Production **of orphan medicines at BioConnection** is growing fast

CEO Alexander Willemse:

"BioConnection is flexible and large at the same time"

"What BioConnection has experienced during its twelve-year existence reads like an exciting book whereby the last chapter has yet to be written. Our fate did hang in the balance a couple of times, but we survived and are now growing by thirty to forty percent annually ", says Alexander Willemse, CEO at BioConnection in Oss.

Small biopharmaceutical companies can turn to BioConnection when they want to manufacture their new product formulations for clinical trials according to European EMA and U.S. FDA standards. This involves new medications produced as sterile injectable liquids that are manufactured in liquid or freeze-dried vials or liquid ampoules, syringes or *blow-fill seal packs*.

For a few years now, BioConnection also provides commercial production for customers bringing their product to the market after successful clinical research. The company achieved a turnover of approximately EUR 7 million in 2017 and has about 40 employees.

At the moment, BioConnection has some twenty-five clients ranging from young biotech companies to commercial parties. "They often remain clients after clinical research, so that during the introduction of their product to the market, they do not need to invest in their own production capacity straight away; this in turn provides us with extra growth", according to Willemse.

Partners at driving distance

BioConnection owes its success to collaborations with six partners within driving distance. "Injectable liquids can be placed into vials with a rubber stopper, glass or plastic ampoules or into syringes. Initially we only had vials. A customer who dealt with us would thus be restricted to bottles from the start. Just like someone who goes to a VW dealer is sure to leave the showroom with a VW and not with a brand new Renault.

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We have been able to overcome this restriction by involving partners at locations such as Leiden and Brussels. This allows us to always offer customers the best solution and delegate part or all of the work to partners, for instance, the manufacture of ampoules and blow-fill seals. However, we do remain responsible for what happens there and thus relieve the customer of any concerns in this respect."

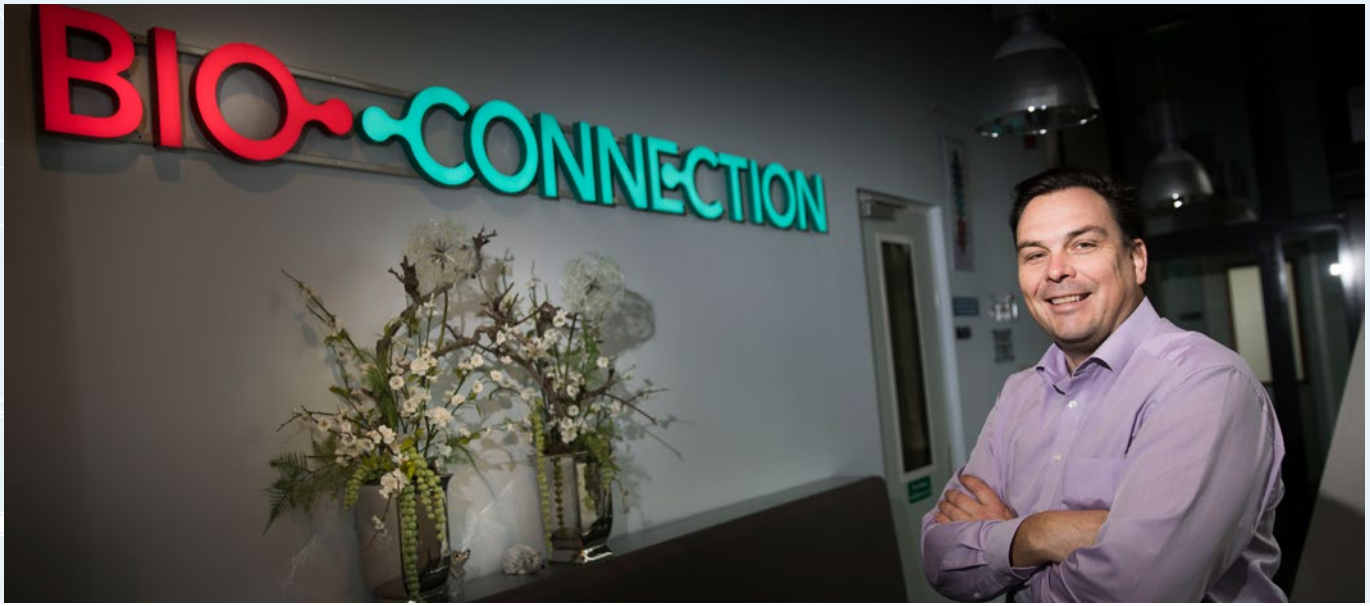
"At the same time, our approach is straightforward: If there is something we cannot offer, such as tablets, we refer customers to another company and work then falls beyond our responsibility. It is also possible that a potential customer is not in accordance with our ways of working together. If a customer does not accept this, we do not try to string them along with all kinds of artificial constructions, and we refer them on. We either do things right or not at all. By being honest, we build up and maintain our good name."

Hybrid structure

The said network of partners only partly explains the company's strong growth. The fact that the company is growing at thirty to forty percent a year is also due to its hybrid structure, according to Willemse: "BioConnection is a relatively small company, which since 2016 has occupied a relatively large top quality production site, namely the so-called Aletta Jacobs building, which is actually more suited to *big pharma*". To explain how this came about, Willemse refers to the company's history.

BioConnection was founded in 2005 by Organon (an AkzoNobel pharmaceutical company at the time). Shareholders of this young company were Organon, *M*ibiton and the Brabantse Ontwikkelings Maatschappij (BOM). *M*ibiton made available a subordinated loan of 1 million euro plus one million euro shares capital.

