Doctors, patients, and industry want to make the drug available to the entire patient population, including adults, as quickly as possible for a variety of reasons. But the European Medicines Agency and the US Food and Drug Administration, in turn, want to see evidence for each individual target group, which could take years. These requirements are at odds with each other.

Schuring: "A so-called broad label, i.e., for all Pompe patients, was our absolute goal. Everyone could see that 90%, almost 100%, of the treated babies survived, while in our natural history study we saw 90% die within two years. So that was a fairly straightforward story. The main discussion would undoubtedly be about the indication: for everyone or only for babies."[193]

On February 18, 2003, Genzyme announced the details of the upcoming studies with babies in a statement. "Genzyme plans to conduct two clinical trials with [alfaGlu...] this year. Both studies will focus on patients with the infantile form of Pompe disease, in which symptoms manifest themselves in the first year of life." The company reports that it has received approval from medical ethics review committees or similar bodies. "The first trials (study 1702) [...] will start in five academic hospitals: Duke University Medical Center, Cincinnati Children's Hospital Medical Center, the University of Florida in Gainesville in the US, the Royal Manchester Children's Hospital in Great Britain, and the Hôpital Universitaire Debrousse in Lyon, France."[194]

Once again, Erasmus MC is conspicuously absent from the list. Due to the cooling of relations, the collaboration with Duke and Genzyme is on the back burner. This is disappointing for the researchers who are at the forefront of this new drug[195], and no less so for Dutch patients for whom participation in the trials is virtually impossible.

The decision to also start a study with babies older than six months, the

1702, was made deliberately, mainly because the demand for compassionate use was so urgent, says Priya Krishnani of Duke University. She supervised the studies. "We started the central study, the 1602, with eighteen children. This was the study for the registration of Myozyme. During the same period, a second study, the 1702, was conducted for children with a more advanced stage of Pompe disease. Formally, this was not compassionate use, but the intention was to give these babies a chance as well." Ultimately, 21 babies participated in this study.

Once again, Kishnani encountered a phenomenon she had already encountered in the first Duke study in 1999: immune reactions. Children who do not produce any alpha-Glu in their cells[196] are at high risk of developing antibodies against the enzyme. As a result, the results of the treatment lag behind those of children who still produce some alpha-Glu. This prompted Krishnani to experiment with drugs that suppress the immune system.

The 1602 study also serves to determine the correct dosage, as there is still uncertainty about this. Coincidentally, in June 2003, an article by the Rotterdam research group appeared about the 1999 study involving four Pompe babies. They describe the results after 72 weeks of treatment: 20 milligrams per kilogram of body weight once every two weeks does not produce optimal results. There is still an accumulation of glycogen in the muscles. Only when the dose is doubled after 21 weeks does the glycogen begin to disappear. The Rotterdam researchers cautiously conclude that a dosage of 40 milligrams per kilogram is necessary.[197]

But that concerns the rabbit enzyme, and there are people who do not think very highly of it. Some Genzyme employees are convinced – or perhaps rather, cherish the hope – that their enzyme is superior and that a lower dose will therefore suffice. That would also reduce the pressure on production capacity.

The new studies in 2003 and 2004 should provide a definitive answer. Unfortunately, that didn't work out. Kishnani: "In the design of study 1602, we assumed two doses: 20 milligrams per kilogram and 40 milligrams per kilogram once every two weeks. When the results were analyzed, it turned out that the 40-milligram group happened to have more patients with a severe immune response than the 20-milligram group. So

we couldn't draw any conclusions about dosage from this study. The idea that the dose needed to be increased already existed, but we lacked the data to substantiate it."
Because no clarity can be obtained about the dosage, the discussion will continue to rage for another twenty years before a consensus is reached: 40 milligrams per week.[198]
Apart from the dosage, the results of the study are clear. "We had established that babies with Pompe disease die within a year without treatment," says Kishnani. "That also became the most important measurement point in the 1602 study: do the babies survive longer than a year? Of the eighteen children, three were put on ventilators, but the vast majority developed motor skills and did not need permanent respiratory support."
The studies therefore provide convincing evidence of the drug's effectiveness. The big challenge now is to make the drug available for all ages, with that limited data, without the need for years of studies in older patients. Nobody wants that.

39

MARYZE

BUBBLES IN THE ICU

Over the years, my condition continued to deteriorate, and in the late 1990s, it went downhill fast. While Robert gradually recovered and regained his zest for life, I became more dependent on my wheelchair and ventilator. What I remember most about that period is the bottomless fatigue. Everything was an effort. To get through the day, I would go to bed in the afternoon. Around six o'clock, my father would wake me up. That way, I managed to stay up until ten o'clock. My only comfort was the conviction that one day it would be my turn to receive the medication. I had no idea how long that would take, but it would be okay. I just had to make sure I kept my head above water until then.
During a meeting on rare diseases in the European Parliament, Pharming had suggested in the corridors that I would soon be eligible for enzyme treatment. But when Genzyme took over the Pompe program in 2001, that was no longer an option.
In 2002, I changed doctors. Until then, I had been going to Radboud for checkups. When my doctor, Fons Gabreëls, retired, I switched to Erasmus MC in Rotterdam. I had known Ans van der Ploeg since I was sixteen, but we mainly saw each other at international conferences and other meetings, not in the consultation room. In April of that year, she examined me for the first time. As the examination progressed, I noticed that she was becoming emotional. She knew me from my

presentations and conversations during coffee breaks and thought I was doing well. During that examination, she realized how I was really doing: downright bad. Trials were already planned for adult patients, but it was unlikely that I would be eligible for them given my condition. I have both the infantile variant and a rare adult form of Pompe disease in my genes. I showed certain symptoms immediately after birth, but I did not have an enlarged heart.

In that same year, 2002, Genzyme had started building up an enzyme supply for patients who could no longer wait. I was unaware of this, as it had not been publicized. In the fall, Italian Rossella Passero was the first baby outside of the trials to be administered the enzyme. The commotion caused by the mother to draw attention to her terminally ill daughter and the administration of the drug made international headlines. The drug came just in time for Rossella.[199] Suddenly, I too had the wind in my sails. It was finally going to happen: I could participate in the so-called compassionate use program that Genzyme had created especially for patients like me.

I have told this story hundreds of times, but I am happy to tell it again here. It is December 11, 2002. At four o'clock in the still pitch-dark morning, there is already a lot of activity in the house. Lights are on everywhere. My mother is busy packing things, my father is helping me out of bed. It is an old-fashioned winter morning. Bitterly cold. Your breath freezes on your upper lip. The car heater is blowing at full power.

It is a long journey from Varsseveld to Rotterdam. We drive into the city via the Maasboulevard. The roar of the engine, the silhouettes of the tall buildings across the water in the blue glow of the moon, and then the fluorescent lights in the hall of the awakening hospital. A nurse is waiting for us in the intensive care unit. It has to happen there, because no one can predict whether it will go well. Allergic reactions are a possibility. I am the fourth adult in the world to be given the drug. Checks and tests follow, and I am meticulously covered with sensors and connected to all kinds of equipment via cables. Heart, blood pressure: everything must be monitored. A needle is inserted into my hand. Of course, it hurts, but it also feels like a liberation. It is the gateway

through which my medication, my hope for new life, must enter my body.

When everyone who needs to be there is present, it can happen. Gerard de Jong, my internist, connects the IV, the tap is opened, and drop by drop, the liquid gold flows into my vein. This is it. This is what I have been looking forward to. I am no longer a drowning man, struggling to stay afloat. I am saved, I am in the boat. Now it's up to me, I tell myself, to get as many fellow sufferers as possible into this lifeboat.

Ans van der Ploeg comes by, and Arnold Reuser, and later also Ria Broekgaarden from the VSN, with whom I have worked so much. She has a toy in her bag, a dancing hamster, as a nod to the CHO cells, the hamster cells with which my enzyme is produced. My mother has brought a bouquet of flowers for Ans, and someone conjures up glasses and a bottle of champagne. And so, a little later, everyone is sitting around my bed with a glass of bubbly in their hands. Except me, I have my IV.

I look at my parents next to me. For them, it is also an important moment. For years, they lived with the prospect of losing their eldest child. Now, suddenly, everything is different, and the future looks promising. They are overjoyed.

The story about the champagne in the ICU spreads throughout the hospital. What was going on there? Normally, the ICU is a place of fear, hope, anxiety, and sadness. Champagne doesn't belong there. This champagne toast in the ICU was special and unprecedented.

And does the medicine work? Yes, it does. Let me start by saying that I never expected to get out of my wheelchair. That didn't happen. So what? Many people spend hours a day in their cars, I spend them in my wheelchair. On four wheels, you can go almost anywhere. In my opinion, the ability to walk is greatly overrated.

Gerard de Jong was the first to notice a modest change. That was after about five months. I hadn't noticed anything myself. That's what happens with an illness that creeps up on you and then quietly retreats: you don't notice it.

For me, the improvement only became clear a month or so later. I was lying in bed in my room watching TV, As the World Turns, as I

I told the UWV that I no longer needed benefits, as I was going to earn my own money.

did every day, because there wasn't much else to watch. Suddenly I thought: why am I lying here? Why in bed? I'm not tired at all. During dinner, I said that afternoon naps were over. My parents were worried, of course. Was that really a good idea? I said, “The bed isn't going anywhere. If I don't feel well, I can get back in it.” Since that day, I have never gone to bed in the afternoon. In fact, my parents regularly asked me around midnight if I wanted to go to bed. They used to put me to bed at that time.

I was actually far too busy to go to bed. I had my energy back, my fitness had improved, I could go longer without ventilation, that kind of thing. It was great. I could do things again, be even more active on behalf of my fellow patients worldwide. I wrote informational texts about Pompe disease, provided translations in Arabic, Turkish, Czech, Russian, and Japanese, expanded the international patient network, gave presentations worldwide to doctors, scientists, and patients, all as a volunteer for the IPA, the International Pompe Association.

When alglucodidase alfa was approved by the EMA and FDA and my energy levels had improved to such an extent that I was ready, I decided to start my own small consultancy. With the experience I had built up over the years, I should be able to earn an income. I had grown up with the slogan “a smart girl is prepared for her future.” Well, I suddenly had a future, so something had to be done. I registered with the Chamber of Commerce and notified the UWV (the Dutch agency for employee benefits) that I no longer needed benefits because I was going to earn my own money. They looked at me as if they had seen water burning. The UWV employee I spoke to was about to retire. He had never before had such a request from someone with such a serious life-threatening condition and disability.

Of course, I needed a website for my small consulting firm, and a logo. Juan, a fellow patient and friend in Manila, created the website. I had helped him with the medication, and now he was helping me. In January 2007, my business was launched. I gave presentations during internal training sessions for company employees, wrote informational texts, participated in workshops for patients—things like that. Mostly, it was about teaching professionals to see through the eyes of a patient and making them aware of what a patient's daily life is like. Genzyme was my first client: writing a brochure. Then came other pharmaceutical companies, advocacy groups, and patient associations. My knowledge, experience, and expertise were now being paid for, as is the case with other people.

I had become a professional consultant, with expertise and experience that were valued. I was proud of that.

40
MONEY, MONEY, MONEY
2005

The letter that Johan Bakker wrote to Dutch minister Edith Schippers in December 2004 was the harbinger of a storm that broke at the beginning of 2005. The reason was Minister Hoogervorst's announced plan to have hospitals contribute to the costs of orphan drugs that they prescribe to their patients. On January 24, he states in a letter to the House of Representatives: "I therefore intend to draw up a separate policy rule for the funding of intramural orphan drugs. Orphan drugs that are admitted to this policy rule will be reimbursed at 95 percent. Here too, the 5 percent that is not reimbursed must be paid from the regular hospital budget." Apparently, there is no problem, because he assures the House: "The starting point [...] is the accessibility of orphan drugs for all indicated patients." This co-payment is primarily intended to stimulate cost awareness within hospital care. It could also encourage doctors to prescribe cheaper, perhaps slightly less effective alternatives. The ultimate goal is to curb the growth of spending on orphan drugs, which at that time still accounted for 0.6 percent of the total drug budget.
At the same time, Hoogervorst wants to concentrate patient care 'in one, at most two, centers per disease'. That concentration in itself is an excellent idea, because it allows for more efficient research. But since it also concentrates the administration of very expensive drugs within a few academic centers, the plan could cost hospitals millions of euros per year. After all, 5 percent of a large amount is still a large amount. One way or another, this will be at the expense of patients. The comments are therefore endless.
Johan Bakker expresses his concerns widely in the press. He outlines his situation in the magazine *Binnenlands Bestuur*.[200] He fears that academic hospitals will decline the honor when the drug becomes available in 2006. He accuses the government of promoting the development of orphan drugs at the European level, but then frustrating market access when they finally become available. "Giving hope for recovery and then turning your back when it comes to payment is not what I call governance, but torture." Because, in his view, the situation is much better organized in Belgium and England, he suggests that he could well become the Netherlands' first drug refugee.
Carla Hollak of the AMC (Academic Medical Centre) also speaks out. She is a professor specializing in metabolic diseases and sees many patients with rare conditions during her consultations, including people with Gaucher and Fabry diseases. They are also dependent on new, expensive medicines. In the February 1 edition of the *NRC* newspaper, she writes: "Since care for such rare diseases is concentrated at the AMC in Amsterdam and also at the Erasmus MC in Rotterdam, these hospitals will face an enormous strain on their budgets. The AMC currently treats about fifty such patients, and this number will only increase in the future. Already, this represents an annual cost of 10 to 12 million euros for medication alone. This amount comprises 20 percent of the academic budget intended for the treatment of thousands of patients per year. The continuity of care for patients with rare diseases and the centralized approach that is so important in this regard are therefore at risk. As a result, new medicines for this category of diseases will find it even more difficult to reach patients in the future than is already the case now.[201]
Louise Gunning, chair of the AMC board, takes a broader perspective in a letter to the editor. "*New medicines for everyone*" is the provocative headline. "If you ask me, most Dutch people would choose to have new diagnostic and treatment options added to the package if they deliver reasonable health benefits. It is true that new medicines and technologies are often very expensive at first, but those high costs often decrease

rapidly over time. Suppose that after World War II, you had decided that penicillin was far too expensive. Then we would now label ourselves a developing country in terms of public health."
Regarding orphan drugs in the basic package, she says: "This means that they are kept accessible to everyone through mutual solidarity. I cannot imagine that we would make new possibilities that actually yield health benefits, even if they involve expensive drugs or orphan drugs, available only to a limited group that can afford them."
She proposes controlling costs with clear protocols, concentrating treatment and care in one or a few centers, optimal diagnosis, and innovative research to develop alternative and hopefully cheaper treatments. "But if you want to concentrate those patients and therefore those costs for quality reasons, you cannot expect these costs to be paid out of the existing budgets of individual institutions without further ado."[202]
Genzyme is watching developments in the Netherlands with concern. Hans Schikan, the manager for Europe, also fears that the cabinet plans to change the financing of drugs for very rare diseases. "The government had a fund for these so-called orphan drugs. But," he warns in an interview, "the cabinet now wants hospitals to pay for them themselves." Because they are often extremely expensive—the Fabry drug, for example, costs around €150,000 per patient per year—Schikan believes that access to treatment is at risk. As it has not yet been approved, Genzyme is paying for the therapy of trial participants and patients for whom the drug may be the last resort. "But we are a commercial company, and we assume that the government will soon have a role to play in providing funding."[203]
The discussion about the financing of orphan drugs in the Netherlands is once again fueling unrest among patients. They feel that they are 'too expensive'. The situation is not improved when, later in June 2006, the Council for Public Health and Care recommends[204] setting the upper limit for reimbursements at 80,000 euros. We will return to this later. After the problem of 5% financing by hospitals, the discussion about reimbursements is added to the mix.
The optimism that prevailed during the conference in Heidelberg is now fading as the outlook is once again less rosy. And that while the barrier

of EMA approval still has to be overcome.
The fact that the discussion about financing by hospitals has real consequences becomes apparent in the same year. UMC Utrecht has made agreements with Erasmus MC to conduct a study into the effect of enzyme therapy in young people and adults, the LOTS study (we will come back to this later). But the board of directors put a stop to it. They feared that the large number of Pompe patients who would be treated would entail too many financial risks. At the last minute, they decided not to participate in the study.[205] This ended UMC Utrecht's role in Pompe research.
The board of directors of Erasmus MC also questioned whether it was financially responsible to continue Pompe research and treat more patients. Nevertheless, they decided that the role played by the Rotterdam Pompe researchers over the years left them with no choice but to continue. It was a gamble; no one could predict how the discussion about funding would end.[206]

41

MARYZE

AN S.O.S.

Sometimes it seemed as if I knew everyone, and everyone knew me. Or rather, almost everyone, because you never know who you don't know. In 1998, when the International Pompe Association was founded, I was appointed liaison officer for all affiliated organizations. This brought me into contact with patients all over the world. From Taiwan, the Philippines, the Czech Republic, Peru, Russia, you name it. Our digital forum GSDNet played a crucial role in this. My numerous presentations on Pompe disease at medical and scientific conferences and workshops also brought me more and more into the spotlight. Not only among fellow sufferers and parents of Pompe children, but also among doctors.

In 2003, I came into contact with a man from Peru whose son had died of an enlarged heart and severe breathing problems. His newborn daughter showed similar symptoms, but the doctors dismissed his concerned questions. The father was convinced that something was wrong. He persisted, and unfortunately, his daughter was also found to have an enlarged heart. She was diagnosed with Pompe disease. Her father got in touch with me through mutual acquaintances. I called someone at Genzyme, who referred the father to Duke University in North Carolina, where Priya Kishnani had just started a large study, code-named 1602 (see chapter 38). It was the right moment,

because the doctors at Duke were having difficulty finding babies younger than six months who were not yet seriously affected. The girl was able to participate and the whole family promptly moved to North Carolina. They still live in the US. I met them once when I was visiting my brother Leonard, who was working at the National Institutes of Health at the time.

It took a while for enzyme production at Genzyme to get underway, but once it did, almost every month a new patient could participate in the expanded access program, to which I also owe my life.

I knew the criteria for the program. They were public, anyone could see them, but not everyone did. I knew how many patients were doing and could assess whether they might be eligible. Then I would call or send an email: “Hey, did you know you might be able to participate in the compassionate use program? Ask your doctor to sign you up.” Most patients and doctors didn't know this program existed. By informing them, I was able to help them further. This allowed more and more patients to take advantage of it. It was my way of fulfilling the promise I made to myself and getting more Pompe patients into the lifeboat.

Of course, I didn't decide who could or couldn't participate. Genzyme had set up an indication committee with independent doctors for that purpose. They assessed whether someone met the criteria and in what order people would be considered.

The situation changed in 2006 when a ‘broad label’, as it is called, was approved in Europe. This meant that enzyme therapy was approved for all Pompe patients. From that moment on, Myozyme was reimbursed in more and more countries, that is, in countries where the government could afford it. People in Africa and Asia in particular were left out. There was no money there, not even for cheap medicines. Something like health insurance is a pipe dream there. Those who have the money buy their own care and medicines. The rest have to fend for themselves. Genzyme has a Humanitarian Program for these people. People with Pompe disease in these countries can obtain Genzyme's drug free of charge. But they need to know that this option exists.

This was also true for my friend Juan, whom I mentioned earlier. He was born in 1977, is slightly younger than me, is well educated, and

lives in Manila. He runs a web design company. Like me, he receives a lot of support from his parents and family. I advised him to apply to Genzyme.

He was able to participate, but then came the real challenge. Sending the enzyme is one thing, but getting it to the patient is a huge task. The Philippines has a very sluggish bureaucracy, and at every step you take, someone is holding out their hand. They call it 'red tape'. Of course, Genzyme had no intention of paying import duties and other taxes when they were providing someone with free medication, so that took a lot of phone calls. It took a year for the medication to be delivered to Juan. In 2005, he had his first infusion.

Juan and I are opposites, but we have become friends over time. We are cut from the same cloth: we don't give up, and our motto is 'no whining'. We understand each other, both have the childhood form of Pompe disease, and are from the same generation. Juan has a tough life. His father died at Christmas 2022. It was an emotional blow, and a financial one. Juan now has to keep working at his IT company to ensure that his income remains stable. Not only food, but also healthcare costs money. He has to pay his caregivers himself.

At one point, I asked him how his ventilator was working. Fine, he said. To me, that was a sign that he needed a new device. Through my contacts, I was able to arrange that and send it to him. He built a website for me. You do things like that for each other because you know how difficult it is. How he manages, I admire him for the way he lives his life.

Alyasghar, another story. He lives in Nairobi. He's in his thirties. He had contacted Genzyme, but they couldn't—or rather, weren't allowed to—help him because of laws and regulations. So they asked if I would talk to him. They gave him my number, and sure enough, he called.

For some reason, his name didn't sound very Kenyan to me, and that turned out to be true. His ancestors had once crossed the Arabian Sea from India to start a trading company in Kenya, like so many of their compatriots. He belongs to Dawoodi Bohra, a sect within Islam.

I asked him if he was getting the medicine. He wasn't. Why not, I asked. "My doctor said I have to go to the United States for that. But I don't want to go to America."

I knew I was giving him some difficult advice and that he might have been hoping for something else.

That's not true, I replied. "That may have been the case in the past, when the studies were done. Now you can get it right here in Nairobi, at home." And maybe you can participate in the Humanitarian Program, I added. He was delighted. If that was possible, then he would love to. I took care of the registration. I called the ladies from the Humanitarian Program—one works in southern Germany, the other in Boston—and it was arranged in no time. A month and a half later, I received word: the enzyme for Alyasghar was ready. You tell him, they said to me at Genzyme. Well, he was absolutely elated. At the time, he was in India for an important religious celebration, which was also attended by the spiritual leader, a central figure in his religion. "Can I tell him too?" he asked. "Of course," I said. He did, and the leader then blessed him. And me too, Alyasghar told me enthusiastically later.

While a supply of enzyme was being shipped to Nairobi, I received a call from Genzyme. The shipment would be delivered to his home address. Not to the hospital, to prevent it from being stored improperly there. He must have a good refrigerator, was the message. How big, I asked. They had no idea. After some calculations, it turned out to be not too bad: a large tabletop model would suffice. So Alyasghar had to go out and buy a refrigerator quickly. That was in February 2018.

Shortly after that, we met. He had to be in Düsseldorf for a large trade fair on car parts: spoilers, hubcaps, exhausts, that sort of thing. He really wanted to visit. I picked him up in Düsseldorf and we talked for a long time that evening. It was very strange: while I was deep in conversation with him in Varsseveld, his wife was on her way to Mumbai, India, with her mother to give birth to their second daughter.

He asked me if he could have more children. "Of course you can," I said, "but is it wise? Do you know what your physical condition will be like in ten years? Your daughters will go to school, maybe study, which costs a lot of money. Your care is expensive, you have to be able to pay for that too. Will you still be able to work and earn as much as you do now?"

Of course, I knew I was giving him difficult advice and that he might

have hoped for a different answer. But I felt I had to tell him, as a friend, and knowing that Pompe is a serious disease.

