Interview: Sijmen de Vries – CEO, Pharming Group, The Netherlands

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Pharming Group CEO Sijmen de Vries discusses the advantages of his company's transgenic platform for recombinant protein production, the commercial progress of their lead product Ruconest, and the company's plans for developing new applications through the platform, including a partnership with the SinoPharm subsidiary SIPI.

From a production point of view, what are some of the advantages of using a transgenic production platform over a bioreactor and cell-line, and of rabbits over other species?

When compared to a cell-line, a transgenic rabbit platform has many advantages. Once you create a founder generation, you have your final fully-structured protein in the rabbit's milk, you have your bioreactor, and the protein is at its final concentration in the milk. The production process is constant and instantaneous in a sense, as you can collect milk on a daily basis, unlike cell-line systems where it can take up to a few months to produce a single batch. As such, scaling up is relatively simple, and there are few challenges or hurdles to overcome, whereas with a cell-line system problems with the protein's structure and yields are often encountered when you scale up production.

Compared to other animals that can be used as transgenic platforms, rabbits are strongly preferred for a variety of reasons. Pharming was the pioneer in research on transgenic cattle, and we discontinued this research three years ago. Primarily this is because the protein content of a cow's milk is much lower than many other animals, and thus yields of desired proteins are much lower. Rabbits are small, are easy to house and care for, have very high protein concentrations in their milk, and of course breed like rabbits, allowing production to be scaled up relatively quickly. Each rabbit produces 150-200 ml of milk per day, and we get yields of 12 grams of our C1 inhibitor protein per liter of milk. After purification, this equates to nearly three doses of Ruconest per rabbit per day.

Furthermore, rabbit milk can be frozen for up to three years before being purified into the drug substance, which itself can also be kept for three years, followed by the final production step (sterile Fill & Finish). The finished product (Vials) have a shelf life of four years at room temperature. This has allowed us to build up significant stocks in our freezers, with very low storage cost, without having to finance the expensive purification process. Managing our rabbits with proper husbandry only accounts for lees than 20 per cent of the overall cost of producing Ruconest, and given our ability to build up milk stocks we have quite a flexible and versatile supply chain. The milk of a cow or goat cannot be stored as easily, as the protein content is much lower, and the larger volumes make maintaining GMP standards more difficult.

Looking at the final therapy, how does a rabbit-produced protein compare to one derived from plasma or produced using a Chinese hamster ovary (CHO) cell-line?

In the late 1990s Pharming's first project was to develop alpha-glucosidase, and the company went into a 50-50 partnership with Genzyme to develop the enzyme replacement therapy for Pompe's disease; founder rabbits and a candidate product were developed, and a phase I/II clinical trial was conducted. Pharming unfortunately ended up filing for bankruptcy and had to drop this collaboration, so Genzyme ended up moving forward with their Chinese hamster ovary (CHO) cell product; since then, we have heard several anecdotes from this trial that it seemed to be better tolerated and more effective than the cell-line products, but there has been no study yet to prove this.

15 years later with Ruconest, we do have evidence that rabbits are able to produce highly-glycosylated proteins – proteins bound up with sugars as in the body – in such a way that you have no significant side effects and no immunogenicity issues, and it is very effective. This is part of the reason that we have decided to move forward with developing alpha-glycosidase in rabbits from scratch, because it is also a very complex highly-glycosylated protein, and we expect that our

efforts will show that the quality and practicality of the proteins produced in this platform will be higher than that of the CHO cell-line equivalent, which has significant immunogenicity issues and a very significant side effect profile. The hope is that we will find a protein that won't have these issues, and that may actually be more effective, or may be safe to administer in much higher doses, much as is the case with Ruconest versus plasma-derived C1 inhibitors.

With Ruconest approved in the EU and US, Pharming came close to breaking even last year; how does 2015 look so far in comparison?

Coming close to breaking even last year was based almost solely on a one off USD 20 million milestone payment that we received from our US partner Salix Pharmaceuticals, which has since been acquired by Valeant, for our first commercial sale in the US. Our sales numbers are still quite modest, but we have significantly increased sales over the first half of 2015, and we expect sales to continue to grow throughout the remainder of the year and onwards. We still have some way to go before we will be cash-flow positive on an operational basis.

American patients are steadily enrolling in our full service Ruconest Solutions program, which is operated by our US partner Valeant. Patients with hereditary angioedema (HAE) can enter into this program and receive two free treatments while administrative procedures and confirmation of their benefits are carried out, which typically takes one to two months. Ruconest is approved for home self-treatment in the US as are some of the other HAE treatments, so once confirmation is received patients are given training for self-administration of Ruconest using a slow-IV injection, and then they are supplied with the commercial product.

This business model is effective and we have a growing patient base in the US, but the base is still quite small and there is a huge range in terms of the severity of their HAE symptoms and frequency of attacks. Ruconest is used to treat acute attacks of HAE, with one dose administered to counteract a given attack, and patients can have anywhere from fewer than two attacks per month to as many as two or three attacks per week, so the volume of Ruconest needed per patient varies widely. Overall, we are very pleased with the efforts of our partner Valeant, and are convinced that Ruconest will continue to become a very significant product amongst the options for the treatment of HAE in the US market and elsewhere.

What are some of the advantages of Ruconest over other HAE treatments, and what is your strategy for driving the adoption of Ruconest by patients?