Willemse: “Organon anticipated that through BioConnection, they would gain more insight into what was happening in the world around them. This allowed the young company access to 35 percent of the capacity of the Aletta Jacobs building. For Mibiton, BioConnection formed a uniquely shared GMP-production facility, where young (bio) pharmaceutical companies could manufacture their products for their first clinical trials. The GMP (Good Manufacturing Practice) facility was then still called the RY-building and in that same year, it was opened to allow production of testing compounds for clinical research. BioConnection could also make use of one quarter of the capacity of another building, the CP building, for commercial production for its customers. People who worked in these buildings were employed by Organon, while BioConnection, which then employed four people, functioned as a type of broker attracting work contracts. Organon mostly focused on maximising their own expertise and on joining BioConnection in exploring what the latest innovations were in other companies.



Fate hanging in the balance

Shortly after Willemse joined the company in 2008, Organon went from AkzoNobel to the American company Schering-Plough. This meant uncertain times for BioConnection. To top things off, Schering-Plough itself was swallowed up by the American pharmaceutical giant MSD. This pharmaceutical company decided to pull out of BioConnection by 2011, because the group no longer wished to be a shareholder of a service company. This left BioConnection's fate hanging by a fine thread. The BOM and *M*ibiton shareholders however, decided to continue with the company with a view to work options and opportunities in medical innovations. Willemse: "They have helped us through this. Fortunately, we were allowed to continue to use MSD's facilities in Oss. Separation from MSD has even given us wings. Previously, many customers accepted that Organon kept an eye on us by looking over our shoulder, but customers no longer wanted this from MSD. Withdrawal by MSD as a shareholder was a solution to this problem".

In 2015 BioConnection faced crossroads once more. MSD announced the closure of the RY-building because the company had sufficient production capacity elsewhere. "So then, as a small company of eight people, that was only just profitable, we made a big move and announced that we wanted to take over the building, including some of the staff. The challenge was not so much producing the acquisition payment but meeting the ongoing running costs: including fifteen additional members of staff, energy costs, rent, and so on, explains Willemse. "On January 1st 2016 we became the owners of the RY-building and we renamed it the 'Aletta Jacobs building'. Moreover, business campus Pivot Park owns the exterior of the building, but the

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entire interior is ours. The assistance we received from MSD was fantastic: for an additional fee we could continue to use all kinds of facilities in order to maintain our GMP-chain and had time to convert this to our completely own chain. Just as important was permission from IGY (Health and Youth care Inspectorate) to take over the active building operations from MSD.

All final MSD qualifications could thus be our starting qualifications. Of course, we still had to prove to the IGY that we could do everything independently and that we had everything under control. This took 6 months to finalise, after which we could actively take part in the market from May 2016 under own banner. What also helped us was that customers for commercial production liked

seeing that we would continue their production as the new owner of the building. This provided us with clientele straight away.

Shortly after this and especially in 2017, our production expanded enormously. Our employee figures have doubled to 40. We now produce at top capacity and at the same time continue to do business with our six partners who are growing along with us.

Big pharma building

Acquisition of the RY-building has been a strategic decision, which has worked very well for BioConnection. "If you want to establish a manufacturing facility under GMP as a small business, you need to make concessions, because there is not a lot of money. Through a combination of circumstances and a bold decision, we as a company with forty people now have a building with little to no concessions and with an FDA license. This building has cost forty million and can be considered of part of *big pharma*. Normally a company is small and flexible, or large and inflexible, but we are flexible and large at the same time. This is catching on. We have customers all over the world."

The Aletta Jacobs building is filling up fast. In 2017, BioConnection started using a new laboratory here and a space for process development using the latest *tangential flow filtration* equipment to concentrate and 'buffer' raw materials. "We receive everything and convert it into the correct formulation", Willemse explains.

Immunotherapy

On the fifth floor of the GMP facility, BioConnection also wants to start work with cell cultures for immunotherapy needs. For this therapy, doctors extract tumour cells from a cancer patient that are not properly recognised by the patient's immune system. BioConnection then wants to grow and modify those cells for its customers, so that they are once again recognisable as being harmful to the patient's immune system. After injecting them, the immune system will react to the tumour cells again and remove them all. This involves a one-on-one individual treatment: for every patient, individual cells need to be cultured, otherwise this process does not work. "We will soon have the facilities for this. We hope to be able to make an important contribution to this new development" says Willemse.

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New production line coming up

"Meanwhile, BioConnection is growing extremely fast with its current production line. Customers who have completed phase two ('compound efficacy') and phase three ('larger patient groups') clinical research, find it very convenient to stay at BioConnection when it comes to production for the market. "Thus, we now run at full capacity and a new production line that can produce four times as much will commence. This will be operational by the end of 2019 or early 2020", says Willemse.

He points out that BioConnection focuses and will continue to focus on the niche market for orphan medicines and so-called small scale indications. "We can produce these in Oss perfectly for both clinical research as well as commercially and this is going well. For large volumes of one hundred million bottles, however, we are not your company. We prefer to leave this to other parties. We focus on medical indications with relatively small numbers of patients, for whom, in addition to clinical products, commercial products should also be available."

Willemse concludes: "After we started our company in 2005, we went through quite a lot of different phases: Organon was taken over by MSD who then stopped being a shareholder and the factory threatened to close. But we have survived everything and have become stronger as a result".

"Mibiton and the BOM have helped us through this."

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