And then there's baby Masha from Ukraine. In 2014, I was invited by a Ukrainian organization of patients with rare diseases. Would I be willing to give a presentation there about the reimbursement of orphan drugs? They wanted to pay for my travel and accommodation expenses, so I went, together with my mother and sister as caregivers. It was the middle of winter, so I was afraid that my wheelchair would get stuck in the snowdrifts, but fortunately, there wasn't a single flake of snow. The trip went smoothly, the hotel in Kyiv was wheelchair accessible, and the room was wonderfully spacious. Everything was well organized. The next morning, we were driven to the meeting. I was shocked when I entered the room. A large stage with tables and microphones and TV cameras everywhere. It was a bit bigger than I had prepared for, but it went well. The presentation and the forum discussion. There was simultaneous English-Ukrainian translation and afterwards I got a big kiss from a lady from a ministry who had also been in the forum. She said, “You are my hero.”

That evening, I appeared with others on Ukrainian TV news; I still have the recordings. The next day, the chairwoman of the patient organization had a meeting with the ministry. She returned with the message that the financing had been secured.

Since that trip, I have been in a WhatsApp group with Ukrainians. Some of the conversations were in English, some in Ukrainian. Google Translate helped me to follow the conversations. There were seven known patients in Ukraine, all of them children. All but one of the parents were in the group.

Anna is Masha's mother. In February 2022, the girl will be nine months old. She is being treated at the hospital in Kyiv, but her condition is worrying. The dose of enzyme she is receiving is insufficient.

On February 24, at ten to five in the morning, the Russians invade Ukraine. I am woken up by a text message informing me that bombs are falling and that I will not get much rest for the time being. When Anna and her husband Pavlo put their daughter in the car that morning to drive to Kyiv for her infusion, the air raid siren goes off. The

infusion takes priority, so they go. Anna texts me that they are one of the few people driving into Kyiv; most people are driving out of the city. They reach the hospital with Masha, where they spend the night in the bomb shelter because of the attacks.

We text again. I tell Anna that they have to leave, leave Ukraine. But I don't know anyone outside Ukraine, she argues. Me: “You can't stay there.” “I have nowhere to go,” she replies. “I don't know anyone.” I answer, “Yes, you do. You know me.” She texts back, “I mean family.” I reply, “I am your family. You can't stay there. Masha won't survive.”

Pavlo is also reluctant to leave. He has all kinds of objections; as a man, he doesn't want to abandon his country. But as the hours pass and the war escalates, they decide to go anyway. Gasoline is a problem. There is a ration of 20 liters, but they manage to fill up the tank. Via the already poorly passable roads along the Moldovan, Romanian, and Hungarian borders, they reach Poland. After five days, they are in Berlin. The next day, they arrive here. I have already told my father and mother that they will have guests staying with them. They are fine with it; they are used to it. After all, they have previously had fellow patients from Namibia, Kenya, Malaysia, and Taiwan staying with them.

I call the doctors at Erasmus MC. “I have a patient for you,” I say. “From Ukraine.” The family is welcome. Through my doctor, an apartment is arranged in Rotterdam where they can stay for a while. It happens to be opposite the house of Mayor Ahmed Aboutaleb, and there are uniformed security guards walking around their street. They don't mind; they have escaped. Masha is finally getting the treatment she needs. “A week later and she would have been dead,” the pediatrician tells me. Masha is doing well now. As ironic as it may be, the Russian invasion saved her life.

Of the other six Ukrainian children with Pompe disease, two ended up in Poland, two in Italy, one in Frankfurt—I visited her there—and one family stayed at home in Cherkasy, in a relatively quiet part of Ukraine. They have an eight-year-old girl. I was able to arrange a set of virtually new respiratory equipment for her, complete with a cough machine and a resuscitation bag. It had been sitting unused in a cupboard at the home of a child with a different muscle disease. Genzyme

sponsored the transport. Over the years, I have built up an excellent relationship with the man in the mailroom.

42
FALLING FROM THE SKY
2005

In 2005, at the factory in Geel, which Genzyme had taken over from the nearly bankrupt Pharming, developments were taking place—unseen by the world—that would later prove to be of great benefit to Pompe patients in Europe.

Luc Kupers, then Director of Science and Communications, looks back on this with some surprise. He has been working at Genzyme's Flemish branch since 1999, when everything still revolved around rabbit milk. "Officially, we became part of Genzyme in November 2001. In the beginning, there were already plans to set up a factory to produce proteins from cells on a large scale, such as the one in Allston, Massachusetts, where the enzymes for Gaucher, Fabry, and MPS I were produced."[207]

In addition, he continues, there was the idea of producing monoclonal antibodies. These are artificially produced proteins for the treatment of cancer, for example. That was where the future lay.

Kupers says that it was then decided to halt production, which was planned in the US, and transfer it to Geel. "I remember from a meeting in Brussels that even people who had been working at Genzyme for some time were terribly surprised by this. The message was: we are installing bioreactors in Geel for the production of monoclonal antibodies with a capacity of twice 10,000 liters."

So two large bioreactors were to be installed in the factory where

Pharming originally had rabbit cages. First, a design had to be made, and it would take time before construction could begin. Ultimately, according to Kupers, the reactors were only used for one product, which was developed in collaboration with the biotech company Cambridge Antibody Technology. That drug failed in phase II trials. So what do we do with Geel, Genzyme wondered. Kupers: “In hindsight, we heard that they were considering selling it. But they kept the factory open with the intention of making deals with other companies for the joint development of those monoclonal antibodies.”

Then the plans suddenly changed, Kupers recalls. "In 2005, there was a meeting in Geel with Henri Termeer and his management team. Once or twice a year, Henri flew to almost all of Genzyme's locations, and that's how he ended up with us. We always had an advantage. I can't prove it, but I think the fact that he came from Tilburg, not far from Geel, and that his mother lived there, made the difference. When he visited us, his mother was always there. During that particular meeting, Henri suddenly suggested, ‘Why don't we produce alglucosidase alfa here?’ Everyone was taken completely by surprise. It seemed that his idea had not been discussed with his management.[208] But when the big boss says we're going to do something, that's what happens. And that's how it went."

At that time, alglucosidase alfa was produced in the US in 160-liter vats. These had been approved by the Food and Drug Administration. Scaling up was necessary, and large 2,000-liter reactors were added. However, the enzyme produced in these reactors turned out to be too different from that produced in the small vats and was therefore not approved. Curiously, the quality of the enzyme from a 4,000-liter vat was more similar to that from a 160-liter vat. The 2000-liter vats are set aside and production is focused on 4000-liter vats. In early 2009, ‘Geel’ receives FDA approval for production in these reactors, four years after construction began.

On September 20, 2005, long before the first commercial alfaGlu flows from the boilers in Geel, the official opening of the factory takes place. As previously agreed, this is performed by Belgian Princess Astrid. During the tour, she asks Maryze, who has also been invited, how the girl she had worked so hard for is doing. She is visibly moved when she learns

that the child has died.[209] The girl is one of many children for whom the medicine has come too late.

Other prominent figures are also present, such as Inge Vervotte, the Flemish Minister for Culture and Family. Of course, the boss, Henri Termeer, is there, accompanied by his mother, who has been picked up from Tilburg. Nobel Prize winner Christian De Duve also makes an appearance for this special occasion. He gives a lecture on his discovery of lysosomes, the discovery that—admittedly with a few intermediate steps—led to the development of alglucosidase alfa. De Duve, already well into his eighties, causes quite a stir by arriving in this high-tech environment with a stack of framed 35mm slides in his bag, but the organization manages to find an antique slide projector in the attic. Maryze also gets the opportunity to tell her story that day. An impressive performance, according to Kupers. “Many in the audience had to wipe away a tear. I have always said that visits from people like Maryze are very important to impress upon our employees how much energy we have to put into making a good product. Sometimes they don't immediately have a picture of the people they work for. Hearing and seeing someone like Maryze makes it very tangible for them that they are doing something important.”[210]

During the drinks reception, Maryze's mother has a pleasant chat with Termeers' mother. They conclude that they have brought special children into the world.

41

MARYZE

A DRINK WITH THE MINISTER

2004-2005

We were all very concerned about how the reimbursement of Myozyme would be arranged in the Netherlands. The European Medicines Agency still had to approve the drug for the European market, but even if that went well, what was the point if there was no proper reimbursement scheme? Minister Hans Hoogervorst of Health, Welfare and Sport had plans to have the hospitals where the infusion was administered pay the bill. Initially, this would be the full amount, but later it was reduced to 5 percent. But even so, 5 percent of a large amount is still a lot. Combined with the idea of concentrating patients with rare conditions in a single treatment center, it was simply a bad plan. There is no solidarity whatsoever when a treatment center, as the only center of expertise, has to pay all the costs.

But how do you get rid of a bad plan? Fortunately, the Ministry of Health, Welfare and Sport offered me an excellent opportunity. From July 1, 2004, the Netherlands held the presidency of the European Union. This resulted in a series of congresses and conferences on European cooperation. I received an invitation to one of these because of my board membership of the International Pompe Association. The conference's theme was: priority medicines, medicines for the treatment of serious diseases for which there are no alternatives. An important topic, but I found the announcement that Minister Hoogervorst would be hosting the conference just as interesting. So, on November 14, my mother and I went to the conference with the aim of talking to the minister about reimbursement. We didn't know how to go about it, but we were convinced that we would succeed.

The conference was held in a church. During the coffee break, we were standing in an aisle with some acquaintances. In the next aisle, separated from us by an impenetrable barrier of chairs, stood the minister, surrounded by a group of people. My mother walked up to him, tapped him on the shoulder, and said, “My daughter would like to speak to you, but she can't get to you. She's in a wheelchair.” The minister turned around, saw my mother, excused himself from his conversation partners, and walked with her.

Hans Hoogervorst and I shook hands. “I am concerned,” I said, “about how you want to arrange the financing of orphan drugs. As it stands now, serious bottlenecks will arise and patients with rare conditions will not be able to obtain expensive medicines in the future.”

He was genuinely surprised and replied that this was not the intention and that these medicines should indeed reach the patients. I explained to him that the proposed scheme would be counterproductive and that patients with rare diseases would be left behind. He listened with interest. Peter Streng, director of research at the Dutch Muscular Diseases Association, was standing next to us and asked him to come by for further discussion. The minister was very willing to do so.

After the conference, all guests were transported by bus to the ministry for dinner. Wheelchair-inaccessible buses, of course. For me and Peter Streng, also a wheelchair user, there was no other option than to drive ourselves to the ministry through the chilly November rain. Accompanied by a kind security guard, that is.

It turned out to be very close by and we arrived well ahead of the other guests. Hoogervorst was waiting for us at the ministry. He saw us coming and called out, raising a glass: “Hi Maryze, would you like a glass too?” And while I, dripping with rain, sipped my champagne, Peter took the opportunity to make an appointment with officials for a working visit by the minister to the VSN.

That visit took place a few months later, on March 14, 2005, and I was there. We introduced Hoogervorst to Pompe disease and showed him what the drug does for patients. He listened attentively. “Do you really mean that?” he asked when he was told that it was a matter of life and death for babies. And whether we meant it.

In the policy rule, Pompe disease was later cited as an example of a rare disease with expensive medication. Did our meeting and the ministerial visit to the VSN help? The fact is that the financing arrangement was scrapped and that these types of expensive drugs are now simply paid for by basic insurance.

Hans Schikan, who saw it all happen as a brand-new manager at Genzyme—he was also one of the guests at the conference—described the incident in a book.[211] In it, he recounts how, many years later, he happened to sit next to Hans Hoogervorst, who was then chairman of the Netherlands Authority for the Financial Markets, on a plane. When he introduced himself as a former Genzyme employee, Hoogervorst's eyes lit up. “Oh yes, Maryze,” he said, “that visit. How is she? Is she still there?”

Thank you, Mr. Hoogervorst. Yes, I'm still here and living my life. Perhaps we contributed to that together.

44
THE LION'S DEN
2005 – 2006

While Genzyme's new factory in Geel is being opened with great fanfare, elsewhere the debate rages on about the market approval of Myozyme. Is there convincing evidence of its effectiveness? The debate takes place in the scientific committee of the EMA, the CHMP, or Committee for Medicinal Products for Human Use. This committee assesses and advises on the quality, safety, and efficacy of medicines for human use. It also looks at the group of patients for whom the medicine should be available. If this is the entire group, it is referred to as a ‘broad label’. If it is a subgroup, the label is called ‘narrow’.

If a medicine is to gain access to the European market, the manufacturer must submit reliable studies with solid, statistical evidence. In the submitted dossiers, patients are abstracted to numbers in the appendices. Emotions are kept out of the equation as much as possible. This changed in 2005.

For pharmaceutical companies, it is very important that drugs are admitted to the major markets, such as the US and the European Union. This is certainly true when it comes to orphan drugs. To ensure that the approval process runs smoothly, they call in specialists in the field of regulatory affairs, which is the jargon for everything related to legislation and regulations.

At Genzyme, Carlo Incerti, an Italian doctor, is responsible for the

approval of Myozyme in Europe. “We were involved with Gaucher and Fabry,” he says, “but I remember the Pompe project best because it was one of the most complicated in terms of clinical development and approval.”
The big challenge for Genzyme lies with the *late onset* patients. Incerti: “If you look at it economically, perhaps somewhat cynically, it wasn't the babies, but the late onset patients who represented the market for us.”
In terms of convincing evidence, the situation is exactly the opposite. The results in babies are indisputably positive, but it would take years of research to provide the same evidence for older patients. Genzyme must convince the members of the CHMP and the Food and Drug Administration that the evidence in babies can also be considered evidence for older patients. That is by no means an easy task. Several committee members still assume that, from a medical point of view, there are two completely different variants of Pompe disease: early onset and late onset. Ria Broekgaarden of the VSN wrote in an internal email in April: “We don't know whether Myozyme will be registered for the adult form (...I fear...) and what the alternatives are.”
Frits Lekkerkerker is closely involved in the assessment process. In 1991, he becomes chairman of the CBG, the Medicines Evaluation Board, and is involved from the outset in the European Union's health policy and the establishment of the EMA. From 2000 to 2007, he was a member of the CHMP as the representative for the Netherlands. “When a pharmaceutical company submits an application for a drug,” he explains, “it is discussed in the meeting and a rapporteur and co-rapporteur are appointed. In the case of Genzyme, these were Belgium and France.”
The rapporteur and co-rapporteur play a crucial role in the assessment process. As experts, they guide the assessment. They are responsible for drawing up the evaluation report, which assesses the safety, quality, and efficacy of the drug based on the data provided.
Henk Schuring, a pharmacist by training, is part of Genzyme's regulatory team. The CHMP's commitment is clear: not only approval for babies, but for all patients, i.e., a broad label. “The discussion about the indication was the most interesting and important. The members of the CHMP were reasonably open to it. We had a heated discussion with

Belgium and France.”
Schuring is convinced of Belgium's positive role. "We were based in Geel with our factory, which created a bond. The chairman of the CHMP, Daniël Brasseur, was the only pediatrician on the committee. He linked us to Bruno Flamion from Belgium, the man who had to analyze and assess the scientific basis of our story for the committee. Unfortunately, at that time, Belgium was not held in high regard within the committee, unlike England, France, Sweden, Germany, and also the Netherlands. That is why we got France as co-rapporteur, and France was absolutely not in favor of a broad label."
Lekkerkerker explains the procedure. "The rapporteur and co-rapporteur each draw up an assessment report independently of each other. Then it is a matter of waiting to see whether those reports differ too much. They are then discussed in the CHMP. Countries have often already commented on them by then. After that initial discussion, a list of questions is drawn up at the rapporteur's suggestion and approved by the meeting. The industry is then given the opportunity to respond in writing. This is followed by a joint second-round report, again with any questions and a proposal for a final conclusion. At that point, a company can request a hearing, an oral explanation, which is its right."
Schuring explains: “So we knew exactly what the discussion would be about and we prepared ourselves as well as possible.” The run-up to the hearing is somewhat depressing. “There you are: December 2005, at Canary Wharf, in a chilly London, where the EMA was based at the time.” The Genzyme delegation consists of several experts, including Ans van der Ploeg. Schuring: "Everyone was extremely nervous. You start off immediately at a disadvantage, 0-1 on the scoreboard. The committee members don't agree with you."
In fact, Genzyme's team was actually starting a lost battle, Lekkerkerker recalls. "In the eyes of the CHMP, Myozyme was a clear benefit for babies, but that clarity certainly did not apply to adults. The mood in the committee was: we'll make it clear to that company that the data for adults and adolescents is completely insufficient and that the CHMP cannot accept it.”
“The environment also worked against us," says Schuring. “You enter a

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definitely
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in the development.

rather intimidating room. With two rows of chairs: a large ellipse with a small one inside, like a kind of English parliament. Call it a lion's den. It felt oppressive. You know you're the underdog. Here you have to engage in a tough debate to tip the scales in your favor."

First, Genzyme gives an introduction, then the experts have their say. Schuring: "We wanted it to be about the facts: scientific facts, but also facts from a human life. It was obvious that we would ask a patient to do this, and that turned out to be Maryze. It couldn't be aggressive, as it is in America. Our goal was to present an objective picture, including someone who was already receiving IV treatment. Someone who could make it clear that she would be at the end of her life if she were not treated. We were, of course, aware that this could also bring emotion into the discussion, but it went well."

Maryze was in the meeting room before she even realized it. "Khazal Paradis, who was working on the EMA process from Genzyme, called me and asked, 'Are you coming to London?' We had just returned from North Carolina, where my brother had had a baby boy. I said, 'Sure, we haven't unpacked our suitcases yet anyway.' I had no idea what was going to happen or what the procedure was. I remember how nervous I was. I just told my own story and how much more energy I had since I started the infusion."

Never before had a patient told their own story at a CHMP meeting. It made an impression on those present, including Lekkerkerker. "Maryze explained how alglucosidase alfa had improved her health. She answered questions very openly, and that made an impact. Experts who are brought in by a company are always viewed critically. CHMP members tend to think, 'His master's voice.' This was suddenly different: a patient who was given a role in the CHMP."

Schuring: "By explaining what the medicine meant to her, Maryze emphasized the importance of rapid approval for the broad label. Several CHMP members applauded our decision, while others were not happy about it. I am convinced that we would not have obtained a broad label if we had not done so."

When the hearing was over, the majority of the members had changed their minds. No had become yes. Myozyme would be available in Europe not only for babies, but also for older, late-onset patients. The European public assessment report, the description and explanation that accompanies a drug from the EMA, states that Genzyme is obliged to conduct further research into the effects on adult patients.

Schuring looks back with pride on the episode and on the decision to let a patient—in this case, a female patient—tell her story. "I think it was absolutely the right way to involve the patient in the development. It was unique, the first step. Now you see it much more often, and I wholeheartedly welcome that. Because imagine: you develop a therapy and a patient's breathing capacity improves by a few percent. That's great. But if you can't explain what that means for someone's daily life, the real value of the therapy remains invisible."

On March 29, 2006, Myozyme is approved for the European market with a broad label. At the same time, a patient meeting is held in the Netherlands. When the news is announced, there is hardly any reaction from the audience. No one believes that the final hurdle has been cleared. Only when the champagne corks pop does it sink in for the patients, and there is laughter and tears.

Two weeks after approval, a young boy in Germany receives his first infusion. He is eight years old, the same age as Maryze when she was diagnosed. He was not eligible for compassionate use, she says, but now the time had come. "When he received his infusion, I thought: this is why I do it. I can still see him in front of me, little Nico. He is living his life, just like me."

Six years later, it unfortunately turns out that the last hurdle was not the last after all. An even bigger barrier awaits in the Netherlands.

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HOME CARE LAND
2006 – 2008

From the moment alglucosidase alfa becomes available in the Netherlands, pressure on the treatment capacity of Erasmus MC increases. The number of patients receiving enzyme therapy is growing rapidly. First, there are the children and adults who previously participated in the studies. At the end of 2005, dozens of adults participating in a new study, LOTS (more on this in chapter 48), are added to this group. And there is a queue of Pompe patients who are eager to qualify for compassionate use. Of course, this cannot all be done at once. If only because, at the beginning of 2006, far too little enzyme is still being produced.
Another problem is the available manpower at Erasmus MC. It simply takes time to 'put a patient on therapy', as doctors call it. Measurements and tests have to be carried out, and there has to be proper monitoring during the initial treatments, including for allergic reactions.
So there is a rush at the front door: who gets to go first? In general terms, the doctors' answer is quite simple: those who need the therapy most. But who will decide that? And in such a way that no uncomfortable discussions arise? Is this a role for the treating physicians? Won't that lead to unpleasant situations in the consultation room?
It is asking for trouble. That is why an independent indication committee is being set up. It will determine the 'start and stop criteria': establishing who is eligible for therapy under what conditions and who should stop,

for example if someone develops malignant, untreatable cancer. The first chair of the committee will be John Wokke, a neurologist at UMC Utrecht.
Partly because this hospital withdrew as a treatment center in 2005 for financial reasons, the day treatment center in Rotterdam has become increasingly busy. All Pompe patients undergoing therapy spend one day every two weeks at Erasmus MC. The group is growing from week to week. A spontaneous 'Pompe café' has even been created, where patients meet and exchange experiences. This is one of the reasons why the older Pompe patients have formed such a close-knit group.
These biweekly meetings are enjoyable, but also cause for concern. How can the estimated 140 Dutch Pompe patients be treated here in the near future? You don't need to be a mathematician to calculate that this influx will exceed treatment capacity in the foreseeable future.
And then there is the burden on the patients: once every two weeks, they have to travel to Rotterdam, whether they are from Zeeland, Limburg, or Groningen. Some spend five hours traveling on a treatment day. This is a heavy burden, especially for people who already have to conserve their energy. There are also social disadvantages. Working people have to take a day off, children miss twenty school days a year. Patients take it for granted, but still, if there were another way...
The question of how to avoid a heart attack during infusion is therefore becoming increasingly urgent. Does it really have to be in a hospital? Can't it just be done at home? "No, that wasn't really possible," says Jaap de Boer, who was Medical Director at Genzyme Netherlands at the time. "T*he Summary of Product Characteristics (SmPC)* of the CBG clearly states that administration must be supervised by a treating physician. Period. So Dr. Ans van der Ploeg always remained ultimately responsible. But we had the idea that it might be possible after all via the so-called extended arm construction."
It is a somewhat bizarre name for an approach in which the treating physician retains ultimate responsibility, but the medical procedure is performed elsewhere by someone with the necessary medical knowledge and skills. De Boer: "We had to write a risk management plan and protocols for this. Among other things, it stated that when administering

treatment at home, there must always be a doctor nearby who knows that the patient is being treated at home. It was all very complicated, but it worked."

A nurse, Gisela Linthorst, was brought in to work out the details of the plans. She had worked at the Antoni van Leeuwenhoek Hospital for a long time and later moved to a small pharmaceutical company, Eurocept, which also had a home care division. "At Genzyme, I was tasked with finding out whether alglucosidase alfa could also be administered at home. I didn't have any examples; what we wanted was new. It was an advantage that the Netherlands has a real home care culture and infrastructure. We do just about everything at home. If home infusion had any chance of success, it was here."

The process had to be planned down to the last detail, says Linthorts. "There was a certain amount of reluctance within the parent company. It's American, and people are always wary of claims if something goes wrong. I also understand very well that an American who is unfamiliar with our home care culture sees liability issues looming everywhere. At the same time, people were curious about how the project would unfold."

