Evergreening the world's most profitable medicine

By Lucien Hordijk, The Investigative Desk[1]

Even after the expiration of Humira's patent protection, pharmaceutical company AbbVie almost completely fended off biosimilar competition for this blockbuster medicine in the Netherlands. 'Their behaviour defies any description.'

On Monday, 29 October 2018, two sales representatives of US pharmaceutical giant AbbVie gatecrashed a Board meeting at the Maasstad Hospital in Rotterdam, the Netherlands. Their business was urgent, they had told the secretariat. They immediately came to the point. AbbVie was prepared to offer the hospital an 84 per cent discount on Humira, a widely used anti-inflammatory medicine against rheumatoid arthritis, colitis and psoriasis. The hospital was spending approximately half a million euros a month on this medicine, so this was an offer no one could arguably refuse.

Two weeks earlier, Humira's main patents had expired in Europe. After a monopoly of more than 16 years, the pharmaceutical company in all likelihood had more than recouped its investments in developing this best-selling biological medicine. So-called biosimilar companies were now allowed to launch cheaper copies – more popularly known as 'copycat drugs'.

In the Netherlands, more than 220 million euros are spent on Humira every year, making it the unrivalled number one on the list of expensive medicines, measured by expenditure. In 2018, worldwide turnover reached 19.9 billion dollars, twice the annual turnover of eBay. Since its market approval in 2002, Humira has generated more than 130 billion dollars in sales.

Maasstad Hospital is part of the Santeon group, an alliance of seven hospitals that formed a joint purchasing organization for expensive medicines. Like other hospitals, they have been waiting eagerly for Humira to become cheaper. But the two Abbvie-representatives who managed to get a foot in the door in Rotterdam were too late. A week earlier, just four days after the Humira patent expired, the Santeon group had signed a deal with Amgen, one of the biosimilar companies that could now offer a Humira copy.

However, Abbvie was not prepared to take a loss that easily. Since October last year, the company has been fighting an unprecedentedly fierce battle to uphold its monopoly on Humira. Pharmacists and buyers on the Dutch side are still reeling from the pharmaceutical company's strategy. By sabotaging tender procedures and playing off hospitals against each other, AbbVie managed to drive competitors out of the market. Most strikingly, the company offered a price reduction of up to 89 per cent to prevent competitors from gaining a foothold.

During the research for this article, we interviewed dozens of people familiar with the matter. According to documents acquired by De Groene, at least 70 per cent of all Dutch patients continue to be treated with the original Humira.

Some of these sources blame AbbVie for what they call a *scorched earth tactic*. 'This form of ruthlessness we only see in the US market,' said Arnold Vulto, honorary professor of hospital pharmacy at Erasmus MC. He thinks AbbVie's strategy could eventually lead to a renewed market monopoly with renewed high prices.

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As a result of these complaints, the Dutch competition authority (ACM) decided to dig into the matter. According to ACM, this inquiry covers the entire class of medicines to which Humira belongs: the tumor necrosis factor (TNF) alpha inhibitors.

'ACM does not comment on specific cases', says a spokesperson, who does add, however, that the authority seeks to prevent a situation 'where the competition is driven out of the market to the point at which prices can then be raised significantly by the last remaining pharmaceutical company'.

'The most egregious example of over-patenting'

The discovery of Humira is a classic success story. In 1993, a spin-off company from the University of Cambridge and German pharmaceutical BASF-Knoll started a unique collaboration to produce antibodies from bacteria.

The BASF-Knoll researchers discovered an antibody for treating rheumatoid arthritis. They gave it the working title D2E7 and it was administered to humans for the first time in 1997. Alfons den Broeder, now an experienced rheumatologist and at that time working at the Radboud University Medical Center in Nijmegen, prepared the first injection. He remembers that at the time, expectations about medicines like D2E7 were very high. 'This would do for rheumatoid arthritis what penicillin did for pneumonia,' he says. Abbott Laboratories (which later became AbbVie) acquired BASF-Knoll for 6.9 billion dollars in 2000. D2E7 would later be called adalimumab, the active substance in Humira.