Linthorst started in November 2006, and in April 2008, home infusion became available. It took a year to sort out all the legal issues: whether it was even possible, who was responsible and liable, what about safety, payment, insurance, and other such matters. Erasmus MC drew up the protocols. "Genzyme also didn't know whether it was allowed to play a role in this as a company. Are you allowed to facilitate home care if you also have a product on the market? It turned out you were."

Together with Erasmus MC, Linthorst and Genzyme select the home care organization that will provide the specialized nurses. They receive training on the clinical picture and the product, first at Genzyme, then at Erasmus MC. "They had to know the safety regulations inside out. And, of course, they had to know how to administer the drug and what to look out for. We practiced 'dry' first, and the first real infusion was always supervised."

Anaphylactic shock is the biggest risk, or an infusion reaction. "It remains a biological product. If you let it run in too quickly, someone

can have a reaction: skin rash, palpitations, or shortness of breath. The needle can also become clogged by small strands or flakes in the infusion. The nurse must therefore keep a close eye on whether everything is going well and whether people are experiencing any complaints. We had an agreement that if there were any complaints, the infusion would be stopped and Erasmus MC would be called. Someone would always be available there, during the day and in the evening. To my knowledge, there has never been a major problem. An ambulance has never had to be called." Ans van der Ploeg of Erasmus MC adds: "We have a separate nurse who is responsible for home infusions. We are still training new nurses."

The next step is to find a good pharmacy, centrally located in the country, that can prepare the infusion. This is a time-consuming and specialized task. On average, each patient receives thirty ampoules in the infusion, depending on their body weight. A special device with a swivel arm is used for mixing. The enzyme dissolves slowly and is then injected into the infusion bag. This must be done very carefully to prevent the proteins from flocculating. From the central pharmacy, the infusion is transported by refrigerated transport to a pharmacy in the patient's area. Linthorst: "The entire process took 24 hours. We started with a pilot involving five people and four nurses to see if it was feasible and safe. Based on that, we were able to improve the organization and iron out any kinks in the process."

Speaking of irregularities, she says: "That's quite a story. We worked with a separate supplier for the administration materials. Maryze was the first to receive the home infusion on December 21, 2007. The nurse had picked up the infusion bag from the pharmacy that morning. Not long after, a huge box arrived at Maryze's house, big enough for a washing machine. Everything was in it: the infusion supplies, gauze pads, tubes, taps, needles. Except for the infusion tubes. I immediately called the supplier. Someone jumped in their car and brought the tubes to a dark parking lot near Woerden, where I picked them up. The entourage, the darkness, the chilly, empty asphalt plain: it was like something out of a mafia movie. A little later, I was sitting next to Maryze during her first home treatment. And it went well. It almost felt festive with her family

there. While the IV slowly dripped in Varsseveld, my team in Naarden celebrated the first with a big piece of cake."
In March and April 2008, five patients were treated at home several times. It was time for an evaluation. Linthorst: "Together with Erasmus MC, we concluded that the approach was sound, feasible, safe, and meaningful. That's how MyozymeThuis came into being, thanks to the fruitful collaboration between the hospital, the patient organization, and the pharmaceutical company."
The patient organization VSN played an important role in providing information about the home infusion. During a meeting, Linthorst gave a presentation about the new treatment option. There was a lot of enthusiasm, and not long after, people were able to exchange experiences in discussion groups. "We then started to scale up," she says. "It's an advantage that all care is concentrated in one place: Erasmus MC. Dr. Van der Ploeg was able to indicate exactly which patients would benefit from home infusion and which would not. People could also always opt for infusion at Erasmus MC. Some people may feel comfortable with that, others may not. I think most patients quickly joined the home care project."
The project was ultimately so successful that the principle of home administration has been adopted in the treatment of similar conditions, such as Gaucher and Fabry. Not only in the Netherlands, but also abroad.

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MARYZE

CONCERT FOR CIVILIZATION

I first spoke to Johan Bakker in the corridors of Erasmus MC. It was a chance encounter. I was there for my biweekly infusion, which had become routine for me. Other Pompe patients were walking in the corridor. We chatted about our medication and how special it was. A chat here, a chat there: finding some distraction to get through the day.
For Johan, there was more at stake. It was his first time. Because he was being treated as part of a study—the LOTS, which I'll talk more about later in this book—he didn't know if he was getting the medicine or a placebo. He was nervous, he said, and had no idea what to expect. I tried to put him at ease.
Johan was 48, but had known since he was 26 that he had Pompe disease. At the time, he had vague symptoms and there was something strange about his blood count, so he was referred to Radboudumc. After several tests, he was diagnosed. "That was it; the doctor couldn't give me a prognosis," Johan told me. "I thought: if even the specialist doesn't know how it will turn out for me, I'll just have to ignore the disease." That period of denial was now clearly over. I wished him luck.
Since then, we have spoken several times, but we never talked about his first infusions. We always talked about business, advocacy, the association, never about ourselves. Because I want to hear his story, I contact him. We talk via Zoom.

How did you fare after the diagnosis, I ask him. “Things went well for a long time, I remained stable,” he says. "Then the decline began, first insidiously, later alarmingly quickly. The problems came to light when I lost consciousness during a car ride and grazed the guardrail over a distance of hundreds of meters. Fortunately, it was a straight stretch of road, and no other cars were involved. An ambulance took me to Radboudumc, where they determined that the carbon dioxide level in my blood was much too high. That explained why I had already had several episodes of loss of consciousness that day, right up until I arrived at the hospital. At Radboud, they didn't really know what to do with me. No one made the connection with my previous diagnosis. They thought it was something in my brain. A Mr. Braakhekke, a name I will never forget, stuck a thermometer in my butt and put me on a bike, an exercise bike. I wasn't allowed to eat anything before that test, and I really felt it. Within two minutes, I was hanging over the handlebars, vomiting, limp as a rag. It turned out that my body temperature had dropped dramatically in that short time because the thermometer had slipped out of my butt. Chocolate bars and jugs of coffee were rushed in to help me regain my strength. No explanation was found for my blackouts."

Johan's story reminds me of the time I ran through the center of Doetinchem in tears, dragged along by a nurse. He continues: "That bicycle test was in 2002. Not long after, I was led into an amphitheater at Radboud University, filled with doctors, professors, students, and nurses. Did anyone have an explanation for my symptoms? All kinds of suggestions were made, but they were quickly dismissed. It was a nurse who finally made the correct observation. ‘Look at those respiratory muscles,’ she said, ‘there's something completely wrong with them.’ And so I was referred to the Center for Home Ventilation in Utrecht. That's when the penny dropped. Pompe disease and breathing problems go hand in hand, said the first doctor who examined me there."

In the years that followed, Johan's condition deteriorated rapidly, he says. "In 2003, I was still doing ski ballet, but when I fell, I could hardly get up. During those years, my wife Mia and I went on a cycling trip through Umbria. She cycled ahead of me up the hill. I had to walk the last part, but I made it to the top. Two years later, I couldn't do that anymore. We had to install a stair lift at home, the wheelchair was ready, and I had night ventilation. I also had to slow down more and more at my job at the Rivierenland Water Board. Sixteen-hour workdays were a thing of the past. You could say that the LOTS study in Rotterdam started at exactly the right time for me. After some hassle, I passed the tests and was able to start my infusion in 2006. Within a few weeks, I noticed that something had changed. You might think it was a placebo effect, but the fact is that I could get up from a chair independently again. Months later, I was able to resume my work and was once again able to work hard all day. I still work, albeit fewer hours."

In 2006, Johan took over the chairmanship of the Pompe group from Tanneke, my mother. Myozyme had since been approved for the European market, but in the near future, the discussion about reimbursement and inclusion in the basic health insurance package would take place in the Netherlands. With a price tag of €400,000 to €700,000 per patient per year, it was clear that it would not be a walk in the park. The patients in the Pompe group faced a tough challenge.

Johan hates long meetings, he admits in our Zoom conversation. For him, it has to be short and sweet, with clear agreements. He wants to get started; activism is in his blood. "I worked at Milieudefensie (a well known Dutch pressure group for the environment, ed.) for eight years, where I learned to use every opportunity, every little loophole, to get publicity. At the time, I had made a CD with piano music, improvisations of my own, entitled *Concert for Civilization*. I wondered how I could use it to support our cause. I put 150 copies in envelopes, added a personal letter, and delivered them to the House of Representatives the day before the Christmas recess. I knew it was the perfect moment: everyone was going home, packing their bags, settling down quietly under the Christmas tree. Plenty of time to pick up that CD and read the letter. A third of the members of parliament sent me a personal response, which is an excellent result."

Johan and his theater group also once ‘crashed’ a conference where the then Minister of Health, Welfare and Sport, Edith Schippers, was

speaking. She had to decide on the reimbursement of the drug. "We made our position clear to her in a friendly manner and afterwards I had a pleasant conversation with her. I think I struck the right chord. I come from an authentic VVD family. My mother was a member of the Provincial Council, and I have been familiar with liberal argumentation since I was young. I told her that I was the director of a water board and that I wanted to work. That I could do that very well, provided I got my medication. That was, of course, exactly the story she wanted to hear: personal initiative, personal responsibility. But that is also in me." Despite his firm language, Johan acknowledges in our conversation that the struggle at the time affected him more than he expected. “I was always in fighting mode during those years. Only now, years later, do I notice that the emotions are still lingering. I am still processing what happened during that period.”

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SMALL CREATURES WITH BIG CONSEQUENCES
2006 – 2011

After Myozyme was approved for the European and American markets in 2006, Genzyme was finally able to start selling the enzyme. Until then, it had only invested in it. In 2009, the company calculated that it had invested a billion dollars in development up to that point. That includes the costs of acquiring Novazyme and building the new factory in Geel. So it was high time for the efforts to start paying off.

However, there is a financial catch. Even though Genzyme has developed its own version of the alphaGlu enzyme, it still owes royalties to Synpac, the Taiwanese company that holds patents on enzyme production and treatment. The ‘patent lawyers’, as researcher Johan Van Hove called them, have done their job well. Between 2006 and 2013, Synpac will receive 13.5 percent of net sales in the US, and thereafter—until 2023—as much as 15 percent. In a 2006 press release, the company estimated that total revenues, depending on sales, would be between US$423 million and US$821 million.[212]

The agreement led to major disagreements and lawsuits between the companies. These resulted in a final settlement of US$180 million in 2021.[213]

However, this snag is not the only problem lurking in the shadows. The danger comes from a completely different angle.

In 2006, Genzyme has a portfolio of four enzyme replacement therapies: for Gaucher, Fabry, Pompe, and, since 2002, MPS I. The latter is a very rare and serious condition that is similar to the other three in terms of disease mechanism. Demand for enzyme therapies is growing, and Genzyme is working hard to further expand the market.

Rapid growth is putting a lot of pressure on production facilities. Alglucosidase alfa is a cause for concern because it requires a large amount per patient: 20 or even 40 milligrams per kilogram of body weight. For Gaucher, for example, it is only 1 milligram.

Between 1990 and 1997, Genzyme built a huge factory, the Allston, in the heart of Boston, on the banks of the Charles River. Because of its size and appearance, it was soon nicknamed *The Cathedral*. One bioreactor after another is added to the production lines. The number of patients undergoing treatment is growing so rapidly that it is difficult to keep production up to speed and at the same time ensure sufficient stock in case of an emergency. Because you never know, such complex processes can easily be disrupted.

The 2005 decision to set up the factory in Geel for enzyme production as well is in line with the aim of increasing production capacity. In Belgium, apart from the transgenic Pharming rabbits, there is no experience with the manufacture of enzymes. So it takes some time before the installation is ready for production: plans have to be made, materials purchased, training organized.

As already mentioned, it proves difficult to replicate the enzyme from the 160-liter vats in Allston exactly in Geel. The European regulator EMA ultimately approves the production line, but the US FDA has more difficulty with it. Genzyme is not allowed to market the product from the Belgian 4,000-liter vats in the US under the brand name Myozyme. The differences with the enzyme from the small vats are too great for that. The name in the US becomes Lumizyme. This creates a confusing situation for patients and practitioners.

A lot of time is lost with this wrangling. It also limits the number of people who can be admitted to studies and the compassionate use program.

When the facility in Geel is finally ready to start in 2008, a contagious virus, vesivirus 2117,[214] is detected in the system. It appears to thrive

in the CHO cells, the hamster cells, with which the bioreactor is filled. It is a potentially pathogenic virus and certainly does not belong in a medicine. It turns out to be the same virus that caused major problems in Boehringer Ingelheim's facilities in 2002.

There is no choice but to sterilize the new production unit screw by screw and tube by tube. That helps. In April 2009, the factory finally delivered the first alglucosidase alfa. The doctors in Rotterdam sent their patients an email with the good news that there were no more stock shortages and that they could start treating new patients again.

Less than three months later, something happens that once again strikes fear into the hearts of patients. During an inspection of a production line in America, vesivirus 2117 is also detected there. On June 16, Genzyme sends out a press release announcing that it has shut down the factory in Boston/Allston due to a virus contamination and that the facilities will be thoroughly cleaned. The company reassures everyone that the production process is expected to resume at the end of July. This is bad news for patients, especially those with Fabry and Gaucher disease. They are dependent on the enzymes, because they are only produced in Allston. Patients with Pompe disease, certainly in Europe, do not have much to worry about. After all, there is a brand-new production unit in Geel. So perhaps it will not be such a big deal after all.

Even though the tone of the press release is controlled and reassuring, internally all the alarm bells are ringing. Employees had previously warned their CEO, Henri Termeer, that a production unit needed to be added. As a backup facility, precisely to deal with emergencies such as this. That never happened. It was a question of money, because why spend half a billion dollars on a facility that might never be needed? But when, as is now the case, it is needed, the costs quickly run up to many times that half billion. Plus a lot of suffering and misery. Employees immediately understand that the announced month for decontamination is far too optimistic an estimate. It then emerges that there was a similar contamination in 2008, and it later becomes clear that the vesivirus had been proliferating in the cell cultures for months, causing cell growth and thus enzyme yield to decline sharply.[215]

It also becomes known that, following an inspection less than a year ear-

Our reputation has taken a serious hit; we were no longer the reliable partner we used to be.

lier, the FDA had sent Genzyme a warning letter due to shortcomings in the production process. That doesn't make things any better. After crisis talks between the production managers, the decision is made to dismantle all the equipment and disinfect it piece by piece with hydrogen peroxide. From the floor to the roof. It is a huge job, which is completed in eight weeks thanks to the efforts of all available employees.

There is even more bad news. There is a chance that the virus has ended up in the enzyme stock. As a result, there is no other option but to destroy virtually the entire stock of Gaucher and Fabry enzymes. And that while production in Allston has not yet started.

The crisis goes virtually unnoticed by Pompe patients, but hits people with Fabry[216] and Gaucher all the harder. There is also no certainty as to when stocks will be back to normal. First it is the end of July, but July becomes October and October becomes December. All this time, patients live in uncertainty. It is a nightmare for everyone involved, including Genzyme employees.

Then the word 'rationing' is mentioned. On June 25, the European regulator EMA issues a recommendation for healthcare professionals. It states how the scarce enzyme supplies can best be used. Nothing changes for children, young people, and specific groups of adults, but for other patients, the dosage or treatment frequency can be halved. The EMA adds, with foresight, that these measures will probably remain in force until the end of the year.

Patient confidence in Genzyme declined, says Luc Kupers, then Director of Science and Communications in Geel. "We had a good reputation with patients. We were one of the few companies working in this field and had done a lot of pioneering work. Our reputation took a serious hit; we were no longer the reliable partner we had been in previous years."

The reactions from the patient community were sometimes extremely fierce. "We are the last to be informed and the first to die," railed one Gaucher patient.[217] In his biography of the Genzyme CEO, author John

Hawkins argues that the failure to build a second production unit was a monumental blunder that Henri Termeer would regret for the rest of his life.

Developments are also being watched with suspicion on the stock market. Since the success of the Gaucher enzyme, Genzyme shares have been highly sought after by investors. But stock market analysts quickly realize that the clean-up operation will not be completed within a month. After the announcement of the contamination on June 16, the share price immediately fell by 7 percent. And that was only the beginning. Kupers: "I have to be honest: Genzyme never paid much attention to its shareholders. It never paid dividends either; all profits went back into research."

It is crystal clear that revenues for 2009 will be disappointing due to the temporary loss of the two most profitable products, the enzymes for Fabry and Gaucher. The weakening financial position and increasingly vocal criticism of the acquisition policy—Genzyme had acquired no fewer than thirty very diverse companies up to that point—attracted the interest of activist investors. They began buying up shares, enough to be able to influence company policy.

Meanwhile, the company was still unable to bring production up to the required level. The FDA's decision to place the Allston plant under supervision due to the identified deficiencies and negligence was another heavy blow. This meant that the company lost control of its most important production facility in Boston. The decline continues: major investors take seats on the board, loss-making business units are put up for sale, and a thousand jobs are cut. A shockwave runs through the ranks. Never before have so many people been laid off.

Across the ocean, French pharmaceutical giant Sanofi is on the acquisition trail. CEO Chris Viehbacher sets his sights on the vulnerable Genzyme. He contacts Termeer, who initially wants nothing to do with the French advances. But Genzyme's big man finds himself in an increasingly tight spot and soon has to accept the inevitable. On January 27, 2011, during the World Economic Forum in Davos, Termeer and Viehbacher seal the deal: Genzyme is going French. On February 16, the news is announced during a joint press conference. Due to a virus, the hunter

had become the prey.
Not much changed for patients, as the companies continued to coexist for a long time. The acquisition took Sanofi into a different field. The traditional pharmaceutical company was used to marketing powders and pills by the ton. Its new acquisition used biotechnology to manufacture only a few kilograms of protein per year.
After leaving Genzyme, Henri Termeer held various positions within the pharmaceutical industry. He died on May 12, 2017, from the effects of a heart attack.

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MARYZE

HINKE AND THE LOTS

I have known Hinke Kleiker from Oosterwolde for a long time from the meetings at the VSN. She is always there. She was diagnosed with Pompe disease at a later age. It is a familiar story. She often fell, for no apparent reason, for example when she was standing in line at the supermarket checkout and suddenly collapsed. Or when she was walking to the toilet block in the dark at a French campsite one evening and suddenly found herself lying flat on her back in the grass.
She was 36 at the time. Her GP referred her to a neurologist in Drachten who initially suspected MS. But when he asked her to lie down on the floor and get up, he saw how she pushed herself up with her hands on her thighs. “That looks like a muscle disease to me,” he said. Hinke ended up with John Wokke at the UMC Utrecht. He diagnosed her with Pompe disease. She is not the only one in the family. Her sister and two of her brothers were also diagnosed over time. Only the middle brother escaped. Four of the five children, in other words.
I contact her because I know that Hinke participated in the LOTS study in 2006: *Late Onset Treatment Study*. The aim of this study is to demonstrate the efficacy of alglucosidase alfa in patients with the non-classical form. That is to say: patients in whom the disease was diagnosed after infancy.
First, our conversation is about the years before the study. “In the be-

ginning, the symptoms weren't too bad," she says. "I was diagnosed in 1991, but I was able to continue working until 1994. As long as I didn't have to bend over, lift things, or climb stairs, I was fine. But I gradually deteriorated, so we had to get more and more aids for the house, including a mobility scooter. I got that because I had fallen off my bike with my youngest child on the back. I couldn't do that anymore." I think of my yellow children's bike. Apparently, falling off bikes is also part of Pompe disease.

"At first, I hated the wheelchair the most," Hinke admits. "We were in the gardens of Versailles and Berend, my husband, went to buy tickets. 'How much did it cost?' I asked him when he came back. He showed me the receipt. 'And you're free,' he said. I burst into tears. That free ticket meant to me that I no longer counted, no longer had any value, had been pushed aside. That has changed now, though. Now I always ask if I'm free."

She recounts how her condition slowly deteriorated and that even nighttime ventilation was considered. "That was frightening, but there was always the prospect of a drug in the pipeline. We had that hope to hold on to. People with other muscle diseases didn't have that. When it was announced that the LOTS study would be conducted, I signed up immediately. It was the only way to qualify for the drug, because even if you received the placebo during the study, you would still be entitled to the real drug later on."

She continues: "The study was initially going to take place in Utrecht. A few weeks before it was due to start, the plans were suddenly changed because the board of UMC Utrecht decided to stop the Pompe study. So we went to Rotterdam. There were four of us adults: Jan, Joke, Johan Bakker, and me. We were thoroughly screened because we had to meet strict conditions. Not too good and not too bad, because then the results would be the clearest. I was on the edge. Lung function had to be at least 20 percent, and mine was 26. The limit for the six-minute walk test was 60 meters, and I barely made it to 70."

On the day of the first infusion, there were six or seven people standing around her bed, Hinke recalls. "It was an important moment. The exercise took two days in total. First the measurements, then the infusion, and the next day more measurements. In the beginning, this was done every two weeks. Later, everything was shortened to one day. Once every three months, two American ladies flew in to accurately record our progress or regression. Extra time was set aside for this."

"And did you get the placebo or 'the real thing'?" I ask. "I had the medicine, no doubt about it. Within six months, I could walk twice as far."

Hinke beams as she tells the story; it's a fond memory. "Johan and Jan were also lucky. Joke was not, that was clear. Nothing changed in her measurements. The study lasted a year and a half, not one as intended. During that period, we made the trip from Oosterwolde to Rotterdam every two weeks, but we didn't mind. We turned it into a trip. The night ventilation did eventually happen, but only six years later, in 2012. And lately, I've been using the ventilator for half an hour in the evening to get through the night."

She concludes: "All these years, I have remained active for the VSN and the Princess Beatrix Muscle Foundation. I have welcomed people in our region, listened to them, and given them advice. Nowadays, I live with my husband in a care home, with my daughter just a stone's throw away. During the day, my grandchildren regularly come to visit. Isn't that wonderful? And you know, without medication, I would never have been able to experience this. I'm sure of that."

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ADULTS ALONG THE MEASURING STICK
2002 – 2010

The effects of Pompe disease in babies are clear: a severely enlarged heart, paralysis, increasingly weak breathing, and death before their first birthday. This is the early onset form. But what about children, young people, and adults with Pompe? What is the picture for them? What can you expect with late onset Pompe?

In January 1998, Maryze compiled an extensive list of her physical complaints.[218] At that time, she was not yet receiving enzyme therapy. The list clearly shows how diverse her symptoms are: when sleeping, for example, she has great difficulty turning over in bed and, because her shoulders sag, her blood vessels become constricted and her arms go numb. She can stand, but only if she locks her knees. Walking a few meters requires extreme concentration, and she cannot walk more than a few meters. She sits with her legs raised almost permanently to facilitate her breathing. Getting up from a sitting position is impossible. A teapot is too heavy for her to lift: she has no strength in her upper arms. When she uses her muscles, she suffers from acidification and cramps. She also often has pain in her neck and back. When she is lying down, she needs respiratory support.

Maryze is just one patient, one story. In 2002, Ans van der Ploeg from Erasmus MC, with financial support from the Princess Beatrix Muscle Foundation, launched a survey to identify the symptoms of Pompe patients worldwide. What is unique is that this is being done in collaboration with the International Pompe Association (IPA), the global patient organization. The questionnaire is the same for patients all over the world. The goal is to gain insight into the progression of the disease. The questionnaires are not filled out by researchers, but by patients or their caregivers. This has never been done before.