In the subsequent two decades, adalimumab has become an important medicine. However, it is not a panacea, Den Broeder says. 'Methotrexate is still the first choice in all rheumatoid arthritis guidelines, but medicines like Humira are a very good second choice.' Commercially, however, Humira is in a league of its own. AbbVie won additional approval for using it in treatments of Crohn's disease, psoriasis, ankylosing spondylitis (Bechterew's disease) and some types of eye inflammation. That helped the company to rake in sales of over 130 billion dollars.

AbbVie's annual reports show that almost 70 per cent of its revenues come from its most famous product. If those revenues would be halved in the short term, the pharmaceutical giant, worth 120 billion dollars on the stock market, would risk a shareholder revolt or a takeover battle. To prevent this, AbbVie, as explained in internal documents, has set up a 'patent estate' that must extend the Humira monopoly for many more years to come. In addition to the active ingredient, applications for new approvals, production methods, dosing regiments and administration methods, for example, were also patented.

Ultimately, a total of 247 patent applications for Humira were filed in the United States, 136 of which were granted. European patent law is stricter: of 76 patent applications fewer than 10 were in force in October last year.

This stacking of patents has nothing to do with protecting R&D-investments, says US consumer group I-MAK (Initiative for Medicines, Access & Knowledge. More than half of the 247 applications were submitted after 2014, long after the main Humira applications were discovered (between 1996 and 2002). In fact, Abbvie protects its business interests 'by an aggressive evergreening patent strategy to extend the life cycle of Humira in order to deliberately delay competition', I-MAK concludes in a study on AbbVie. The organization calls Humira 'the most egregious example of overpatenting'.

Delaying tactic

In 2017, it became clear in the United Kingdom how AbbVie uses its patents as a delaying tactic. When several biosimilar companies contested two European patents on Humira's dosage regiments, AbbVie quickly withdrew the relevant patent claims in order to prevent a court decision. However, the judge did not go along with that. He observed that through this withdrawal AbbVie was 'shielding patents within the portfolio from scrutiny by the court´.

AbbVie lost the British case, which was closely followed by industry insiders. Even so, because of AbbVie's 'over-patenting' of Humira other companies could still not enter the European market with cheaper versions without concerns. And in the United States too, uncertainty remained. Some of the patents there already expired in 2016, but others will not expire until 2022 and yet others in 2034.

Deals were struck outside the courts. In order to be able to compete with AbbVie, its competitors-in-waiting had to promise not to launch their biosimilars of Humira on the US market until 2023. The date for Europe was set on 16 October 2018. Since 2017, eight competitors have signed such an agreement, and more are expected to follow. The manufacturers will pay AbbVie a royalty on the sales of their biosimilars. They do not disclose any percentages. 'It's a simple calculation,' hospital pharmacist Vulto says. 'Companies have estimated the costs of patent litigation and decided they'd better compromise and make a deal that at least allows them to safely enter the market.'

In the Netherlands, expensive medicines such as Humira are only prescribed and purchased by hospitals. The government had instituted this to strengthen the hospitals when negotiating price discounts. The hospitals themselves form purchasing blocks in order to obtain additional discounts.

One of these alliances is Santeon, a group of seven large hospitals and, in the Humira case, three small ones. They are treating more than 10 per cent of all Humira patients in the Netherlands and spend about 20 million euros a year on the medicine. When 16 October 2018 approached, they reduced their Humira stocks so they could immediately switch to a new supplier. 'We know from experience that the original manufacturers are hardly willing to give discounts after the patent expires,' says Yuhan Kho, a hospital pharmacist at one of the Santeon hospitals. 'That's why we assumed that we would switch all our patients to a biosimilar.'

Within a week, the group opted for Amgen, one of the four new manufacturers, as their new supplier. This quick move caused a panic at the Dutch AbbVie office, according to pharmacists from various purchasing groups who were in close contact with the company during this period. AbbVie Netherlands contacted the Chicago headquarters and was given permission to offer high discounts to maintain its market share at all costs.