The industry was not very enthusiastic about it at first, says Van der Ploeg. They were afraid that the research could slow down the approval process. The opposite turned out to be true. Van der Ploeg believes that her research has yielded many results. “We recognized the importance of this type of research from the outset. We wanted to know how patients experience the disease, as this can tell us a lot. Collaboration with the IPA has enabled us to conduct the study internationally. This resulted in *Patient Reported Outcome*: outcomes reported by patients. Everyone is talking about this now, but at the time it was completely new.”

Such a study provides insight into the impact of disease symptoms on a patient's daily life. Can you comb your own hair? Lift your grandchild onto your lap? Do you wake up tired in the morning? Is a train or bus trip feasible? These may seem like trivialities, but for a patient they are essential matters. They have to do with independence and quality of life.

Van der Ploeg: "In 2004, we started a standardized follow-up study with all our patients, including those who were not yet receiving enzyme therapy. This allowed us to compare the effects of the therapy with the natural course of the disease. Through the IPA, we also conducted survival studies: how old do patients live to be? We were able to use that data to determine what the therapy does for survival with the disease. We did a tremendous amount of research on that."

Much of this work was done by Marloes Hagemans[219]. In her dissertation, she emphasizes that this is a spectrum disease, a disease with a variety of symptoms and varying degrees of severity. She sees major differences in the age at which Pompe manifests itself (the first symptoms can occur in early childhood, but also after the age of 60), the age at which the diagnosis is made, and the moment when someone becomes wheelchair-bound and dependent on ventilation. She also concludes that, based on the data, it is not possible to divide patients with the late

onset form into subgroups. Furthermore, the figures show that the severity of the symptoms is related to the duration of the disease, not to the age at which the first symptoms appear. She also notes that in the older group, the disease does not affect heart function, but that the lungs are affected in three-quarters of patients.

Hagemans also investigated whether fatigue plays a role in Pompe disease, the paralysing feeling that you have to drag yourself through the day. "The average score of patients with Pompe disease was much higher than that of healthy control subjects. Fatigue appears to be an important symptom of Pompe disease, occurring in both mildly and severely affected patients."[220]

The conclusion emphasizes the importance of not only looking at spectacular results, the so-called 'Lourdes effect' (the patient getting out of their wheelchair), in studies on the effectiveness of a therapy. Attention must also be paid to symptoms that have a significant impact on quality of life, i.e., the Patient Reported Outcome. The disappearance of that debilitating fatigue is a must-have for Pompe patients, while outsiders, professional assessors, are more likely to consider it a nice-to-have.

The survey is still conducted every year, together with the IPA, among Pompe patients around the world. It provides a great deal of insight into the course of the disease. It is a textbook example of how researchers and patients can work together. The research is funded by the American Pompe Disease Association (AMDA).

At the end of 2005, Genzyme launched the Late Onset Treatment Study, or LOTS for short, a large-scale study to investigate the efficacy of alglucosidase alfa. Hinke Kleiker already mentioned this in chapter 48. Neurologist Nadine van der Beek[221] from Erasmus MC is closely involved in the study. "We participated with twenty patients," she says. A center in Paris participated with ten patients, and sixty came from centers in the US. "So a total of ninety subjects, sixty of whom received alglucosidase alfa and thirty a placebo."[222]

It is somewhat unfortunate that the LOTS study is starting at almost the same time that the drug is becoming available to everyone in Europe. Patients who have registered for the study have a 30 percent chance of receiving a placebo. If they withdraw from the study, they are guaranteed to receive the real drug.

Van der Beek: "The LOTS study was supposed to last a year. After an interim analysis, it was extended by six months because more time was needed to measure clear statistical results. Then we thought: oh dear, what if participants now want to switch? But everyone from Rotterdam completed the study, with no dropouts."

There was something else at play, Van der Beek explains. "When we were able to start treating people who were not participating in LOTS, the most severely affected patients were given priority. They needed the therapy the most. We couldn't put a hundred people on therapy at the same time; there simply wasn't enough medication available. The people from the LOTS were selected because they were in better condition. They did not require invasive ventilation, did not need ventilation during the day, and were still able to walk a short distance. If they decided to withdraw from the study, they would only be treated later. By communicating all of this clearly, everyone participated until the end of the study."

Van der Beek published her findings in 2010: patients who received the enzyme scored better on the six-minute walk test and their lung function stabilized. You would think that there could be little debate about the efficacy of the drug. But that is not the case.

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BUREAUCRATIC RED TAPE
2012

When the European Medicines Agency approved Myozyme for the European market in 2006, it seemed that the battle was over for patients. Hospital capacity and enzyme yield were still limiting factors, however, making it impossible to put everyone on therapy at the same time. Home treatment did free up more space in hospitals, but the reality was that patients had to wait their turn. Those who were in the worst condition were treated first. Those waiting accepted their fate, knowing that eventually everyone would be treated. And that is what happened.
However, the future was not as carefree as the patients assumed, because during those years, the Dutch Health Care Insurance Board (College voor zorgverzekeringen, CvZ[223]) became increasingly concerned about the rise in drug prices. The cost of treatment with alfaGlu was around three to five hundred thousand euros per year, depending on the patient's weight.
Ans van der Ploeg is surprised that the impact on the CvZ's expenditure does not seem to have been clear earlier. "We immediately saw that it was going to be a costly business. We had already made a realistic budget of the costs over time, but the CvZ downplayed it. They said: 'Patients go on vacation from time to time, they'll skip a treatment now and then.' But that wasn't the case."
During that period, orphan drugs entered the market in the Netherlands

virtually unhindered. Attention was already being paid to their special position. Since 2006, the *policy rule for orphan drugs in academic hospitals* has been in force specifically for this group of medicines. There were concerns about the rapidly rising costs of healthcare, but the increase was mainly in the costs of personnel and buildings. Medication accounted for less than 10 percent of the total healthcare budget. Policymakers believed that there was little to be gained in this area.
This attitude began to change after the publication of the advisory report *Zinnige en duurzame zorg* (Sensible and sustainable healthcare) by the Council for Public Health and Care (Raad voor de Volksgezondheid en Zorg, RvZ[224]) in June 2006. The council, now called the Council for Public Health and Society, advocates using a quantitative measure when approving a drug for the market: the QALY. This is an abbreviation of quality-adjusted life year and represents the number of years of life in good health gained thanks to a drug.[225] It is an attempt to introduce 'hard' data into the discussion about the effectiveness of a medical intervention in relation to its costs. The RvZ proposes an upper limit of €80,000 for a QALY. In the discussions that followed in the media, this advice was translated as: a drug may cost a maximum of €80,000. This is incorrect, but nuances are a scarce commodity in the public debate.
The RvZ also adds an important caveat to its recommendation. Such a quantitative approach using QALYs can lead to a decision in principle not to reimburse a treatment from collective funds, the council states. However, the RvZ also says that a social assessment of fairness and solidarity must also be carried out, and that assessment may result in a change to that decision in principle. The council cites orphan drugs as an example. Because the patient population is very small, the pharmaceutical industry can only develop such drugs at very high costs. The costs per QALY are therefore generally already high. For this reason, the RvZ is of the opinion that it is unfair to allow patients with a rare disease to suffer because their disease occurs sporadically. Orphan drugs may therefore exceed the €80,000 limit without this immediately leading to a decision not to reimburse them.
Whether the price of Myozyme is within acceptable limits in the eyes of the Health Care Insurance Board remains uncertain for a long time.

The CvZ would assess the drug four years after it became available in the Netherlands; that much was clear. Van der Ploeg recalls that she had early discussions with the CvZ about the design of the study into the effect of alglucosidase alfa. “The message was: cost-effectiveness is not an issue. The focus is on effectiveness.”

Linda Daniels-van Saase, who moved to the position of manager of pharmaceutical care within the CvZ in October 2011, can imagine that message. "I think she's right. Cost-effectiveness was relatively new, wasn't it? We had, of course, been looking at effectiveness for much longer, but cost-effectiveness only started to play a role from 2000 onwards. It was discussed in the *policy rule on expensive medicines*[226], which was in force from 2006 to 2012. The main focus there was on how to use the medicine effectively, which is already somewhat related to cost-effectiveness. At the time, we did say that we were going to look at cost-effectiveness, but we didn't realize how we were going to work that out."

The assessment focused on two questions: does the drug meet the conditions for expensive drugs and does it fit into the insured package, the basic package? Daniels-van Saase: "In 2006, the CvZ had its hands full assessing extramural drugs, i.e., drugs that you get from your pharmacy. These drugs still had a substantial margin for pharmacists, so that was our focus. I thought: how strange that we are not looking at intramural drugs at all, the drugs that are dispensed in hospitals."

She explains that the CvZ had agreed with the Dutch Healthcare Authority that it would advise on which medicines should fall under the policy rule on expensive medicines. "Then I thought: we should actually consider that advice as advice on whether or not to include it in the insured package. We then took that up. We started making statements about intramural medicines that were already in the package, and that's when the Pompe medicine came to the fore. It was very expensive. A medicine about which we said: let's investigate whether it is worthy of inclusion in the package.”

While Van der Ploeg was working on the design for an international study in older patients, the Late Onset Treatment Study (LOTS), it became apparent that CvZ employees viewed patients with early-onset disease, i.e., babies, differently from older patients. Van der Ploeg: “I

If people had dropped out en masse, that would have been the death knell for this study.

thought: if the drug works for babies, it must also work for adults. It's as simple as that. The CvZ was not prepared to apply this basic principle. That has always remained a difference of opinion. Which is remarkable, because the reverse translation is made effortlessly. It is assumed that a drug will also work in children if it works in adults."

Jaap de Boer, who was involved in the reimbursement process in the Netherlands as Medical Director at Genzyme, was not entirely confident about the outcome of the process. Van der Ploeg's efficacy study was to last four years. After that, a decision would be made about its inclusion in the insured package. Van der Ploeg's efficacy study was the basis for this. At the same time, the study jeopardized another international study, LOTS, in which she was also closely involved.

As described earlier, doctors and Genzyme were afraid that patients would opt en masse for the certainty of the real drug. De Boer calls it ‘admirable’ that this did not happen and that patients remained loyal to the study. “It is an expression of solidarity within the patient community. If people had dropped out en masse, it would have been the death knell for this study, with all the consequences that would have had for the approval of the drug.”

There are therefore two simultaneous studies into the efficacy and effectiveness of alglucosidase alfa: the LOTS (a double-blind placebo-controlled study) and the ‘open-label’ study for the Health Care Insurance Board. All patients who have been administered the drug since 2006 and who meet the criteria automatically participate in the latter. They are examined once every three months, during which their muscle strength and breathing, among other things, are checked. The researchers compare the results with those of an earlier study among patients who were not treated. If the drug works, there should be clear differences between the groups.

“We couldn't put all patients on the enzyme at the same time in this study,” says Van der Ploeg, “so we started with the patients who were most severely affected. We believed they needed it the most. But that

approach did have consequences for the results of the study. The effects of the drug are greatest in people who still have few symptoms."
She continues: "Once the drug is reimbursed, a doctor will not wait to treat a patient until they are very severely affected. That meant that after three years, when we had to write the report, we still had little data to describe 'the real world'. And that data was also from the patients who were in the worst condition and therefore showed the least recovery."
Van der Ploeg and her colleagues are required by the CvZ to include cost-effectiveness in their research, she says. They do this in collaboration with the iMTA, the Institute for Medical Technology Assessment, which specializes in such exercises. "Even though everyone agreed in advance that this drug would never be cost-effective. It's too expensive for that. And that turned out to be the case. The results of the LOTS were published in 2010 in *The New England Journal of Medicine*.[227] They were positive: the treated patients were able to walk further and their lung function improved. During the discussions, I noticed how much the discussions about effectiveness on the one hand and costs on the other began to overlap."
Coincidentally, in addition to the reimbursement process for Myozyme, two other enzyme replacement therapies are being assessed in the same procedure: Fabrazyme and Replagal, both for the treatment of Fabry disease. Fabrazyme is marketed by Genzyme, while Replagal was developed in the 1990s by Transkaryotic Therapies. TKT had fought a tough battle with Genzyme over this drug. In the US, the battle was decided in Genzyme's favor, but in Europe it ended in a draw. TKT has since been taken over by Shire.
Van der Ploeg is not happy about this linking of cases. "The drug for Pompe was lumped together with the discussion about Fabry in the procedure and treatment. In my opinion, these were two very different cases that could not be combined."
The approach also caused confusion among less well-informed journalists, to such an extent that the media sometimes referred to 'the drug for Pompe-Fabry disease'.

51
HARSH WORDS
2012

In the run-up to the assessment, there was regular contact between CvZ employees on the one hand and doctors and the manufacturer on the other. Then came the moment when the files containing all the data and research results had to be submitted so that the scientific assessment could take place. Daniels-van Saase: "Requesting the files from the manufacturer was new, even for us. We felt we had no leverage if we didn't get the files, but I counted on it being important for a manufacturer to get the stamp: approved for the insured package."
She continues: "The assessment by the CvZ takes quite some time. You have to study the file carefully. The CFH, Pharmaceutical Assistance Committee—as our scientific advisory board was called at the time—examines it very carefully from a scientific perspective. There was some contact in between, but it was mostly radio silence because you had to be able to do your work. With the knowledge we have now, I think we should have communicated more during that period."
The CFH is critical in its assessment. There is still some consideration for the results in babies. In that group, the effect of the therapy has been clearly demonstrated, even though many of these patients remain dependent on wheelchairs and ventilation even with treatment. The main objections focus on the effect in young people and adults. The committee considers the effect to be substandard and assesses the cost-effectiveness as low.

The tone of the report is decidedly negative. At the end of December 2011, Van der Ploeg responded in a letter.[228] She strongly disagrees with the CFH's assessment of the results in younger and adult patients. Despite the relatively short duration, the study has shown a favorable effect on survival, she argues. "Taking this into account and assuming that this is a rare condition, we believe that the significant improvements achieved are already very considerable."

The discussion about dosage has also flared up again. The CFH sees no evidence in the figures provided to increase the dose from 20 to 40 milligrams per kilogram per week in children with the classic form. Van der Ploeg argues that "increasing the dosage in individual situations can be of great importance for the well-being of the child".

Her letter is not a reason for the committee to revise the report. The conclusion remains that the drug has limited efficacy in adults and that its cost-effectiveness is minimal. It is an ominous start to the process.

It is now the turn of the CvZ's Advisory Committee on Health Care Insurance (ACP). It must assess the drug from a social perspective and formulate a recommendation for the board of the Health Care Insurance Board on whether or not it should be reimbursed. The members of the ACP come from various sectors of society and may be ethicists, nursing home doctors, health economists, surgeons, insurers, or patient representatives. They are appointed on the basis of their expertise, administrative experience, and patient perspective.

Hedi Schelleman, an epidemiologist and medical biologist, started as an advisor at the CvZ at the end of 2010. She was tasked with writing the draft advice. "I had been in the United States for four years and had never heard of the CvZ. It was a completely new world for me. Coming from a research background, I found myself in a policy culture. My role in the process was limited to compiling the draft advice for the Package Advisory Committee."

Schelleman had to work on two reports. "The pharmacotherapeutic report on the question: does the drug meet the state of the art in science and practice? And the report on cost-effectiveness. That was difficult. There were enormous differences in how patients responded to the drug. Some responded well, others responded very poorly."

It was a learning process for her, Schelleman says. "At a certain point, you become aware of the possible implications of what you write. You constantly wonder how the outside world might read it. I struggled a lot to write the story well, because numbers are just numbers. How do you get all the pros and cons and ifs and buts down on paper without turning it into a whole book? One advantage was that a colleague wrote the advice about Fabry. So we went through the struggle together as we wrote. If one of us found a good way to phrase something, the other could use it. And finally, we had to draw conclusions. Hard conclusions that I hadn't foreseen at the beginning of the process."

Linda Daniels-Van Saase believes that decisive action was needed. "I thought: you have to see now whether this drug is suitable for inclusion in the reimbursement package. It didn't meet the requirements; it didn't produce any improvement. Actually, we already knew that. We had already had two or three drugs before that, with which we had been very cautious: it doesn't meet the requirements, but maybe we should give it some more time. I didn't think that was right, because you have to have a frank discussion about whether it is suitable for inclusion in the package. Even though you realize that there are people behind it – because we have always realized that. So when we knew that the CFH would issue a negative opinion, the manufacturer, doctors, and patient association were understandably concerned. I wondered how we could best move forward with this. I wanted—and I take full responsibility for this—us to enter the discussion with a clear no."

The provisional CvZ recommendation, which will be published in June 2012, leaves no room for misunderstanding about that clear no. Page 21 of the draft recommendation states: "The CvZ advises the Minister of Health, Welfare, and Sport (VWS) to take targeted action. The main reasons for this are:

- In the classic form of Pompe disease, a patient must be treated for approximately three years to gain two years of survival, while a patient with the non-classic form will likely need to be treated for more than 40 years to gain two years of survival.
- The total budget impact of alglucosidase alfa (Myozyme®) is high, namely €44 million in 2010. The share of the non-classical form is

greater (~85 percent) than that of the classical form (~15 percent).
- The cost-benefit ratio is unacceptable for patients with the non-classical form. The CvZ is of the opinion that entitlement to alglucosidase alfa (Myozyme®) for the indication Pompe disease should currently be legally restricted to patients with the classical form of Pompe disease."

The preceding twenty pages inevitably lead to this conclusion. The gist: the drug has little or no effect on the non-classical form, and the price is disproportionate to the health benefits it provides. New Pompe patients will no longer receive it. For patients already undergoing treatment, it must be phased out.

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SILLY SEASON DISCUSSIONS
2012

Daniels-van Saase's observation that the CvZ's draft recommendation caused concern among the manufacturer, doctors, and patient associations is an understatement. Medical Director Jaap de Boer recalls the reaction at Genzyme. "We were very sad and tense because it created so much uncertainty for patients, but also because this decision could have a huge impact on the whole of Europe. Everyone was looking at us."
It is also extremely disappointing for Ans van der Ploeg and the VSN patient association. It seems that a joint effort of thirty years, in which so many obstacles have been overcome, is about to fail at the last minute. And that in the very country where the therapy was developed.
At that point, the patients had no idea what was in store for them, because the draft recommendation had been sent to the parties involved under strict confidentiality. No communication about it was allowed.
That changed dramatically on July 29, 2012. Someone 'left' the confidential advice at the offices of the NOS (Dutch broadcasting company) health editorial team. The editors immediately recognized its news value, as it was a matter of life and death. The news came out when the Netherlands had packed its bags and set off. Some of those involved hear the bad news via the *NOS news*, others receive the message via via while lying on a remote beach somewhere.
The VSN immediately sends an email to its members with Pompe

disease to emphasize that this is a draft opinion, which is still subject to change. “We still assume,” the association writes with forced optimism, “that nothing will change for you in practice in the future. Together with our partners, we will do everything we can to ensure that the reimbursement of Myozyme remains guaranteed.”

The unrest is also palpable at Erasmus MC. Van der Ploeg: "I was on vacation when the news suddenly hit the press. Patients knew nothing about it and were shocked. I had a young patient who had also heard the news on TV. He said to his teacher with great flair: ‘I'm going to die.’ His mother couldn't take it anymore; it affected her deeply. There were people who were approached on the street and accused of their child being so expensive. It led to a strange but also unpleasant discussion in society."

It's summertime, the silly season, and for the media, the news is a gift. Everyone has an opinion, and the newspaper columns fill themselves. On talk shows, experts are falling over themselves to give their views on expensive medicines, cold-hearted accountants, and greedy pharmaceutical companies. The same question keeps coming up: how much should a human life cost? The figure of 80,000 euros invariably pops up, a sum whose origin is unknown to almost everyone.

Jacqueline Zwaap, secretary of the CvZ's Advisory Committee on Health Insurance, looks back on that period with mixed feelings. “At the time, we were still working with confidential drafts, which we no longer do. We didn't have any experience with them being leaked, even though we knew it could happen. In this case, the chance was greater because it was an extreme report. Our timing was not ideal: releasing such a report just before the summer when you're not going to discuss it until after the summer. The period during which you have no control is then too long.”

It remains an unanswered question who leaked the report. The parties point fingers at each other, but no one has any evidence.

In the first days of August, the newspapers are still full of comments on the advice, with the CvZ initially bearing the brunt of the criticism. For example, Youp van 't Hek (a famous Dutch entertainer, writer and columnist) writes in his Saturday column in the *NRC*: "Surely there must have been people in the vicinity of the Health Insurers Committee this

week who told these boors straight to their faces what a bunch of clumsy losers they are? That you must be out of your mind if you even dare to wonder whether you should stop medication for hopeless patients with Pompe disease because they are becoming too expensive. Because in some cases they cost as much as 700,000 euros per year. Instead of going to the management of the insurers and pharmaceutical companies and telling them that they should hand in their criminal Wassenaar salaries and ditto Blaricum bonuses because human lives need to be saved, they scare the poor patients half to death by threatening to stop their expensive medication. Cowards!”

In doing so, Van 't Hek makes the mistake that many people make in those days: he refers to the Commission of *health insurers* instead of *health insurance companies*. The image of health insurers is already somewhat shaky, and they are therefore reluctant to be made the scapegoats in this discussion. They write a highly critical letter to the CvZ, in which they also attempt to put an end to the confusion:

"Zorgverzekeraars Nederland (ZN) has informed the Health Insurance Board (CvZ) in a letter that it does not support the proposal to stop reimbursing expensive medicines [...]. The draft advice from the CvZ (a government advisory body) that was recently leaked wrongly gives the impression that health insurers support this plan.

ZN is surprised by this because health insurers had never expressed an opinion on this subject. The management of the basic package is the responsibility of the government. Health insurers implement the basic insurance on the basis of the Health Insurance Act. That is why they do not comment on the substance of proposals for changes to the basic package. [...]

ZN welcomes the broad social debate on the costs of healthcare, but in ZN's opinion, expensive orphan drugs for small groups of patients suffering from very rare diseases are not a good starting point for this debate. If only because the government has committed itself to European incentive policy to bring orphan drugs to market, among other things by creating favorable reimbursement conditions.”

That same week, in response to the draft advice, the SP asked critical questions in parliament to VVD minister Schippers. With the parlia-

mentary elections approaching, she wisely remained noncommittal. "The CvZ has not yet issued any advice," she writes. "This is a draft that, after consultation with stakeholders, will be discussed in the CvZ's Advisory Committee on Health Care Benefits (ACP). I do not want to prejudge the outcome of this process." She does make it clear, however, that she considers the cost-effectiveness of a medicine to be important, but that effectiveness is the leading factor in determining whether a medicine will be reimbursed.

Incidentally, a letter about the strategy on rare diseases, which she sent to the House of Representatives earlier that year, makes no mention of the high costs of orphan drugs. It deals with how their reimbursement is arranged, not with cost control.

The pharmaceutical industry is also coming under fire in the media. People are asking why a drug has to cost so much and what that price is actually based on. Genzyme answers that question in an article. It lists nine variables that influence the price: the rarity of the condition, the amount of scientific research available, the degree of uncertainty about effectiveness, the measures required in the follow-up process (such as keeping records), the severity of the disease, its impact, the availability of alternative treatments, the breadth of the indication, and the complexity of production.[229] And alphaGlu, Genzyme argues, is a protein that is difficult to produce. That much is now clear.

This latter point is strongly disputed by Professor Huub Schellekens, who teaches innovation in medical biotechnology at Utrecht University. In other words, someone who can be assumed to know what he is talking about. In a widely quoted interview in *de Volkskrant*, he says: "If there is one thing that does not cost much in the pharmaceutical sector, it is the development of an orphan drug. In fact, it costs next to nothing."

In his opinion, developing this drug for Pompe disease is a piece of cake, because the target group for rare diseases is by definition small. His students could develop and produce the protein for Pompe in their kitchen.[230]

Two years later, in an article in the daily newspaper *Trouw*[231], he even claimed that the drug could be produced for €15,000 per patient. Not everyone takes his statements seriously. He has never been able to substantiate his claims. But these are actions that set the tone and confirm the prevailing image of the pharmaceutical industry: that it enriches itself at the expense of patients.

While patient organizations and Erasmus MC did not want to respond publicly to the leaked draft advice, CvZ employees were vocal in the media. According to Linda Daniels-van Saase, this was a conscious choice. "When it was leaked, we held an emergency meeting. The leak was obviously not pleasant, but the question was: do we keep quiet or do we provide an explanation? We have gone through a scientific process, so are we now going to bring that to the fore? And that is what we decided to do."

Among others, the chairman of the CvZ, Arnold Moerkamp, who has been in office for less than a year, is making his voice heard. In the *NRC* of August 8, 2012, he argues: "The drug is not effective enough in people with non-classical Pompe disease. Besides, even if the drug were not so expensive, you might wonder whether it should be reimbursed. Because it is not effective, and that is what we are looking at. The research shows, among other things, that older patients only live a few months longer if they use the drug for years. Babies who do have the classic form of Pompe disease only die after their third birthday instead of after their first birthday thanks to the drug." These statements are at odds with the experiences of patients who have been using the drug for years and are benefiting from it. The babies in his argument are now not three, but twelve years old.

According to Jaqueline Zwaap, the negative reactions to the leaked report hit the CvZ staff hard. "It was very much about us. In his column, Youp van 't Hek said: who are these people who think they can decide about the lives of others and how much a life is worth? We also received emails with, for example, a drawing that said: 'You want me dead'. That kind of message."

The turmoil that suddenly invaded the usually quiet offices of the CvZ in many forms will continue to reverberate there for years to come.

53
STORM OVER DIEMEN
2012

In the run-up to the meeting of the Package Advisory Committee on September 21, 2012, Pompe disease and the drug—invariably accompanied by the adjective 'extremely expensive'—continue to feature in the media. In the week before the meeting, the *NOS news* program focuses on the issue three times. An extensive portrait of Johan Bakker was broadcast, who, thanks to the therapy, has resumed his work at the Water Authority. This was followed by an interview with Marcel Timmen, director of the VSN, and a report on a patient meeting. The reason for the broadcast was a letter written to the CvZ by a dozen professors of neurology from the seven academic centers that existed at the time. They argued for reimbursement of the drug.[232] They felt that their own research into innovative therapies for rare diseases was also at stake.
The monthly meetings of the ACP in Diemen are open to the public, but there are few attendees. A single representative of a manufacturer fills the room, a member of a patient organization, perhaps also someone who has responded to the invitation to address the ACP members and possibly change their minds. But no, the deliberations are not exciting in the least.
The meeting culminates in a recommendation prepared by a CvZ employee. This recommendation, together with that of the scientific council (the aforementioned Pharmaceutical Assistance Committee), is sent to

the CvZ's board of directors. Based on this, the board formulates its own recommendation and sends it to the minister. The minister then makes a final decision, which rarely deviates from the CvZ's recommendation. ACP meetings are seen as a formality in this process. Necessary, but generally of little interest.
Until September 21, 2012. Linda Daniels-van Saase believes that this time there should be a real discussion in the ACP. "I wanted us to go into that discussion with a 'no'. I had already experienced that the discussion lacked sharpness. I suggested within the CvZ that the committee should take a break, so to speak. I could see that it was going to be a tough discussion, also for our employees. No one wanted to hear that. As the meeting approached, I said, 'Guys, it could get busy. With lots of interested parties and possibly media attention. So maybe we should practice as if there were television cameras present.' No, that wasn't necessary, because—and I found this a particularly compelling argument—it was only the ACP issuing a recommendation."
It soon became clear that it was going to be busy. A week before the meeting, the courtroom was fully booked. On September 19, there are also no more seats available in the second room with a video screen, which has been hastily prepared. To their frustration, a few people are placed on the waiting list. The largest group of interested parties consists of patients, but many journalists have also announced their arrival. At the eleventh hour, the *NOS news* also shows up. On the morning of the hearing on September 21, a line of wheelchairs quickly forms in front of the CvZ. The entrance can only be reached by a slow platform lift. Never before has the CvZ been confronted with such large numbers of wheelchair users.
Inside, patients walk and wheel around wearing T-shirts distributed by the patient association with the slogan: 'It works for me'. The VSN has chosen to focus all presentations on the effectiveness of the drug in adults. The repeated message is: it works. The costs are not mentioned because the patient has no influence on them.
Daniels-van Saase can still vividly remember that morning. "It was all new to the ACP members. Normally, there were just a few people in the room, and suddenly you had a large group of people around you. I

remember the signs in the room: 'I'm too expensive and I'll get the death penalty' and more of that kind of thing. Yes, that made an impression on the staff and the ACP members. On me too."

Due to the large influx of people and the traffic jam at the elevator outside, the meeting starts later than planned. There is a nervous atmosphere. It is crackling. The discussion of the draft advice on Fabry and Pompe begins with a short introduction by Arnold Moerkamp[233], the chairman of the CvZ's executive board. In it, he seems to be anticipating the outcome of the discussion. "We are well aware that science uses statistics and averages. The spread around the average can be large. In Pompe disease, that spread is also large, in Fabry disease less so. Individual patients rarely recognize themselves in statistics or averages. Every patient is an individual. Patients who respond well to the drug logically have difficulty recognizing themselves in the results of scientific research. I therefore believe that a transitional regime should be put in place for this purpose."[234] Transition, someone wonders, from where to where?

Carla Hollak, an internist specializing in hereditary metabolic diseases at the AMC, focuses her attention on the procedure followed. "Since quality of life does not improve immediately in the case of a chronic disease, it is easy to calculate that the price per QALY, per year of life gained, will run into the millions. We didn't need all that research to figure that out. What is needed now is a better discussion about how we can investigate the effectiveness of these treatments more quickly and more effectively, what is a socially acceptable price, and whether traditional cost-effectiveness research is suitable for rare diseases. If it is decided to exclude enzyme therapy for all forty Fabry patients from the insured package at this time, then the CvZ is essentially saying: there is too much uncertainty, we cannot resolve it, so reimbursement must be discontinued."

She then makes a plea for European cooperation in scientific research, improving therapies instead of indiscriminately rejecting them, and a European system for linking price to effectiveness.

Maryze, Johan Bakker, and Wilma Treur, all three Pompe patients, talk about what the therapy means to them from their own experience. They all mention their regained energy, the opportunity to contribute to society again, and the independence they have regained. Maryze talks about Nynke, an eight-year-old girl she recently met who, unlike her, has the prospect of a life without limitations, provided she can continue to use the medication. Maryze herself is able to run her consulting firm. Wilma works three days a week and, as a single mother, is able to raise her child. Johan is back at work as director of the Water Board. He recounts how, to his own surprise and emotion, he was able to visit Venice without a wheelchair during the summer holidays. The room is silent.

Then Ans van der Ploeg takes the floor. Like everyone else, she is nervous. Thirty years of research and the well-being of the patients are at stake here, her patients. She makes it clear that she disagrees with the CvZ, which considers the results in older patients to be too limited. She, on the other hand, observes remarkable progress. "In that short period, we already see significant effects in adults on walking distance, lung function, muscle strength, and even survival. We find the conclusions that the survival benefit for patients would be very limited to be downright misleading."

But there is much more at stake today, she argues. "If the CvZ's preliminary advice is followed, it even raises the question of whether it still makes sense to develop innovative treatments for other orphan diseases in the future if it ultimately turns out that these orphan drugs are considered unaffordable. We are aware of the rising costs in healthcare and of the fact that the CvZ has to make choices. In our opinion, the Dutch government should therefore draw up guidelines in advance with regard to the funding of orphan drugs. And not after the fact, as is currently the case, which is detrimental to our patients. We find this unethical."

The arguments of the patients and doctors impress the members of the ACP. Before the meeting started, there was a majority in favor of adopting the draft advice, but the discrepancy between the CvZ report on the one hand and the positive experiences of those involved on the other is sowing doubt among the committee members. One member argues that it is unacceptable to exclude people for whom the therapy works well

He intends
to resign if
the committee adopts the
recommendation
without amendment.

from treatment.
The most outspoken opponent of the draft recommendation is Cees Smit, patient representative within the ACP and active for many years in national and international hemophilia organizations. He explicitly advocates keeping the therapy available, despite the costs. In fact, he intends to resign if the committee decides to adopt the recommendation unchanged. The accompanying statement is in his inside pocket, because he is by no means certain of a positive outcome.
When one of the committee members finally changes her vote, there is a narrow majority in favor of including the drugs in the basic insurance package. However, it is unclear what conclusions should be drawn from the discussion, despite the attempts of ACP chairman Bert Boer to summarize the recommendations.
As the committee continues the discussion for some time, the confusion in the gallery increases. Smit adds that the advice must clearly state that, in the opinion of the Rotterdam researchers, no distinction can be made between the classic and non-classic forms of Pompe disease. In doing so, he undermines the basis of the draft advice for Pompe disease, because in that advice, the reimbursement of the drug is linked precisely to that distinction. The meeting ends in chaos.

54
THE LONG WAIT
2012 - 2013

The patients leave the room in complete confusion. Some have heard that the drugs will continue to be reimbursed, while others doubt this. This uncertainty is no less great for the doctors, journalists, and even ACP members. The NOS interviews CvZ chairman Moerkamp, who says he has been moved by the patients' stories. “We haven't paid enough attention to people,” he tells the NOS. “The stories and emotions of these patients leave you deeply moved.” The NOS website reports that the CvZ will be presenting the minister with a significantly revised recommendation. “The CvZ will now recommend that the drugs for Pompe and Fabry disease be reimbursed for both current and new patients.”
The newspapers all have their own version of the ACP decisions. *Trouw* seems to have the best understanding of the situation. "It remains unclear whether new patients with Pompe or Fabry disease will be eligible for medication. This could be done through a special innovation fund to combine treatment and scientific research. But whether the Health Care Insurance Board (CvZ) will advise the government to do so is still uncertain, contrary to what some media reported yesterday, the influential advisory body emphasizes. Financing has not yet been arranged either." ACP member Smit confirms this in an email to patient organizations.[235] He writes: “Thanks to the powerful input from patients, patient associations, and doctors, the ACP has been able to give a provisionally

favorable turn to the CvZ's proposed recommendation to partially discontinue treatment. Whether this provisional decision will remain in place is still to be seen. The CvZ board of directors still has to review it (but may not be able to deviate from it given their statements) and the Minister of Health, Welfare and Sport still has to decide on it. […] For now, we should take advantage of this confusion. However, it is important to remain alert, because the hangover at the CvZ will be significant internally, and the question is whether the Ministry of Health, Welfare and Sport is happy with all this publicity, which has been going on for almost two months now."

Indeed, the mood at the CvZ in those days is far from cheerful. ACP secretary Jacqueline Zwaap sees the meeting as a turning point. "The people who have been with us longer talk about before and after Pompe and Fabry. Trauma may be a big word, but it has been a turning point in the process."

On October 23, 2012, the ACP's final recommendation is published. It looks back on the leak of the draft recommendation and the heated public debate that ensued. "[This has] caused great unrest and uncertainty among people with Pompe and Fabry disease, their families, and their practitioners. The committee understands these emotions well. Nevertheless, the committee considers it important that the discussion be held about the limits of the package and the criteria for it."

The opposing views within the committee are then explained. Some members look purely at cost-effectiveness, because collective resources must be used in such a way that they yield the greatest health benefits for the population as a whole. In this context, individual interests must give way to those of the collective, and expensive orphan drugs will be at the back of the queue. Other members believe that collective resources should contribute to creating equal opportunities, or should be used to optimize outcomes for those who are worst off. "They note that there is a very high disease burden. They also note that the drugs appear to be very effective for some patients. For them, these two facts are sufficient reason to finance the costs of treatment with these drugs from collective resources."[236] We are now awaiting the CvZ's final advice to the minister.

The commotion in September also has far-reaching consequences for the CvZ. On November 28, a report by communications agency Schinkelshoek & Verhoog will be presented. It contains an analysis of the current situation. The report culminates in a whole series of recommendations in the area of organization and working methods, with a strong emphasis on better communication; from a social risk analysis to an improved website and from an assessment of publicity opportunities to clear summaries of complex, technical documents.

A day later, on November 29, the final recommendation to the minister on the reimbursement of Pompe and Fabry drugs is published. Patients can breathe a sigh of relief for now, because the CvZ proposes to continue to reimburse the drugs from the basic package for the time being. This applies to babies, children, and adults alike. New patients will also continue to be eligible for reimbursement. However, a separate form of financing is needed for these new drugs. Of course, the minister will have to negotiate the price with the manufacturer. Perhaps, the advisory committee suggests, the dosage could be reduced slightly, which would save on costs. An independent committee could also be set up to consider start and stop criteria. This would also improve efficiency. Not much remains of the initial draft advisory report.

A provisional financing arrangement will be put in place for 2013, so that the therapy will remain available to patients during the price negotiations with the manufacturer. A loud cheer? Well, no. There will be no popping champagne corks at the VSN. The minister may rarely deviate from the CvZ's advice, but this reimbursement process is unique. So who can guarantee that there won't be another hitch? The outcome of the price negotiations is particularly uncertain. Price negotiations have only taken place a few times before in the Netherlands.

And sure enough, in her letter of January 30, 2013, to the House of Representatives, Minister Schippers uses threatening language. If the price of the therapy does not drop, reimbursement after 2013 will be in jeopardy. She continues: "I assume that all parties realize this. I would specifically like to point out the responsibility of the manufacturers. They have the greatest influence on whether these orphan drugs will be reimbursed at socially acceptable costs to this vulnerable patient group in 2014." The tone has been set.

On the one hand, it is of course a bad time to start price negotiations when all patients in the Netherlands are already undergoing treatment. On the other hand, the whole world is watching. If the drug is not reimbursed in the country where the therapy was developed and where the world-renowned centers of expertise for Pompe and Fabry are located, this could have major repercussions in Europe and elsewhere in the world. The manufacturer is well aware of this. The stakes are high and patients are holding their breath. Signs indicate that the negotiations are proving difficult. Initially, the results were to be announced in January, but nothing has been heard.

Price negotiations are relatively unfamiliar territory, not only for the government but also for the pharmaceutical company. Bert de Jong, General Manager of Sanofi Genzyme Benelux at the time, says[237]: "In September, it was decided that we had to negotiate with the Ministry of Health, Welfare and Sport. Those negotiations were new to us. That was new in the industry. I think that with Myozyme, we were the second or third drug to be negotiated on the advice of the ACP."

Of course, this concerns the high price of the drug. De Jong: "We set up a task force with a number of international colleagues. After the ACP meeting, we got the green light internally to provide a lot of information about the costs and the investment, right down to the production facilities, in order to demonstrate to the Ministry of Health, Welfare and Sport that the drug was not cost-effective for us as a company."

The press remains remarkably silent, with the exception of a brief eruption in May, which will be discussed later. An internal email from the VSN shows that the patient association has decided to operate under the radar for the time being. It does not want to antagonize the ministry. That does not mean that it is sitting still. It is in contact with the officials responsible for the negotiations and is keeping its finger on the pulse. It seems that both parties want to reach an agreement, even though it is proving difficult.

The association is now turning its attention to parliament. Even though the House of Representatives does not formally decide whether or not to reimburse a specific medicine, in practice this works differently. The association is sending out a call to all Pompe members asking them

to bring their experiences with the new therapy to the attention of the members of the House of Representatives' Health Committee. For some time, the idea of a breakfast meeting in The Hague with relevant members of parliament is considered, but this idea is abandoned.

On April 28, 2013, Nadine van der Beek defends her thesis[238] on the effect of enzyme replacement therapy. Various studies convincingly demonstrate positive effects in 90 percent of patients: endurance and muscle strength improve and lung capacity remains at least the same. With these figures in hand, hardly anyone can argue that the drug has no effect. But they are apparently not an incentive to reach an agreement quickly. Day after day and week after week, there is still no white smoke.

55
A NASTY INCIDENT, JUST BEFORE THE FINISH LINE
2013

While the minister is negotiating with Genzyme/Sanofi and the patients are anxiously awaiting the outcome, disaster suddenly strikes Maryze from an unexpected source. She started her business in 2007, and it has been running smoothly from the start. Combined with temporary positions as a project manager for European projects, she earns enough to support herself. Financially independent, that's exactly what she wants.
The jobs she gets are very varied. Sometimes it involves producing information material, other times she is asked to give a lecture because of her knowledge of and experience with Pompe disease. She is appreciated for her clear, vivid language and the way she describes the impact of the disease. But also for how she deals with limitations and decline. That is where her strength lies.
Genzyme regularly asks her to train new employees in Europe, which means telling them what life is like for someone with Pompe disease and what the medication means to her. She impresses upon her audience how important their work is. She finds other clients within the pharmaceutical industry, but universities, patient organizations, and government agencies also call on her expertise.
In 2012, she was asked by the company Alexion to bring together patients in the Netherlands with the rare, serious kidney disease aHUS.

The pharmaceutical company markets the drug Soliris for this condition, but has no patient organization as a discussion partner. Maryze has done this before; she has been involved in the development of 'her' VSN from the very beginning.
She gets to work. Through a specialist at Radboudumc, she approaches aHUS patients and their parents. She soon has contact with about ten people who are interested in setting up their own organization.
The question is, however, whether such a small association is viable. Everything has to be done on a voluntary basis; there is no money.
Maryze calls the Dutch Association for Kidney Patients, the NVN. Is there room for an aHUS working group? The idea is embraced by everyone, and not long after, the new organization within the professional NVN is a reality. The job is done, the invoice is submitted.
Now, a project may be finished, but the contacts you make with people remain. You email or call this person or that person again. A now good friend of Maryze's, a Dutch mother with a son with aHUS, has spoken to the parents of a boy with the condition in Flanders. She is quite shocked to hear that Soliris is not reimbursed there and asks Maryze if, with all her experience, she would be willing to call the Belgian parents. She does so. If she can help, she will not hesitate. During the phone call, the father tells her that the press has already been notified and will be at their door the next morning. Maryze wishes them luck.
Time for a short vacation. Maryze and her boyfriend have booked a small hotel in Germany. They haven't even unpacked their suitcases yet when the phone starts ringing. She gets one journalist after another on the line. What's the deal with Alexion? And why did she accept payment to put pressure on Flemish Minister Onkelinx through the media? Maryze is completely overwhelmed.
On Saturday, May 4, an article appears in the Belgian newspaper *Het Nieuwsblad* about the 'lobbyist' Maryze Schoneveld van der Linde.
On Tuesday, *De Morgen* and *de Volkskrant* follow suit. The *NOS news* devotes considerable attention to it, *Elsevier* talks about the media-savvy Pompe patient who has been 'unmasked'. '*Schoneveld van der Linde on manufacturer's payroll*', it says.
And all this while Minister Schippers threatens not to reimburse

Myozyme if the manufacturer does not meet her further in the price negotiations. A drama unfolds, and at a very bad moment.
Maryze is deeply shocked. She desperately wants to tell her side of the story, but she doesn't know how to get it out there. People she talks to advise her not to stir up the fire and to keep her mouth shut. She thinks it's unfair. Many people around her remain silent. A few dare to approach her and ask what happened. Only a handful express their support for her.
She doesn't understand. She didn't keep anything secret. The journalists never asked her about her work. Her work as a consultant has been listed in detail on her website for years. The same goes for LinkedIn. As does an overview of her volunteer work. How could she have foreseen that all her efforts would backfire on her? She never accepted payment for any media appearances. No one openly stands up for her. On the contrary, she is shocked by the fear that prevails for the power of the media. It takes more than a week. Then the storm subsides and it becomes quiet. Maryze is left behind, bewildered.
When she withdraws as a speaker at a masterclass at the University of Amsterdam a few days later, she receives a call back from Alexander Rinnooy Kan, professor and former chairman of the SER. He is leading the meeting, which focuses on ethics, healthcare, and costs. Maryze asks him if he still wants her as a speaker after all the accusations that have been hurled at her. "I know how it is," says Rinnooy Kan. "Tall trees catch a lot of wind. But you're not going to cancel this. Because I want you."
She's in. That feels good. The way others treat her makes it all just a little bit more bearable. Ten years later, the affair is still a sensitive issue, a painful scar from an offense that was never committed.
In The Hague, it remains quiet for the time being. Not a word about the progress of the negotiations. Clarity will come before the start of the summer recess, it is said. But summer arrives without any news from the ministry. In July, Schippers announces that she wants to provide clarity shortly after the recess, but even in September, the redeeming word remains absent.
Then, on October 3, 2013, the minister finally announces her decision: the drugs for Pompe and Fabry diseases will be included in the basic

That confidentiality
is a strict condition imposed
by the manufacturer.
No one is allowed to see it.

insurance.[239] For the time being until 2016, she adds. After that, a new evaluation will take place. In a letter to the House of Representatives, she writes that she has agreed on a 'price arrangement' with the manufacturer. What the negotiations have yielded for the treasury remains confidential 'for competitive reasons'. This secrecy is a strict condition imposed by the manufacturer. No one is given any insight. The insurers pay the manufacturer the full price and at the end of each year, the unknown discount flows back to the ministry through another channel. That's how it works.
Furthermore, the minister indicates that she is very satisfied with the results of the negotiations. Schippers praises the constructive attitude of the manufacturers, the professionalism and cooperative attitude of the doctors, and the patience of the patient associations. And those associations can finally celebrate.
Can patients take credit for part of this result? Coincidentally, scientific research has been done on this. In his 2008 dissertation, *Demanding Dynamics*, Wouter Boon, now a professor at Utrecht University, devoted sixteen pages to the Pompe case. Among other things, he writes[240]: "The patient organizations were involved in the approval process. The IPA contributed to obtaining a broad label for Myozyme, including patients with late onset. […]. In addition, the VSN maintained weekly contact with the doctors at Erasmus MC to keep up the pressure and make home treatment possible." It has all been discussed before, but it has now also been scientifically established.
Incidentally, the interviewees for this book express the same sentiment. "Yes," says Linda Daniëls-Van Saase[241] of the CvZ after some hesitation. "I think it was also good for the visibility of the patient organization, by showing: we matter, we can also form a voice."
Jan van Heek[242], then Vice President at Genzyme, is the most outspoken. "The role of the patients was extremely important. Without the patient organizations, the entire approval and reimbursement process would have been much more difficult. And you can still see today that patients, if they are well and positively organized, can have an enormous influence."

EPILOGUE

56
PHARMING REVISITED

On August 10, 2001, the lights go out at Pharming. The day before, Genzyme announced its acquisition of Novazyme. Pharming is far too short of cash to meet its financial obligations. That leaves CEO George Hersbach with no choice but to apply for a moratorium on payments, usually the precursor to bankruptcy. Together with the receiver, he took stock to see what could still be salvaged. One thing was absolutely clear: Pharming's role in the development of a drug for Pompe disease was now completely over – or so you would think.