When the two AbbVie sales representatives invited themselves to the Board meeting of Rotterdam's Maasstad Hospital, they offered a price that was slightly below Amgen's price. The Maasstad directors were not enamoured. 'We thanked them for their offer and kindly but firmly asked them to leave,' says Hans Feenstra, a Board member of Santeon and the head of the joint purchasing group.

After it lost the Santeon tender, AbbVie Netherlands became more aggressive. The company pilfered the offers already made by competitors and then made slightly better ones, even when tendering procedures had already been closed, as in the case of Santeon. In personal meetings with hesitant hospital pharmacists, AbbVie's representatives used iPads with a live connection to the company's Chicago headquarters. An American employee then explained once more why, as a hospital, you would want to remain an AbbVie customer.

AbbVie's tough negotiating strategy caused division in various other Dutch purchasing groups. The IJmond Group, for example, a group of hospitals in the region west of Amsterdam, fell apart and the individual hospitals continued to negotiate bilaterally. 'AbbVie's attitude and behaviour have defied any description for years,' a concerned pharmacist, who doesn't want to be named, wrote in an email.

Chasing away the competition

One method AbbVie used to keep Dutch hospitals from switching to other suppliers was by focusing on their 'residual financial risk'. After such a switch, some patients will have to continue to use the original product, for example due to allergic reactions or a so-called reverse placebo effect. Hospitals usually sign a separate contract with the original manufacturer for these patients. But AbbVie told the hospitals that considered switching that they would not receive any discount for this residual group of patients and would only get a good deal if at least 80 per cent of their patients were kept on Humira. As a result, the remaining patients would become so expensive that the switch would hardly be worthwhile. One pharmacist who did the math says: 'we had to get 98 per cent of our patients on the new medicine to get the best deal.' Another one: 'We'd already be worse off with a new supplier with only six non-switching patients.'

It was only a matter of time before AbbVie's aggressive marketing strategy in the Netherlands would attract the scrutiny of antitrust regulators. The European Commission had already warned against 'exclusionary practices such as a rebate scheme designed to exclude competitors from hospital tenders'.

No doubt aware of this, on 14 November 2018 AbbVie made a final strategic move. It dropped the exclusion of residual patients from its discount offers. 'In order to avoid misunderstandings about the price and discount conditions applicable at AbbVie, we will inform you as follows', general manager Lennaert Rijken of AbbVie Netherlands wrote in an email to hospitals that were switching their patients to a biosimilar. 'The corresponding discount applies to every purchase of Humira products. The agreement drawn up by AbbVie does not contain an exclusivity clause.'

By that time, AbbVie didn't need the exclusivity clause anymore. Driven by the company's discounts and by the expected 'financial residual risks' it had projected, most Dutch hospitals – an estimated 80 percent – had already decided not to switch their patients to a Humira biosimilar.

As a result, one competitor, Biogen, has sold their biosimilar only to one hospital in the Netherlands. Amgen has a deal with only one Dutch purchasing group and a few individual hospitals. Sandoz, a subsidiary of Swiss company Novartis, achieved a similar result. Yet another manufacturer, Mylan, did not sell one syringe of its biosimilar and decided to export its stocks abroad.

Now that AbbVie has managed to chase the competition away from the Netherlands, some insiders expect that the company will raise the price of Humira again in the foreseeable future. And it may not even need to. On 20 December 2018, AbbVie has submitted an approval dossier to the European Medicines Agency (EMA) for a new medicine called upadacitinib. This JAK1 inhibitor is widely regarded as Humira's successor. If EMA approves it, AbbVie will again have assured itself of patent protection in the coming decades.

When asked for comment, an Abbvie spokesperson said: 'We will not respond to the various claims and speculations that have been made. As usual, what happens at the negotiating table is confidential.' The spokesman did not refute any of the facts described in this article. He added that the company is committed to ensuring that 'patients continue to have access to Humira as a treatment option' and that 'doctors continue to have the choice to prescribe it'.

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