Yet Pharming managed to survive against all odds. Hersbach[243] looks back on this with a certain pride. "We got through it. Those were tough years; I worked day and night. With an administrator, of course. When you're in receivership, the administrator and the director have to work together to solve the problem. We worked hard on that. It would have been beneath my dignity to let the ship run aground."

After Genzyme's departure, Pharming was left with a huge debt, but also with a product that could potentially make money. The drug is intended for the treatment of hereditary angioedema. This is a very rare condition characterized by sudden severe swelling of blood vessels, with potentially fatal consequences. Pharming developed the drug in the shadow of the Pompe hype. As a result, it never received much media attention, but it turned out to be the lifeline that kept Pharming afloat. When Hersbach left in 2002, the company was back on track financially. However, it was

still somewhat unstable, because although there was enough money for the time being, there was hardly any income.

When Sijmen de Vries[244] took over as Pharming's new CEO in 2008, he had a convertible debt of €70.5 million on his plate: a debt that was due within two years. Then the banking crisis broke out, which wasn't such a bad thing for Pharming. Many hedge funds and other lenders panicked and tried to save what they could at any cost. According to De Vries, this is a situation that a company can also benefit from. "A lot of hedge funds that had bought that debt just before the crisis were in deep trouble. We were able to give them a good haircut. We said, 'Okay, guys, you have a problem. You paid $10 million for those bonds at the time. We'll give you back $2.5 million in cash and you'll get another $500,000 in Pharming shares.' Some were so desperate that they accepted, and that's how our debt was reduced to a reasonable level."

The new drug for hereditary angioedema, which will be marketed under the brand name Ruconest at the end of 2010, is not generating sufficient revenue in Europe for various reasons. In addition, the Food and Drug Administration is not satisfied with the research data on which the European Medicines Agency based its decision and is demanding additional data before the drug can be approved for the US market. Nevertheless, Pharming is gradually succeeding in improving its position. Ruconest has been authorized by the FDA. The Danish biopharmaceutical company Santaris Pharma has licensed the drug so that revenue can be generated quickly. Pharming desperately needs the money to survive.

However, the agreement with Santaris is not as solid a foundation as it seems. The company is acquired by Salix, which is in turn taken over by Valeant Pharmaceuticals. That company, in turn, is collapsing like a house of cards. Sales figures are so dismal that in 2016, Sijmen de Vries decides to buy back Ruconest for $60 million, plus a 'milestone payment'[245] totaling $65 million. He says, "They called me at midnight with the message: *it's all yours*. That meant that the next day, 100 percent of the proceeds were ours, instead of 30 percent as before."

The sale added nine salespeople and a sales manager to Pharming. "And we never looked back," says De Vries. "Sales skyrocketed, and we quickly became a profitable company. This makes us the only European company

that has succeeded in selling its own product, developed from its own research, on both sides of the Atlantic. We are unique in this respect. And that's just the beginning."

He cites Genzyme as a shining example. It became a major player in the orphan drug market.

While the old Pharming was convinced that a strong partner like Genzyme was necessary to bring an orphan drug to market, the new Pharming has done the opposite. Not only do they market their own product independently, but they also license orphan drugs from pharmaceutical giants and bring them to market. For example, they have licensed an orphan drug for the treatment of an immune system disorder. The drug was developed by Novartis and has now been launched in the US. De Vries: "We have proven that we absolutely do not need a partner for this. You shouldn't bring one in, because you don't need one in the rare disease market."

The current Pharming has proven something else as well, namely that it is entirely possible to produce specific drugs using rabbits. De Vries: "Our experience has been excellent. It is a super-efficient system. The protein has an extremely high yield: 10 or 12 grams per liter in rabbit milk. If we milk a rabbit every day, we can get one and a half treatments out of it, after production losses. That's amazing. Nobody expected that."

Incidentally, Pharming is not the first company to produce a drug from the milk of transgenic animals. The anticoagulant ATryn, which is produced from the milk of genetically modified goats, has been available in the US since 2009. It was marketed by GTC: Genzyme (!) Transgenics Corporation.

The success of the transgenic rabbits in the production of the drug for hereditary angioedema and the expiry of market protection for Myozyme in 2016 led Pharming to a bold idea. The plan is to once again focus on the development of alfaGlu for the treatment of Pompe disease. Internally, the process is being energetically pursued, but much work needs to be redone. When Pharming and Genzyme split up, a great deal of technical knowledge was lost.

In 2014, Pharming acquired the French company TRM, Transgenic Rabbit Models. That company had the genetic material needed to bring the

alfaGlu-producing rabbits back to life. And it worked. Next, they looked at protein production and the purification process for the material. That also exceeded expectations.

De Vries: "We also spoke with Ans van der Ploeg, Hans Büller, and Ernst Kuipers, who was chairman of the board of directors of Erasmus MC at the time. They shared our enthusiasm. A major advantage of the rabbit product is that it could cause fewer immune reactions than the alphaGlu produced in CHO cells. With our own medicine, we have been able to observe that it never leads to an immune response. And we have sold around 150,000 doses of it."

The story would, of course, be complete if Pharming had been on the verge of bringing its own Pompe drug to market. But that is not going to happen. Development took too long, and new competitors had made the market too uncertain. The alfaGlu that Pharming wanted to develop was the same as 25 years ago. There was a high risk that a competitor would come up with an improved alternative. That is why, in 2023, Sijmen de Vries decided 'with regret' to call off the development process: the definitive end of a rabbit drug for Pompe.

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THE SURVIVORS

In 1999, four babies and three young adults received their first infusion of alfaGlu produced by transgenic rabbits. How have they fared since then? Of the three young adults at the time, the two youngest are still alive. They are doing well. The third, Robert, sadly died on December 6, 2017, from the effects of Pompe disease.

The general picture[246] painted by the Rotterdam researchers is that treatment with alfaGlu in late-onset patients leads to an improvement in symptoms immediately after the start of treatment. This is followed by a 'plateau phase' in which there is no improvement or deterioration. This phase lasts for a number of years. A slow decline then begins. Incidentally, there are also patients who exhibit a strong allergic reaction and therefore have to discontinue treatment.

The best results are achieved when treatment is started immediately after the first symptoms appear. There are major differences in the course of the disease between patients. There is still no conclusive explanation for the deterioration and for the differences between patients. Experts disagree on this. Arnold Reuser does not see the deterioration after the plateau phase as inevitable. He suggests that an improved enzyme product may be able to change the course of the disease.

The situation is different for babies. Three of the four who were treated first have since died. One of the children reached the age of four, the other two were well into their twenties. The last survivor, who perhaps

had the worst prognosis at the start of the trial because she could only be treated from the age of eight months, is Sophie, the daughter of Arno and Ellen from East Flanders. A long time ago, her doctor, Pompe expert Johan Van Hove, nominated her to participate in the study. She is now 25 years old.

In 2003, during the IPA conference in Heidelberg, her parents talked about their then four-year-old daughter and their concerns about her health and the well-being of their two other children. They publicly wondered how long they would be able to continue providing care. More than twenty years have passed since then, and the care has not diminished, but rather increased. For Ellen, it is something you have to deal with. “That's just the way we are. When you bring a child into the world, you have to take responsibility for it. If it is sick, you take care of it.”

It is precisely this care that has them stuck, on the one hand because the Flemish government does not pay the full amount for the care, and on the other hand because it is extremely difficult to find personal assistants. Sophie has a budget for 42 hours of assistance per week, while someone needs to be on call 24/7 in case something goes wrong. Sometimes Ellen and Arno have to take drastic measures to get things done.

“Occasionally, we feel compelled to take legal action if we feel the government is falling short,” says Arno. "A few years ago, that was against our national health institution. Part of the reimbursement of healthcare costs would stop when Sophie turned 18. We fought against that and won. But next week we'll be back in court because the Flemish government still hasn't released the entire budget for the personal assistance Sophie is entitled to. We deal with things like that every day. It shouldn't be that way; it makes things harder."

Twelve years ago, Arno and Ellen renovated their house so that Sophie would have her own room and shower on the ground floor. They sleep upstairs, each with a baby monitor next to their bed. Downstairs, an extra bedroom has been set up for emergencies, for example if Sophie becomes ill. Because her respiratory muscles function poorly or not at all, she is on a ventilator. When she has a cold, even a few seconds can make all the difference.

Arno works full-time, but from home so he can help out when needed.

Ellen is on call all day to take care of Sophie and do activities with her. If they want to go out for a day or evening together, they have to call on their daughter Yvonne or son Patrick. He is a physical therapist and already comes by every Friday to do exercises with Sophie.

It is not only her declining muscle strength that is a problem. Ellen: “Recently, Sophie had a kidney stone that caused her a lot of pain. She also complains a lot about stomach aches, but who can say whether it's her kidneys or her intestines? For every complaint, we have to find a suitable doctor who can help.”

No matter how many physical problems Sophie has, she has developed intellectually beyond expectations. She has completed primary school and secondary school, more or less the equivalent of Dutch pre-university education. And she continues to develop. Arno: “You can have a normal conversation with her, even though speaking is difficult for her. She has an average vocabulary, she writes emails, she chats. All of that is going better than expected.”

Ellen adds: "She has a very good memory, I never have to look at my calendar. She remembers dates, knows exactly how long ago something happened. I used to play *triple mem*o with her, a memory game where you have to find not two, but three matching pictures. She was unbeatable. I had two or three sets, she had the rest. She plays chess with Arno, learned Spanish for a while, and is now passionately studying German."

Psychological research has now shown that Sophie's emotional development has not kept pace with her intellectual development, says Arno. "She has separation anxiety, is very attached to her mother, is very self-centered, and her empathy is very low. That has less to do with the nature of the disease and more with the fact that she has had to discover the world from a bed or wheelchair, that she has not been able to play with other children, has never learned to share. She didn't go to kindergarten, didn't go to elementary school, and did most of her high school education on the computer. She only went to school one afternoon a week, and that was it."

Ellen: "That emotional development also makes it difficult for us. She can be really harsh, you know. When I say, ‘I'm tired,’ she says, ‘Oh no, you're always tired. You'll be tired again soon.’ Sophie was also angry with us for

a while because we let her be born. She was convinced that we knew she was sick. She said, 'Why did you let me be born? It's your fault that I'm sick.' We explained it to her as best we could. We know how things are, so we can understand, but it's not easy. At the same time, Sophie has a strong will to live. If something physical is wrong, the first thing she says is, 'Mommy, I don't want to die yet.' She wants to do everything; she has no problem filling her time."

Since Arno told his story in Heidelberg, their lives have not become any easier. "Recently, a Belgian ultra-runner ran the California Crest Trail in fifty days. Every day a double marathon, or more. That's exactly how it feels for us. That eventually you can't even think normally anymore. That you're hallucinating while you're still running."

Gradually, the years are also starting to count: Ellen is 46, Arno 60. "It's a big sword hanging over our heads," Arno admits. "Sophie has also been worried about that," Ellen adds. "She asks, 'What will happen to me when you die?' It will probably be the other way around: she will go first. I hope so, because otherwise it will be a disaster. I find that a difficult dilemma: you want to have her with you for as long as possible, but in fact she should go first."

She hastens to add: "Don't get us wrong. We are very happy with all the time we have spent with Sophie. We have no regrets about our decision. We were convinced that we were doing the right thing. It was her only chance. We would never have forgiven ourselves if we hadn't given her that chance. You go for it. If we were in that situation again, I think we would do the same thing."

"But," says Arno, "if we had known then what we know now, we probably wouldn't have done it. Then I could certainly have accepted the decision: this is pointless, this is just too hard, this is going to completely take over your life." "Not just for us, but for Sophie too," says Ellen. "The limitations are very severe now."

Experiences with patients like Sophie have led doctors in Rotterdam to decide to no longer treat babies who are already too ill and who have no prospect of a sufficient quality of life—however elastic that concept may be. The adage also applies to early onset: treat before the symptoms become too severe and irreparable damage has occurred.

From the very beginning, the children's cognitive development was closely monitored.

Another limitation of the treatment is that alfaGlu cannot cross the blood-brain barrier. In other words, alfaGlu administered via an IV does not reach the brain. From the outset, therefore, the children's mental development was monitored closely. Everything seemed to be going well. Unfortunately, it now appears that in the long term, the lack of alfaGlu in the central nervous system manifests itself in some children with the classic form in a measurable decline in IQ tests. This is a cause for concern. A solution would have to come from a treatment that is not blocked by the blood-brain barrier. A lot of work is being done on this.

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A LONG ROAD

Despite the positive, sometimes even spectacular results, treatment with alglucosidase alfa is not the end of the road, as doctors quickly realized. During the development phase in the late 1990s, it became apparent that only 5 percent of the administered enzyme ends up in the muscles. To get 2 milligrams into babies (according to current insights), 40 milligrams per kilogram of body weight would have to be administered. For the manufacturer, this amount was a major setback. Initially, 10 or even 5 milligrams had been calculated. However, these low doses appear to have little or no effect. Is the 5 percent that reaches the muscles enough to have a sufficient effect? No one knows. The remaining 95 percent of the drug ends up in the wrong places, such as the liver.

The practitioners therefore have mixed feelings about it. On the one hand, there is euphoria because, for the first time, a hereditary muscle disease can be treated. On the other hand, there are concerns because patients do not always respond well to the drug and sometimes even show severe immune reactions. Ans van der Ploeg[247] puts it this way: "*The road to a cure never ends*, that's what I've learned. Pompe is a good example of this. It remains science. When developing these kinds of complex therapies, you are constantly learning. You learn about Pompe disease and other muscle diseases: what is possible, what works and what doesn't, what happens to a child? We are still in the middle of development, taking one step forward at a time. Children are getting older. Our oldest patient, who has been treated since infancy, is now over twenty. I saw her just last week.

We are still not there for the babies. Today there is a funeral for one of our children, which really hurts me. It confronts you so harshly with your shortcomings. You see the grief of the parents and think: should we be putting them through all this? That is the other side of the coin."

Van der Ploeg believes that enzyme replacement therapy (ERT) has now been proven to work. After approval by the EMA, conditional approval was first granted in the Netherlands. She recalls that the Rotterdam researchers then conducted an efficacy study among late-onset Pompe patients. And that there was still too little data available to properly assess the effects when the results had to be submitted in 2010. She says: "The LOTS study had not yet been published at that time. This led to confusion at the Health Care Insurance Board and its Pharmaceutical Assistance Committee. In the years that followed, we published a lot about ERT and were able to demonstrate positive effects on survival, muscle strength, lung function, walking, fatigue, quality of life, and the degree of limitations in adults. That all came later. But we still cannot cure children and adults of this serious, hereditary condition. So we are certainly not done yet."

Genzyme/Sanofi has since launched a new drug[248], an enzyme that has many more M6P keys and therefore—at least in theory—can enter muscle cells more easily. Remarkable results have been achieved in animal models, but in humans, the high expectations have not yet been met.

Amicus Therapeutics, the company founded in 2005 by John Crowley,[249] the father of two children with Pompe disease, has taken a different approach. The fact that so little enzyme ends up in the muscle cells is largely due to the enthusiasm with which the liver absorbs it from the bloodstream. Amicus has therefore added a second substance to its own variant of alfaGlu, cipaglucosidase alfa: miglustat. This is a so-called 'chaperone', a substance that ensures that the enzyme remains in high concentrations in the blood for longer. Whether this actually works has not yet been proven.

The qualities of both new drugs will have to prove themselves in the longer term. The drugs have been approved by the EMA and FDA, but

neither has orphan drug status in Europe. Nor are they the major breakthrough that doctors and patients are hoping for. They will hopefully improve the uptake of alfaGlu in the muscles, but they will not solve the problems with the central nervous system in children. Like alglucosidase alfa, these enzymes are unable to cross the blood-brain barrier.
Medicines are now being developed that may be able to do this. But there are also disadvantages, says Pim Pijnappel[250], biologist and Pompe researcher at Erasmus MC. He cites as an example a treatment called substrate reduction therapy. This reduces the production of glycogen in the brain. "You could do this by inhibiting the action of glycogen synthase, the enzyme responsible for glycogen production. This would slow down the accumulation of glycogen. The danger is that you go too far and end up with too little glycogen in the cells. That would mean that you treat one muscle disease, Pompe, and cause another muscle disease: glycogen synthase deficiency. That's tricky, but it might be an option after all."
In Pijnappel's view, there is a range of treatment options, but he is most enthusiastic about gene therapy. With this, you would – in theory at least – be done with just one treatment. He says that most interest at the moment is focused on gene therapies using a cold virus, the adeno-associated virus (AAV). The virus acts as a vehicle, or vector, that introduces genetic material into cells. This virus has already been used commercially to treat conditions such as the muscle disease SMA. An AAV gene therapy for Pompe is also in the pipeline. Pijnappel: "This type of therapy can be easily administered through the blood, but it does require a large amount of virus."
He explains that you can direct such an AAV vector to a specific organ, for example the liver. "Then the liver cells will start producing alphaGlu and the liver will become an enzyme factory." The objection is that the virus does not deliver the alphaGlu neatly into the cell nucleus, but leaves it randomly somewhere in the cell. "As a result, when the cell divides, the gene ends up in only one of the two new cells. This slowly dilutes the effect of the gene therapy, and no one dares to predict how quickly this will happen. Maybe after five years, maybe only after twenty. But then it really stops, because a new AAV injection is not possible, as

you have built up antibodies against it after the first treatment."
Another disadvantage is that the alfaGlu produced by the liver does not end up in the central nervous system – a significant drawback for children with the classic infantile form. A third problem is that patients need a large amount of alfaGlu. "It is very difficult to produce enough of it via the liver. So patients are given more and more AAV, with the risk that the liver cells will fail. That has already happened and, unfortunately, some patients have died in those trials."
These are serious objections, and Pijnappel therefore prefers an alternative: gene therapy based on lentiviruses. The big advantage, he believes, is that they nestle in the genetic material of the cell nucleus. As a result, when the cell divides, the material ends up in each of the new cells, not just one. For this reason, there is no dilution of the effect of gene therapy, as is the case with AAV.
Pijnappel: "First, you take stem cells from the patient's bone marrow. Then, using the lentivirus, you introduce the gene for alphaGlu into those cells. We have modified that gene so that the alphaGlu that is produced is better absorbed into the muscle cells. The lentivirus ensures that the gene is incorporated into the genetic material of the stem cells. Once that has been achieved, the cells are returned to the patient. There is no risk of immune reactions, because they are your own cells. From the stem cells, they will spread throughout the body – including to the brain – and release the alphaGlu to other cells, which can then absorb it. In this way, the patient will produce their own enzyme for the rest of their life. It is a permanent change in the genetic material that cannot be reversed. The patient will then no longer need enzyme infusions, which would be a huge advantage."
This method is not as new as it seems, Pijnappel qualifies. "In the clinic, bone marrow transplants have been used for other conditions for years. That works fine. The only difference, of course, is the virus that has to cause the genetic change."
Incidentally, gene therapy with lentiviruses does carry a risk, Pijnappel warns. "Small, admittedly, but still a risk. We have no control over exactly where the virus embeds itself in the DNA. It can end up in a risky place and damage the genetic material there. This can lead to the develop-

He and his colleagues want to develop the therapy as far as possible in-house.

ment of cancer. This risk also exists with AA viruses, albeit to an even lesser extent." Preparations for a study in humans have now begun. The research is supported by the Princess Beatrix Muscle Foundation, among others. An organization has been set up within Erasmus MC to facilitate further development and market approval. Pijnappel would prefer to start tomorrow, but there is still a lot to be done before that can happen.
What is striking is that Erasmus MC has not enlisted the help of a partner from the pharmaceutical industry for this study. The reason for this lies in past experiences, explains Pijnappel. "We see that these expensive therapies for rare diseases go wrong because of the sky-high prices that are charged. There is a fierce battle with the national authorities to get the drug included in the insurance package."
That is why he and his colleagues want to develop the therapy in-house as far as possible. "Firstly, to try to make it available to patients at an acceptable and reasonable price, without a profit motive. Secondly, to find out exactly what it costs. The industry is not providing any clarity on this. This will give us a blueprint for therapy development according to a non-commercial model. We could then apply this to other, similar diseases. We strongly believe in this."
Erasmus MC is not the only organization working on gene therapy for Pompe disease. There are now also pharmaceutical companies that have set their sights on it. However, the University of Rotterdam is the only party that wants to market the therapy on a non-profit basis.

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NEW OBSTACLES

Since the controversial meeting of the Advisory Committee on Health Care Financing on September 21, 2012, the debate about the high prices of orphan drugs has not subsided. Not only in the Netherlands, but also abroad. In 2013, Myozyme was reimbursed in most Western countries, with Australia being the major exception. There, patients had to wait until 2015 before the government made a positive reimbursement decision. Since then, the flow of new orphan drugs has swelled. In some cases, their prices have even risen further. In early 2023, then-Minister Ernst Kuipers decided not to reimburse[251] a successful gene therapy for a metabolic disease, similar to the treatment being developed in Rotterdam for Pompe disease. The manufacturer asked for just under €3 million for a treatment. In January, the drug was approved after agreement was reached with the manufacturer on the conditions and price.

Although orphan drugs are by no means the largest expense item in the healthcare budget, it is becoming increasingly difficult to get a drug into the safe haven of the insured basic package.

In the *Monitor Orphan Drugs in Practice 2021*[252], the Zorginstituut, formerly the College voor zorgverzekeringen (Health Insurance Board), notes an increase in the number of new orphan drugs. At that time, there were no fewer than 67 on the radar. "This is a positive development for people with a rare condition," the report states, "but in addition to patients with a rare condition, the Healthcare Institute must also take into account the interests of premium payers and patients with other conditions."

That sounds ominous for people with a rare disease, and it is: "There is [...] displacement of other care, which leads to a loss of health for the entire population. The Health Care Institute therefore considers it important that these resources are used responsibly and that consideration is given to how cost-effectiveness can be optimized in order to limit the displacement of other care." Yes, but no matter how much you optimize, orphan drugs will never be cheap.

According to Marcel Timmen[253], former director of the Dutch Muscular Diseases Association, the problems stem in part from conflicting cultures. "A drug is manufactured in the commercial world and sold in a public system. In other words, a commercial party operating in the public domain, which is an unfortunate combination." Timmen believes this leads to mutual distrust because people operate from different frameworks.

A recurring point of contention is the industry's refusal to disclose the costs and price structure. Timmen: "Companies also use different pricing models; I have discussed this with various manufacturers. One starts with the investments and calculates a percentage for the capital costs: if I had set aside my money, how much would it have yielded? The other starts with a certain profit target and then calculates backwards."

Timmen explains that the Dutch government is considering a 'cost-plus model'. "This would require manufacturers to demonstrate exactly what the costs are, but they are unable to do so—it is extremely complicated to determine. A profit margin, a distribution surcharge, and a few other items would then have to be added to that amount. I do not see that happening. The criterion for manufacturers is an affordable price. The starting point is not what it cost, but what people are willing to pay."

There are all kinds of ideas about pricing within the industry, even if they are not always easy to defend in public debate. Hans Schikan[254] worked as European manager at Genzyme between 2004 and 2009. He then moved to Prosensa, which had a drug for the serious hereditary muscle disease Duchenne in the pipeline. During the coronavirus pandemic, he worked for the Dutch government as a vaccine envoy.

He recalls an incident during an international medical conference in 2004. "Someone gave a positive presentation on the clinical findings with alglucosidase alfa. A doctor stood up and said, 'Yes, but this drug costs $300,000. That's unethical.' I was responsible for European rare disease products, newly appointed, and I thought: should I now defend our story? I didn't do it. Afterwards, I went to David Meeker, who was head of our entire rare disease organization at the time. I told him how uncomfortable I had felt. I should have stood up, engaged in dialogue, explained how we arrived at that price level, but I didn't dare. It turned out I wasn't the only employee who felt that way. We then gave all our people around the world a toolbox with instructions on how to engage in dialogue about rare diseases and the price of medicines in a transparent manner. You can talk about solidarity, but at the same time, the company must also be able to invest in other rare diseases. Everyone was very happy with that toolbox."

A pharmaceutical company may market medicines and thereby contribute to health and well-being, but a necessary condition for its survival remains profit, or a revenue model that offers the prospect of profit. Schikan cites research into new antibiotics that can combat resistant bacteria as an example. "A company is not readily interested in developing such drugs because doctors are unlikely to prescribe them. They have to remain on the shelf until someone comes along with a bacterium that is resistant to all existing antibiotics. Such a new drug will therefore be used very little, and as a company you earn very little from it. That is why efforts in the field of research and development have declined dramatically."

According to Schikan, other payment models could be considered. "For example, a lump sum could be paid for a new antibiotic, in combination with a subscription structure, regardless of whether or not that drug is used frequently. This could make it attractive again for a pharmaceutical company to invest in its development."

The reimbursement for a new gene therapy is also complicated, Schikan argues. "If you treat a patient for life at a cost of €300,000 per year, that's a lot of money over a long period of time. If you replace that with a single injection – which is possible with gene therapy – and you calculate it

on a one-to-one basis, you might end up with a cost of €8 to €10 million. I have yet to see an injection being reimbursed at €10 million. No way."

Here too, Schikan believes that new models may offer a solution. "For example, an insurer could pay the manufacturer an annual fee for as long as the treatment is effective. This would motivate companies to invest in these types of therapies. This is also being considered in the Netherlands. Think of the government's so-called FAST initiative[255]: *Future, Affordable and Sustainable Therapy development*. Among other things, this initiative is looking at gene and cell therapies, which generally come with a higher price tag."

Cor Oosterwijk[256] is director of the VSOP, the patient umbrella organization for rare and genetic disorders, and, following the departure of Cees Smit, the patient representative on the Healthcare Institute's Package Advisory Committee. He points out that the high price of orphan drugs, and gene therapy in particular, hinders patient access to them. In his view, society itself must take the initiative to bring these drugs to market if necessary. "I do believe that this is legally difficult, but we should try."

Oosterwijk realizes that there are still more obstacles to overcome. "You mustn't forget that you may be able to develop, produce, and distribute a drug for rare diseases yourself, but in most cases you also need a global logistics network. That has to be set up first if you want to turn the current pharmaceutical model into a more social model."

A lot has changed since the reimbursement decision for Myozyme. One important change is that, after approval by the EMA, a new expensive drug ends up 'in the lock' at the Dutch Healthcare Institute. This means that it must first go through the entire assessment process there. The Ministry of Health, Welfare and Sport must then reach agreement with the manufacturer on the price, and only when that has been done can it be admitted to the insured package and reach the patient. That process now takes two years. Due to the growing influx of expensive medicines, that waiting time will only increase, and the experts at the Healthcare Institute are already overwhelmed with work.

Timmen is not reassured. "What worries me is that at some point, the Zorginstituut will decide to offload some of its assessments to the health

insurers. Let them do the testing. The Healthcare Institute has a formal procedure in place for lodging objections. The assessment is transparent and the reports are public. With health insurers, you would lose that. They are not obliged to be transparent about their decision-making."
If things go in that direction, it will become much more difficult for patients to have a say, Timmen believes. "In the assessment process, we want to be able to show what really matters to the patient. More energy or being able to eat independently thanks to treatment is not considered that interesting. More important is whether you live longer, can walk again, that kind of thing. In our discussions with the Healthcare Institute, we try to make it clear that for someone with a muscle disease, maintaining arm and hand function is actually much more important for their independence than being able to continue walking. And having more energy makes a difference to someone's independence, to their ability to organize their own day, to do things and be active. Or to be able to scratch your nose when it itches. That kind of thing is not just in your head. We still have a long way to go."

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MARYZE

NYNKE DANCES

On September 21, 2012, I told the Package Advisory Committee about my experiences with alglucosidase alfa. On March 8, 2024, Nynke Mentink had the honor of attending the ACP meeting on Genzyme's new drug for Pompe disease: Nexviadyme. Like me, Nynke was eight years old when she was diagnosed. That was in March 2010. “I'm doing fine,” she says when I speak to her and her mother Liesbeth via Zoom. “I don't have any problems. Except for the IV, which sometimes gets in the way when I have to make appointments with teachers. They're not always very flexible.”
Liesbeth explains how her daughter's disease was discovered. “She was on the thin side as a child, and in second grade, the school doctor noticed that her weight was below the expected growth curve. We were told to just wait and see. But her weight continued to decline, and my maternal instinct told me that something was wrong.”
The family doctor found elevated liver values in a blood test and referred Nynke to the hospital in Ede. “There, they also saw that something was wrong, but they couldn't put their finger on it.” Nynke went to the Wilhelmina Children's Hospital in Utrecht, where they soon suspected a muscle disease. This led them to the Spieren voor Spieren Children's Center in September 2009. "The doctor, Ludo van der Pol, noticed an abnormality in the knee reflex and in the electromyogram,

a test in which they insert needles into your muscles and then send a small electric current through them. Very painful. I saw a strange pattern on the screen. Not that I know anything about it, it was more of a feeling. They were also going to do a blood test for alpha-glucosidase. I looked it up on the internet and then I was sure: Nynke has Pompe disease. Not long after, this was confirmed by a DNA test and Nynke was referred to Erasmus MC."

So the process went much more smoothly and quickly for Nynke than it did for me at the time, I note, even though I had much clearer symptoms. Progress has been made. “What were Nynke's other symptoms?” I ask. “Nothing particularly unusual, really,” says Liesbeth, "but when you look back, you see possible connections. As a baby, for example, she never drank her bottle in one go. After waiting half an hour, she managed it. Her ballet teacher said that she had more difficulty with certain exercises than the other children. That she lacked a certain flexibility. Later, when we went cycling, she quickly caught up with her father or me because she was tired and wanted to be pushed. Her older sister never asked for that."

See, I think, that bike again. And as a baby, she also had trouble finishing her bottle. I hear the echo of my mother's stories. But when Nynke is diagnosed, it is 2010 and the world looks very different: treatment is available. In July, she receives her first infusion. There is improvement, they say at the hospital, and her ballet teacher also sees that she is making progress.

However, there is a threat of a setback when the Health Insurance Board appears to be coming up with a negative recommendation on alglucosidase alfa. Nynke also goes to Diemen on September 21, 2012, to explain what Pompe therapy means to her. She is interviewed for the NOS news—another parallel with my own history. When asked what would happen if she were to stop receiving the drug, she replies matter-of-factly: “Then I'll die.”

In 2013, following a request from the VSN, she sends a letter to the members of the House of Representatives:

Veenendaal, July 3, 2013

My name is Nynke Mentink (eleven years old) and next year I will be in the eighth grade of elementary school. When I was in the fourth grade, the doctors discovered that I have Pompe disease. Fortunately, I received my first infusion of alglucosidase alfa during the summer vacation.
The medication works fantastically for me. It means I can take part in gym class, do ballet, and take pointe lessons. On June 22, I took part in a dance day at the National Ballet! It was so much fun!
This year, I also participated in the 10-kilometer evening walking event and went on a church camp weekend the next day. My mother used to push me when we went cycling. Now I often cycle faster than my mother and she can't keep up with me.
Now a decision has to be made about whether my medication will still be reimbursed next year. Without medication, I will become weaker and weaker. I hope that next year, when we go on camp with grade eight, I will be able to ride my own bike without pedal assistance.

Ten years later, she is once again speaking on behalf of patients at an ACP meeting, this time to advocate for the reimbursement of a new Pompe medication. It feels like I have passed the baton.

Nynke tells me via Zoom that she is studying Garden and Landscape Design in Velp. She finds it very interesting: the planning, the strategic design, such as the *Room for the River* project. Do I know it? Apart from the IV, once every two weeks on Fridays, the disease hardly plays a role in her life. Most people around her don't even know she has a muscle disease. “I recently told a boy,” she says. “We've known each other for three years. He was surprised because he had no idea.”

She has been on vacation twice with Transavia's Peter Pan Club, which was set up especially for young people with serious illnesses. She has met people there with various muscle diseases. They still talk to each other regularly. “When you're together, you don't have to explain anything about your illness and so on. It makes me realize how lucky I am. It's a blessing in disguise.”

In 2019, she was asked if she wanted to participate in *Free to move*. This is a large, annual dance performance by the Netherlands' most famous dance companies to raise money for research into muscle diseases. It was organized by the Holland Dance Festival together with the Princess Beatrix Muscle Fund. Scapino, the National Ballet, Introdans, and the Nederlands Dans Theater, among others, participated. Nynke proudly tells me: "I was going to be 'the face' of that year. Of course, I said yes, and afterwards I wanted to have my picture taken with Jan Kooijman. I think he's so cool. They made a film in which I talk about my muscle disease and join in the warm-up at the Nederlands Dans Theater. But then COVID-19 hit and the performances were canceled one after the other. When I went to college, I stopped ballet. It was too impractical with traveling. I made the switch to modern dance. More on the ground, more emotion, expression. I really love dancing."

When I ask Nynke how she sees her future, she replies: "Like everyone else, I think. I don't look twenty years ahead, there's no point. But I'm positive. I hope that gene therapy will also become available to me. That would be great. Then I could easily travel abroad. It's possible with the IV, but you have to arrange so much."

Then she gets up, leans forward toward the camera, and waves to me. She has to go. She has an appointment.

LIST OF NAMES

Below are the names of the people who play a key role in this story. Most of them were interviewed for this book, some on several occasions. The roles listed relate to the period in which the story is set. It is quite possible that some of these people now hold a different roles or that those roles are now held by others.

Dutch Researchers

- Nadine van der Beek – physician-researcher Erasmus MC – November 1, 2023
- Hans Büller – Head of Pediatrics Sophia Kinderziekenhuis – December 12, 2022
- Agnes Bijvoet – researcher Erasmus Universiteit – February 2, 2022
- John Fernandes – researcher RU Groningen, deceased –
- Lies Hoefsloot – researcher Erasmus MC, she isolated the AlfaGluy gen
- Hannerieke van den Hout – physician-researcher Erasmus MC – December 13, 2022
- Marian Kroos – researcher, laboratory specialist, Erasmus MC –
- Christa Loonen – physician-researcher Erasmus MC, deceased
- Pim Pijnappel – researcher Erasmus Universiteit – August 16, 2023
- Arnold Reuser – researcher Erasmus Universiteit – January 19, 2022
- Ans van der Ploeg – physician-researcher Erasmus MC – June 6, 2022/ June 21, 2002
- Martin Verbeet – researcher Universiteit Leiden – March 9, 2022
- John Wokke – physician-researcher UMC Utrecht, deceased

Researchers abroad

- Roscoe Brady – physician-researcher, developed therapy Gaucher, deceased
- Y.T. Chen (TW/US) – physician-researcher Duke University – September 26, 2022
- Christian De Duve (BE) – discovered the lysosome, deceased
- Johan Van Hove (BE – physician-researcher Duke University – June 27, 2022
- Priya Kishnani (IN/US) ¬–¬ physician-researcher Duke University – August 18, 2022
- Nina Raben (US) – researcher NIH – December 20, 2023

Patients, VSN and IPA

- Johan Bakker (NL) – patient, Chair working group Pompe VSN – July 5, 2023
- Robin Berman (US) – got her son in the Gaucher trial – January 25, 2022/ February 3, 2022/February 21, 2022
- Ria Broekgaarden (NL) – member board IPA, staff member VSN
- Kevin O'Donnel (UK) – parent, member board IPA
- Randall House (US) – parent, founder and Chair IPA
- Tiffany House (US) – current Chair IPA, patient
- Marylyn House (US) – parent, member board AMDA
- Hinke Kleiker (NL) – patient – July 14, 2023
- Tanneke van der Linde (NL) – parent, Chair working group Pompe VSN – July 27, 2022
- Liesbeth Mentink (NL) – parent, Chair working group Pompe VSN – July 24, 2023
- Nynke Mentink (NL) ¬– patient – July 24, 2023
- Abbey Meyers (US) – parent, took initiative for law orphan drugs US
- Cor Oosterwijk (NL) – Director VSOP, member ACP, parent – November 15, 2023
- Ysbrand Poortman (NL) – Director VSN and VSOP, parent – February 28, 2022
- Marcel Timmen (NL) – Director VSN – July 27, 2023/November 16, 2023

Pharming

- George Hersbach (NL) – President and CEO – March 11, 2022
- Gerben Moolhuizen (NL) – Director Product Development – February 18, 2022
- Rein Strijker (NL) – Chief Com. and Fin. Officer Pharming – February 14, 2022
- Gerard van Beynum (NL) – Vice President – February 17, 2022
- Herman de Boer (NL) – Founder and CEO – March 24, 2022
- Paul Krimpenfort (NL) – Head Embryology Department –November 28, 2022
- Michael Mellink (NL) – Representative Cephalon – March 14, 2022
- Otto Postma (NL) ¬– co founder
- Sijmen de Vries (NL) – CEO – August 9, 2023

Genzyme

- Jaap de Boer (NL) – Medical Director – December 28, 2022
- John Crowley MBA (US) – parent, Genzyme, CEO Novazyme, Amicus – December 18, 2023
- Jan van Heek MBA (NL/US) – Senior Vice President – October 4, 2022
- Carlo Incerti (IT) – Senior Vice President – October 11, 2022
- Bert de Jong (NL) – General Manager Benelux – August 15, 2022
- Luc Kupers (BE) – Dir. Science and Communication – July 25, 2022
- Gisela Linthorst (NL) – Project Home Treatment – January 24, 2023
- Khazal Paradis (FR) – Principal Clinical Investigator – April 4, 2022
- Hans Schikan (NL) – Vice President, LSD Europe & Director Genzyme Nederland – April 7, 2022
- Henk Schuring (NL) – Group Vice President – November 12, 2022/ July 7, 2023
- Erik Tambuyzer (BE) – Senior Vice President – September 26, 2022/ March 14, 2023
- Henri Termeer (NL/US) – President and CEO, deceased

Law Orphan Drugs

- Jolanda Huizer (NL) – Secretary to the Orphan Medicines Steering Group – August 8, 2022
- Frits Lekkerkerker (NL) – menber CHMP, Chair CBG
- Harrie Seeverens (NL) – Policy Officer Ministry VWS – November 14, 2022
- Sonja van Weely (NL) – Secretary to the Orphan Medicines Steering Group – August 8, 2022

College voor zorgverzekeringen CvZ (Zorginstituut Nederland, ZIN)

- Bert Boer (NL) – member Board of Directors, Chair ACP
- Linda Daniels-van Saase (NL) – Manager Medicines – June 30, 2023
- Arnold Moerkamp (NL) – Chair Board of Directors
- Hedi Schelleman (NL) – researcher, advisor – July 12, 2023
- Cees Smit (NL) – patient, member ACP – June 13, 2022/August 14, 2023
- Jacqueline Zwaap (NL) – Secretary ACP CvZ – July 12, 2023

TIMELINE DEVELOPMENT THERAPY

1930	Dec	Joannes Pompe is investigating the case of a baby who died from an as yet unknown illness
1932	Jan	First publication on Pompe disease
1955		Christian De Duve discovers lysosomes
1963		Henri-Géry Hers discovers missing enzyme in Pompe disease
1964		First unsuccessful attempt with an enzyme infusion
1967		Establishment of VSN, e.g. for Pompe patients
1977	July	Arnold Reuser's PhD thesis on lysosomal storage disorders
1981		Genzyme was founded
1983	Jan	The Orphan Drug Act comes into force in the US
1983		Roscoe Brady is conducting studies with Gaucher patients
1985	Oct	Genzyme invests in Gaucher disease drug
1985	Nov	Arnold Reuser and Ans van der Ploeg are contacting
the		VSN to report on the progress of the Research
1988	June	Pharming was founded
1989	July	PhD thesis by Ans van der Ploeg on enzyme replacement therapy
1990		Bull Herman and Pharming are causing a sensation
1991		Genzyme launches Gaucher disease treatment Ceredase)
1991	Feb	Initial contact between Duke University and Erasmus MC
1991	Apr	Long Beach workshop featuring among others Reuser, Y. T. Chen and Brady
1991	May	Death of Wil de Geus
1992		Van der Ploeg, Reuser and Martin Verbeet are launching a study into the production of the Pompe protein
1994		Genzyme is launching Cerezyme, produced using CHO cells
1994		Pharming is set to develop a treatment for Pompe disease
1995		Randall House founds AMDA
1995	Dec	Publication on alfaGlu derived from CHO cells by, among others, Reuser and Van der Ploeg
1996	Jan	Chen publishes a paper on enzyme production for Pompe disease in CHO cells
1996	June	Scientific Conference AMDA
1996	Nov	Pharming press conference in Geel: medicine is on the way
1997	Jan	Meet up House/VSN
1997	Apr	Meeting between Pompe and House at VSN
1997	June	Second AMDA Conference
1997	July	Pharming-VSN meeting on a global approach
1998	Feb	Duke publishes a paper on Pompe quails
1998	Mar	Intention to establish the IPA
1998	Mar	Parliamentary debate on cloning and a possible ban on it
1998	July	Pharming raises 123 million guilders ahead of its IPO in Europe
1998	Aug	John Crowley visits Pharming
1998	Oct	Announcement of the Pharming and Genzyme joint venture
1999	Jan	Trial begins with four babies in Rotterdam
1999	June	Announcement of initial positive results from the Erasmus trial
1999	June	Chen launches first clinical trial
1999	July	IPA Conference in Naarden
1999	Nov	Crowley launches his own organisation
2000	Jan	European Orphan Medicines Regulation comes into force
2000		Genzyme launches its own CHO cell line for Pompe disease
2000	Apr	Crowley joins Novazyme
2000	Apr	Genzyme/Pharming acquire rights Synpac

2000	Apr	Genzyme and Pharming are switching to CHO
2000	Apr	Hearing of the Advertising Code Committee regarding the Proefdiervrij campaign
2000	July	Publication in The Lancet by Hannerieke van den Hout on a trial involving four babies: it works.
2001	Apr	Crowley's presentation at Genzyme
2001	Aug	Genzyme and Novazyme sign a merger agreement
2001	Aug	Pharming applies for a moratorium on payments
2001	Sep	Crowley joins Genzyme
2001	Sep	Genzyme announces acquisition of part of Pharming
2001	Oct	Genzyme acquires factory in Geel
2002	Jan	The mother of all experiments: the choice falls on Genzyme's enzyme
2002	Apr	Glass vials containing Pharming enzyme are breaking, leading to production problems and resulting in shortages
2003	Mar	Genzyme announces two trials involving up to six to ten children
2005	Sep	Opening of the Genzyme plant in Geel
2005	Dec	CHMP/EMA meeting
2006	Mar	EC approval, marketing authorisation, broad-spectrum label
2009	Apr	Start of production of alpha-glucosidase in Geel
2009	June	Outbreak at Allston factory, production halted
2011	Apr	Sanofi acquires Genzyme
2011	Dec	Erasmus responds to the CVZ's draft advice
2012	Sep	ACP/CvZ meeting
2013	Oct	Reimbursement for Myozyme

SOURCES

ARCHIVES

In compiling this book, use was made of the extensive archives of the VSN and the IPA. In addition, the personal archive of Maryze Schoneveld van der Linde was consulted. Frequent use was also made of publications and archives available online, such as those of the EMA, FDA, ZIN, government departments, parliament, the media, etc. Some of these sources are listed in the notes.

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the milk of transgenic rabbits. Rotterdam 2003.
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Pompe, J., *Cardiomegalia glycogenica*. Nijmegen, 1936.
Reuser, A., et al. *Pompe disease*. Bremen, 2021. 3de druk.
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Thanks in part to all these people, we have been able to reconstruct the Pompe story and correct errors.

Maryze Schoneveld van der Linde
Erik van Uden

FOOTNOTES

[1] Kevin O'Donnell has been maintaining an informative and accessible blog for years. These paragraphs about Calum are based on that blog: pompestory.blogspot.com (translation by EvU).

[2] Interview O'Donnell.

[3] Estimates vary widely. Some sources even cite a figure of 10,000

[4] nhg.org/thema/zeldzame-ziekten

[5] Ausems, M., Glycogen storage disease type II: from molecular genetics to clinical practice. Dissertation, Utrecht, 1999. The situation she describes has since improved significantly, and if Pompe disease is suspected, a diagnosis can be made quickly.

[6] In its early years, the organization was called: Muscular Dystrophy Association of the Netherlands.

[7] The story of Poortman is partially excerpted from the VSN's 2016 annual report.

[8] medischcontact.nl/nieuws/laatste-nieuws/artikel/dreiging-nieuwe-polio-epidemie-reeel

[9] In addition to disease-specific funds, there is now also a fund for children with muscular disorders: Spieren voor Spieren.

[10] Porter, R., Geschiedenis van de Geneeskunde, Gent, 2010.

[11] diabetesfonds.nl/over-diabetes/diabetes-in-het-algemeen/geschiedenis-van-diabetes

[12] In: Pompe, 1936, pp. 9–31.

[13] Snapper et al., Bull. Et Mém, de la Soc. Méd. Des Hôp. De Paris. LII 1928. Quoted as such by Pompe in his dissertation in 1936.

[14] Von Gierke E., Hepatonephromegalia Glykogenica: Glykogenspeicherkrankheit der Leber und Niere. Beitr z Path Anat uz Allg Path. 1929;82:497-513.

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[16] erfelijkheid.nl/ziektes/glycogeenstapelingsziektes

[17] Researchers in Germany also published similar findings. See: Reuser, 2021, p. 17.

[18] Humphreys and Kato, *American Journal of Pathology*, 10, 489. 1934.

[19] In his blog, Kevin O'Donnell provides more details about Pompe's life: pompestory.blogspot.com/2009/04/joannes-cassianus-pompe-1901-1945.html

[20] wikiwand.com/nl/Gerty_Cori

[21] About the Cori's research: acs.org/education/whatischemistry/landmarks/carbohydratemetabolism.html

[22] See sources: Reuser 2021, p. 18.

[23] For more on the tragic life of Alex Novikoff, see: wikipedia.org/wiki/Alex_B._Novikoff

[24] See sources: Reuser 2021, p. 19.

[25] See sources: Reuser, 2021, p. 17. Hers also identified a deficiency of acid maltase in Pompe disease, which led to the widespread use of the term *acid maltase deficiency* (AMD). However, this terminology is technically incorrect and is now only used in the name of the American patient organization, the Acid Maltase Deficiency Association (AMDA).

[26] See sources: Reuser 2012. Hij schetst de ontwikkeling van de naamgeving: p. 18.

[27] See the text box titled Explained: Types of Pompe Disease.

[28] See sources: Reuser, 2021, p. 106.

[29] For the history of ERT, see the following sources: Reuser 2021, p. 105.

[30] Hobbs, J.R., Humble, J.G., Anderson, I.M., James, D.C.O., The elective treatment of graft-versus-host disease following a bone marrow graft from a father to a son with severe combined immunodeficiency. 1976 Postgraduate Medical Journal 52, (suppl.5) 90–94.

[31] Christa Loonen in an informational brochure for patients (VSN archives). She rightly notes that this number is likely to be higher, as not all patients have been diagnosed.

[32] Arnold Reuser in an email.

[33] Smit GPA, et al., The dietary treatment of children with type I glycogen storage disease with slow-release carbohydrate, *Pediatr Res*, 1984;18:879-81.

[34] Information about Fernandes is based on: ntvg.nl/artikelen/memoriam-prof-drjfernandes-1921-2006 and email correspondence with A. Reuser.

[35] Chen YT, et al., Corn starch therapy in type I glycogen storage disease. N Engl J Med 1984; 310:171-5.

[36] Oude Elferink RP, et al., Isolation and characterization of a precursor form of lysosomal alpha-glucosidase from human urine. In: JM.Eur J Biochem. 1984 Mar 15;139(3):489-95. doi: 10.1111/j.1432-1033.1984.tb08032.x.PMID: 6365553.

[37] wikipedia.org/wiki/Hans_Galjaard

[38] nrc.nl/nieuws/1995/01/07/klinisch-geneticus-hans-galjaard-de-voorspellen-de-7252297-a469509

[39] See sources: Reuser 1977.

[40] The term ‘adult form’ is somewhat misleading. This is because it also includes children who do exhibit muscle weakness but whose hearts are not affected. See the Explained-box.

[41] Interview Strijker.

[42] Interview Raben.

[43] See sources: Ploeg, 1989.

[44] The letter is located in the VSN Archives.

[45] The story of Roscoe, Gaucher, and the founding of Genzyme is primarily based on the following sources: Geraghty, 2022; Hawkins, 2021; and Meyers, 2016. Regarding the collaboration between Rotterdam, Amsterdam, and the NIH: an email from A. Reuser, October 26, 2022.

[46] Geraghty, 2022, p. 16.

[47] Brady RO, et al., Metabolism of glucocerebrosidase. II. Evidence of an enzymatic deficiency in Gaucher's disease. In: Biochem Biophys Res Commun 1965; 18: 221–225.

[48] Hawkins, 2021, p. 3.

[49] gaucherdisease.org/about-national-gaucher-foundation/our-team/berman/

[50] In: Geraghty, 2022, p. 36 en Hawkins, 2021, pp. 52-53.

[51] In: Smit, 2012, pp. 71 e.v.

[52] Interview Tambuyzer, 14-03-2023.

[53] Interview De Boer and NRC, 27-11-1999: ‘Mengele heeft ons geweten gescherpt’.

[54] Genesis 1:28.

[55] PBTS: grants for programmatic, business-oriented technology promotion.

[56] Quote from: Karel Glastra van Loon et al., 1995 (Sources). Postma declined to be interviewed for this book.

[57] Interview Van Beynum.

[58] For more on the story of Herman the bull, see: nl.wikipedia.org/wiki/Herman_

[59] The public debate about Herman is well documented in the following sources: Glastra van Loon, 1995.

[60] joswassink.nl/inzicht/?p=318

[61] Quote from *Oogst*, 18-12-1998, p. 54.

[62] Quote from *Oogst*, 18-12-1998, p. 65.

[63] wikipedia.org/wiki/Barry_Horne_(activist)

[64] In: NRC, 24-07-1999, p. 2.

[65] An activist group founded in Leiden in 1997 with a broad left-wing social agenda.

[66] In sources: Glastra van Loon, 1995, p. 158.

[67] See also sources: Verhoog, 1990.

[68] This has been Nutricia's new name since 1997.

[69] Pharming, Turning milk into medicine; Ten years Pharming, 1988 -1998. Leiden, 1998. p. 19.

[70] Mahmut Erciyas, ‘Carina Thuijs en het bloedbad van Sivas’, sanalmuze.madimak.org/sanalmuze

[71] Hoefsloot L.H. et al., Characterization of the human lysosomal alpha-glucosidase gene. In: Biochem J. 1990 Dec 1;272(2):493-7.

[72] Email Reuser.

[73] See sources: Bijvoet, 1999.

[74] Interview Strijker, 2022.

[75] According to Rein Strijker, Pharming had been considering the idea of acquiring GTC or merging with it for some time.

[76] Interview Van Beynum, 2022.

[77] Interview Moolhuizen, 2022.

[78] researchgate.net/scientific-contributions/L-M-Houdebine-39310663

[79] N Engl J Med. 1986 Feb 6;314(6):385. doi: 10.1056/nejm198602063140611.*Bone marrow transplantation for glycogen storage disease type II (Pompé's disease)*, J G Watson, D Gardner-Medwin, M E Goldfinch, A D Pearson PMID: 3511378 DOI: 10.1056/nejm198602063140611.

[80] N Engl J Med. 1986 Jul 3;315(1):65-6. doi: 10.1056/NEJM198607033150115. *Bone marrow transplantation for Pompe's disease*. P M Hoogerbrugge, G Wagemaker, D W van Bekkum, A J Reuser, A T vd PloegPMID: 3086726 DOI: 10.1056/NEJM-198607033150115Correspondence vol. 315 no. 1, JUL 03, 1986Archive.

[81] unitedpompe.com/the-myozyme-miracle/

[82] Expression and routeing of human lysosomal alpha-glucosidase in transiently transfected mammalian cells. Hoefsloot LH, Willemsen R, Kroos MA, Hoogeveen-Westerveld M, Hermans MM, Van der Ploeg AT, Oostra BA, Reuser AJ. In: Biochem J. 1990 Dec 1;272(2):485-92. doi: 10.1042/bj2720485. PMID: 2268275-Intravenous administration of phosphorylated acid alpha-glucosidase leads to uptake

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[83] In English: Chinese Hamster Ovary cells, or CHO-cellen

[84] In an interview, Johan Van Hove states that he only became aware of Hopwood's work on Pompe later on.

[85] Fuller M., et al., Isolation and characterisation of a recombinant, precursor form of lysosomal acid alpha-glucosidase. In: Eur J Biochem 1995 Dec 15;234(3):903-9.

[86] Hurler syndrome is the most severe form of mucopolysaccharidosis type 1, abbreviated as MPS I, and, like Pompe disease, is a storage disease. This disease also has a fatal outcome. Emil Kakkis successfully developed an enzyme therapy, which was to be marketed by Genzyme. See sources: Geraghty, 2022, p. 70.

[87] It is now known that Pompe disease occurs naturally in several animal species, including some dog breeds.

[88] Kikuchi T. et al., Clinical and Metabolic Correction of Pompe Disease by Enzyme Therapy in Acid
Maltase–deficient Quail In: J. Clin. Invest., The American Society for Clinical Investigation, Inc., Volume 101, Number 4, February 1998, 827–833.

[89] Boehringer Ingelheim is a contract manufacturing facility, a company that manufactures products on behalf of third parties.

[90] See sources: Geraghty, 2022.

[91] Based in part on: see sources, Meyers, 2016, and an interview with Tambuyzer on March 14, 2023.

[92] See sources: Meyers, 2016.

[93] wikipedia.org/wiki/Quincy,_M.E.

[94] wikipedia.org/wiki/Orphan_Drug_Act_of_1983

[95] Interview Tambuyzer, 26-09-2022.

[96] Various definitions are used for an ultra-rare disease, such as a disease that affects 1 in 50.000 people. According to that definition, Pompe disease is also an ultra-rare disease.

[97] Conference brochure, VSN Archives.

[98] Interview Raben, 2023.

[99] Several interviewees have confirmed this, including Reuser, Moolhuizen, and Schuring.

[100] A summary of: pompestory.blogspot.com/search/label/AGSD-UK

[101] The following paragraphs are based on archival documents from the VSN.

[102] According to the association's figures, 29 adults with Pompe disease and 11 children were registered.

[103] That test was not conducted by Erasmus MC.

[104] Report in English by Gezinus Wolters, posted on GSDNet on March 22, 1998.

[105] In the VSN archives.

[106] De Volkskrant, March 12, 1998, and Parliamentary Document 27 428: Policy Paper on Biotechnology. Memorandum 2 2000/2001.

[107] Based on interviews with Kupers (2022) and Strijker (2022).

[108] De Volkskrant, 07-07-1998.

[109] See sources, Anand, 2010, pp. 56 e.v.

[110] Interview Crowley, 2023.

[111] sec.gov/Archives/edgar/data/732485/000091205702012898/a2073695z10-k.htm

[112] Rein Strijker stated that Genzyme was not aware of Cephalon's offer.

[113] keionline.org/wp-content/uploads/Replagal_Fabrazyme_Timeline.pdf

[114] Until 2004, the EMA was known as the EMEA, the European Medicines Evaluation Agency.

[115] ec.europa.eu/health/documents/community-register/html/reg_od_nact.htm?sort=a

[116] J. Geraghty, Inside the orphan drug revolution, pp. 42-43.

[117] J. Geraghty, Inside the orphan drug revolution, p. 43.

[118] As reported in, among others: Gelders Dagblad, November 7, 1998.

[119] Pharming, Turning milk into medicine; Ten years Pharming, 1988 -1998. Leiden, 1998.

[120] Several interviewees emphasized the importance of follow-up studies, including Van der Ploeg (Erasmus), Schuring (Genzyme), Schikan (Genzyme), and Van den Hout (Erasmus).

[121] Van den Hout, H.M.P. et al., The Natural Course of Infantile Pompe's Disease: 20 Original Cases Compared With 133 Cases From the Literature. In: PEDIATRICS Vol. 112 No. 2 August 2003.

[122] In addition to interviews, the sections on the trials in Rotterdam draw on the article by Van den Hout H.M.P. et al., 'Recombinant human alpha-glucosidase from rabbit milk in Pompe patients,' *The Lancet* 2000; 356 (9227): 397–398.

[123] Interview Schikan, 2022.

[124] amda-pompe.org/first-ipa-conference-held-july-2-4-1999/

[125] Kikuchi T. et al., Clinical and metabolic correction of pompe disease by enzyme therapy in acid maltase-deficient quail. In: *J Clin Invest*. 1998 Feb 15; 101(4): 827–833, p. 831.

[126] Amalfitano A., et al., Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial. In: *Genet Med. 2001* Mar-Apr;3(2):132-8.

[127] An abbreviation for: cross-reactive immunological material negative. This means that a child does not produce any alpha-Glu at all and therefore quickly develops an immune response when the enzyme is administered.

[128] Based in large part on: G. Anand, 'As Their Babies Tested New Drug, A Friendship Grew' – The Wall Street Journal online, February 12, 2012.

[129] pompestory.blogspot.com/2012/08/the-duke-deception-what-should-be-done.html

[130] This refers to the Sophia Kinderziekenhuis at Erasmus MC.

[131] Interview Crowley, 19-12-2023.

[132] See sources: Anand, 2006. The preceding pages on Crowley are based in part on this book and in part on an interview with Crowley, 2023.

[133] The following is a summary of the statement by Paul Kaplan, General Manager of the Genzyme Pharming Joint Venture, VSN Archives.

[134] Various documents from the VSN Archives.

[135] The quotes from Termeer, Koo, and Hersbach are taken from Pharming's press release dated April 20, 2000.

[136] Interview Van Heek, 2022.

[137] G. Hersbach in a Pharming press release, April 20, 2000.

[138] FEM/De Week, 12-08-2000, pp. 48-53

[139] Myocafé (patient forum), August 5, 2000.

[140] The account of the meeting below is based on a report by Kevin O'Donnell. VSN archives.

[141] Jan van Heek, Gene Williams, Willem van Weperen and Philippe van Holle.

[142] Van den Hout H.M.P. et al., Recombinant human alpha-glucosidase from rabbit milk in Pompe patients. In: *Lancet*, 2000 Jul 29;356(9227):397-8.

[143] From its establishment until 2004, the EMA was known as the EMEA: European Medicines Evaluation Agency.

[144] Miller, K. L., et al., Using four decades of FDA orphan drug designations to describe trends in rare disease drug development: substantial growth seen in development of drugs for rare oncologic, neurologic, and pediatric-onset diseases. In: *Orphanet Journal of Rare Diseases*, 2021. doi.org/10.1186/s13023-021-01901-6.

[145] House T., et al., The role of patient advocacy organizations in shaping medical research: the Pompe model. In: *Ann Transl Med*. 2019 Jul; 7(13): 293.

[146] The interview is dated January 29, 2001, and was published in English on GSDNet. The text here is based on the Dutch translation by Gezinus Wolters, a member of the VSN and the working group on metabolic muscle diseases.

[147] Interview Crowley, 2023.

[148] Content partly based on Anand, in Sources, pp. 206–229.

[149] Based on a meeting report in the VSN Archives.

[150] Kevin O'Donnell op GSDNet 28-05-2001, in Archive VSN.

[151] Mozelle W. Thompson.

[152] ftc.gov/system/files/attachments/press-releases/ftc-closes-its-investigation-genzyme-corporations-2001-acquisition-novazyme-pharmaceuticals-inc./thompsongenzymestmt.pdf

[153] ftc.gov/news-events/news/press-releases/2004/01/ftc-closes-its-investigation-genzyme-corporations-2001-acquisition-novazyme-pharmaceuticals-inc

[154] See example: C. Shapiro, Competition and Innovation: Did Arrow Hit the Bull's Eye? In: *The Rate and Direction of Inventive Activity Revisited*. University of Chicago Press. Maart, 2012.

[155] This is going to be an expensive year. In: Beursplein 5, Jan. 27, 2001, p. 10

[156] Pharming out of the red in 2004. In: Haagse Courant, February 24, 2001.

[157] Biotechnology company Pharming sees its losses continue to rise in 2001. In: Agrarisch Dagblad, July 24, 2001, p. 1.

[158] Interview Hersbach, 2022.

[159] De Volkskrant, 15-08-2001, p. 1.

[160] See, among other sources, 'Biotech Pioneer Genzyme Negotiates Toughly and Secures Funding Creatively' in: Het Financieele Dagblad, August 15, 2001, p. 3.

[161] Based on documents in the VSN archives.

[162] Interview Kupers, 2022.

[163] See sources: Anand 2006, p. 255, and interviews with Schuring (2022), Erik Tambuyzer (2022), and Jan van Heek, 2022.

[164] Email correspondence with Bob Mattaliano.

[165] See EMA-website: EU/3/01/018: Orphan designation for the treatment of glyco-

gen storage disease type II (Pompe's disease).

[166] McVie-Wylie, A.J. et al., Biochemical and pharmacological characterization of different recombinant acid a-glucosidase preparations evaluated for the treatment of pompe disease. In: *Mol Genet Metab*. 2008 August; 94(4): 448–455.

[167] Interview Tambuyzer, 26-09-2022.

[168] Interview Incerti, 2022.

[169] See sources: Anand, 2010, p. 269.

[170] See sources Anand, 2010, p. 282.

[171] Interview Büller, 2022.

[172] Interview Van Hove, 2022.

[173] Interview Van der Ploeg, 14-06-2022.

[174] Interview Tambuyzer, 2022.

[175] This refers to children with the classic form.

[176] There are also other programs with a similar purpose, such as *humanitarian use, early access*, and *individual patient access*.

[177] By 2000, a detailed regulation was already in place in the U.S., but in Europe, it was still being drafted. This was just after the European Orphan Drug Regulation had come into effect. See: Elisabeth Bourg en Françoise de Crémiers, Compassionate use and early access to the market in the USA and EU. In: *Regulatory Affairs Journals*, June 2000, pp. 401-404.

[178] R. Nijland, Medicines out of compassion. De Volkskrant, 17-11-2001.

[179] Nowadays: Inspectie Gezondheidszorg en Jeugd.

[180] Post on vsn.nl, 04-02-2002, *Enzymvervangingstherapie bij de ziekte van Pompe*.

[181] See sources: Anand, 2010, pp. 281-287 and 295-309.

[182] Interview Crowley, 2023.

[183] Interview Broekgaarden, 25-01-2022.

[184] Genzyme Expands Pompe Disease Development Program, September 16, 2003. VSN Archive.

[185] In the U.S., the drug was marketed under the name Lumizyme. That second name was necessary because the FDA determined that the enzyme produced in larger 4.000-liter bioreactors did not sufficiently resemble the original enzyme, Myozyme, which was produced in smaller 160-liter vessels. The EMA did not make an issue of this. Lumizyme and Myozyme are two names for the same drug, alglucosidase alfa.

[186] Pompe's Bulletin, 10-02-2003. Published by AGSD. VSN Archives.

[187] pompestory.blogspot.com/search?q=Heidelberg and youtube.com/watch?v=N-p2it-wrqC4&t=2s

[188] Quote from a letter from the VSN to the minister, November 25, 2004. VSN Archives.

[189] Letter from Johan Bakker to Schippers, December 6, 2004, VSN Archives.

[190] Interview Schuring, 2022.

[191] Van den Hout H.M.P. et al., The Natural Course of Infantile Pompe's Disease: 20 Original Cases Compared With 133 Cases From the literature. In: *Pediatrics* Vol. 112 No. 2 August 2003.

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[193] Interview Schuring, 2022.

[194] Archives VSN.

[195] Based on interviews with Van der Ploeg, Reuser, Kishnani, and Paradis.

[196] In her words: children who tested negative for CRIM.

[197] Winkel L.P.F. et al., Morphological changes in muscle tissue of patients with infantile Pompe's disease receiving enzyme replacement therapy. In: *Muscle & Nerve*, june 2003, pp. 743-751.

[198] Interview Van der Ploeg, 21-06-2022.

[199] Rossella passed away on February 26, 2021.

[200] Bekkers H., De eerste medicijnvluchteling (The first medical refugee). In: *Binnenlands Bestuur*, 14-01-2005, p. 32.

[201] Hollak C., Aparte budgettering AMC en Erasmus MC nodig (Separate budgeting is needed for AMC and Erasmus MC). In: NRC, 01-02-2005, p. 6.

[202] Gunning L., Nieuwe geneesmiddelen voor iedereen (New medicines for everyone). In: NRC, 25-02-2005, p. 7.

[203] Schouten E., Blozende baby door toponderzoek (A rosy-cheeked baby thanks to cutting-edge research). In: NRC 17-05-2005, p. 17.

[204] Zinnige en duurzame zorg (Sensible and Sustainable Healthcare): A Report by the Council for Public Health and Healthcare to the Minister of Health, Welfare, and Sport. Zoetermeer, June 2006.

[205] A key figure at UMC Utrecht was John Wokke. He passed away in 2022.

[206] Interviews Schikan, 2022, Broekgaarden, 22-02-2022 and Van der Ploeg, 21-06-2022.

[207] Production of enzymes for Gaucher disease, Fabry disease, MPS I, and Myozyme was concentrated at the large factory in Allston.
[208] According to Jan van Heek, the plan from the start was to manufacture Myozyme in Belgium.
[209] Information from Maryze Schoneveld van der Linde, who spoke with the princess at length.
[210] Interview Kupers, 2022.
[211] Rare diseases; challenges and opportunities for social entrepreneurs. Ed. Nicolas Sireau. Sheffield, 2013, pp. 24, 25
[212] TMCNET News, 04-01-2006, see: tmcnet.com/usubmit/2006/10/04/1960188.htm
[213] fiercepharma.com/pharma/sanofi-coughs-up-180m-to-settle-pompe-disease-drug-royalty-payment-dispute
[214] See: wikipedia.org/wiki/Vesivirus
[215] Conscience and Courage, p. 122.
[216] For Fabry, there was an alternative: Replagal from TKT/Scheier.
[217] See sources: Hawkins, 2019, p. 118.
[218] Archives VSN.
[219] See sources: Hagemans, 2006.
[220] See sources: Hagemans, 2006 p. 194.
[221] Van der Beek, N., Clinical feautures, disease course and effects of enzyme therapy in Pompe disease. Rotterdam, 2013, pp. 137 e.v.
[222] Interview Van der Beek, 2023.
[223] The CvZ changed its name in early 2014; it is now called: Zorginstituut Nederland.
[224] See: raadrvs.nl/documenten/publicaties/2006/06/07/zinnige-en-duurzame-zorg
[225] Entire bookshelves have been filled with writings about the QALY. Incidentally, the QALY is used as a measure for a wide range of interventions, not just for medications.
[226] Not to be confused with the policy on orphan drugs.
[227] Van der Ploeg, A.T., et al., A randomized study of alglucosidase alfa in late-onset Pompe's disease. In: *The New England Journal of medicine*, 2010; 362: 1396-1406.
[228] Letter 30-12-2011.
[229] Hughes-Wilson, W. et al., Orphanet Journal of rare Diseases, 2012.

[230] Jan Tromp, Waarom nu pas ophef over extreem dure medicijnen? (Why is there only now an uproar over extremely expensive medications?) De *Volkskrant*, 01-08-2012.
[231] Alwin Kuiken, Hoogleraar maakt kostbaar medicijn eenvoudig na (Professor successfully replicates expensive drug). Trouw, 13-12-2014.
[232] In Archives VSN.
[233] The account of the ACP meeting is based on the official report from the CvZ, the VSN archives, various interviews, and the authors' own observations.
[234] These and the following quotes are taken from the CvZ report on the ACP meeting.
[235] Email to the VSOP on September 22, 2012, VSN Archives.
[236] Opinion of the Package Advisory Committee (ACP) on whether or not to continue covering Replagal®, Fabrazyme®, and Myozyme® under the basic health insurance package, October 23, 2012.
[237] Interview De Jong, 16-08-2023.
[238] Van der Beek, N., Clinical features, disease course, and effects of enzyme therapy in Pompe disease, Rotterdam, 2013.
[239] Letter to Parliament, October 3, 2013, Position on Pompe and Fabry, Ref. 155165-111008-GMT.
[240] Boon, W., Demanding Dynamics; Demand articulation of intermediary organisations in emerging pharmaceutical innovations. Dissertation, Utrecht, 2008, p. 132.
[241] Interview Daniels-van Saase, 2023.
[242] Interview Van Heek, 2022.
[243] Interview Hersbach, 2022.
[244] Interview De Vries, 2023.
[245] This is a contractually agreed payment by a partner that is contingent upon the achievement of a predefined milestone, such as the successful completion of a clinical trial or FDA approval. See: https://www.dfbonline.nl/begrip/14964/mijlpaalbetaling
[246] Among others, neurologist Hanneriek van den Hout in a lecture for patients in 2023.
[247] Interview Van der Ploeg, 21-06-2022.
[248] In the U.S., the drug has been marketed under the brand name Nexviazyme.
[249] Amicus was led by John Crowley until 2022; he was the man who, together

with William Canfield, founded Novazyme in 2000.

[250] Interview Pijnappel, 2023.

[251] zorginstituutnederland.nl/publicaties/adviezen/2022/09/27/pakketadvies-sluisgeneesmiddel-atidarsagene-autotemcel-libmeldy

[252] zorginstituutnederland.nl/publicaties/rapport/2021/12/07/monitor-weesgeneesmiddelen-2021

[253] Interview Timmen, 2023.

[254] Interview Schikan, 2022.

[255] See: fast.nl

[256] Interview Oosterwijk, 2023.

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