First of all, Ruconest is a C1 inhibitor, which makes it an enzyme replacement therapy (ERT). There are non-ERT products on the market for HAE attacks that use alternative pathways to treat the

symptoms, and the market leader is a subcutaneous product which patients find to be relatively convenient, when compared to the slow IV injection for ERT. However, while we have no direct comparative clinical trials yet, the published data shows that the response rate is consistently better with Ruconest than with these non-ERT alternatives. Specifically, with this subcutaneous product, a breakthrough phenomenon occurs where in up to 30 percent of cases a second or third injection is required; the C1 inhibitors, such as Ruconest, do not have this issue. As these treatments are quite costly, it becomes quite expensive if you need two or three doses to treat just one attack. Some patients in the US are already being restricted by their insurance companies because they use significant volumes of these products, and we are seeing cases where this is motivating the switch to Ruconest, which has a high and consistent response rate.

The other C1 inhibitor ERTs on the market are derived from blood plasma and are harder to purify, and as such have a more significant risk profile in terms of side effects when compared, based on published literature, to Ruconest. Specifically, they can potentially cause blood clots when used in higher doses, while larger doses of Ruconest can be safely administered to patients.

With sales in the US and EU, what new geographic markets are you looking at expanding into next?

Yes, we have gone into several partnerships around the world, the latest being in Venezuela and Colombia, where we are working with a company called CytoBioteck. We also recently went into a global partnership with the international HAE patient organization HAEI, and they have developed an Global patient access program (“HAEi- GAP”) that we have committed to; in fact, we are proud to be the first producer of an HAE treatment to make this commitment. Our partner, Clinigen, is now making Ruconest available under this Global Access Program to patients in countries where we do not have commercial operations ourselves.

On the development side, what are some of the additional indications you are working on for Ruconest?

A pediatric HAE study is ongoing, which we expect to report on early next year; we’ve already announced some very favorable interim results this year. Valeant is our 50-50 partner for developing an HAE prophylaxis indication. We are currently recruiting patients for this study from which we expect to have results by the second quarter of 2016. This study is a three arm, double blind, placebo-controlled, crossover design where we have groups receiving Ruconest and placebos both once and twice per week. Twice a week is the standard for prophylaxis, and the current gold standard product offers a 50 percent reduction in attack frequency; this is the standard we must

improve upon, with either weekly or bi-weekly treatments.

We are also exploring a phase II study for treatment of acute pancreatitis, and are interested in a study for delayed graft function, an acute kidney failure problem, where there is also good evidence that a C1 inhibitor may provide benefits. There are other possibilities too.

How are you moving forward with projects not related to Ruconest?

Pharming is working on lead optimization for alpha-glucosidase for treatment of Pompe disease, and alpha-galactosidase for the treatment of Fabry disease. These two projects are being moved forward by our new French research site, which we developed around assets acquired from TRM, a small contract research organisation that had worked extensively with rabbit models. Now we are using this site to generate the new lines for new products, and they are currently working on new vectors and constructs for these two indications, with the goal of developing a generation of founder rabbits for each product. Developing a founder generation can be challenging and sometimes a bit unpredictable, just as with cell-line development, and you really need good experience working with genetic vectors and constructs to be able to get it right in a timely fashion; this is one of the reasons we were very happy and proud to be able to develop this research site in France with the experienced rabbit developers from TRM.

Looking beyond your current initiatives and pipeline, what sort of other projects do you see as being particularly well suited to this rabbit platform?

The next direction we will be able to take will be to prove that the rabbit platform is suitable to compete strongly against CHO cell-lines in other areas, such as antibody production. We are not sure that the difference in concentration compared to cell-line bioreactors will be as great as we see with the C1 inhibitor, which achieves up to 50 times higher concentration, but we do expect to see significantly higher concentrations as well as probable advantages in terms of lower immunogenicity and improved glycosylation in antibodies if we choose the right sort of project.

Now with our French research site we can create new leads with relative ease and frequency, so it is our goal to demonstrate that our platform can successfully produce other therapeutic molecules, and then begin development ourselves. Depending on the project, we would either proceed ourselves or partner with other companies to develop any candidates further. For example, we expect that we will be able to develop orphan products, such as those for Pompe and Fabry diseases, under our own steam, and we have the ambition to commercialize these ourselves eventually as well.

At present, Pharming is already working with the Shanghai Institute for Pharmaceutical Industry (SIPI) for your development of a Factor VIII; could you expand on what this partnership means for the company?

SIPI is a subsidiary of SinoPharm, which is the largest Chinese state-owned enterprise active in the life sciences industry, and we have had a formal collaboration agreement with them for two years now. The first joint-project is for a recombinant Factor VIII product, which is still in the lead optimization phase. Factor VIII is a very complicated protein with a more complex glycosylation pattern than any of the other molecules that Pharming has worked on so far. Expression levels in a CHO cell-line bioreactor are usually very low, so we are confident that we will see significantly higher yields in rabbits. With higher yields and a very favorable cost structure in China, we expect that we will be able to develop very price-competitive Factor VIII product for the market, while further proving the effectiveness and advantages of our production platform for complex molecules.

However, the first step we are taking as partners is a complete technology transfer to develop Ruconest production in China. This means we are transferring the technology necessary to carry out the entire production process from rabbits to the final dosage form in Shanghai, under FDA and EMA compliant conditions. This will give Pharming a secondary supply chain and lower our cost-of-goods significantly. SIPI will comeercialise Ruconest in China and will pay us four percent royalties on sales. In addition SIPI has agreed to supply us with the purified form of Ruconest on a cost-plus basis, instead of on a full commercial basis as with our current arrangement with our European manaufacturing partners..

The same goes for any other product that we jointly develop. For any lead that we bring to the partnership, SIPI will carry out pre-clinical development and organize clinical trials in China, while Pharming will seek IND approvals from the EMA and FDA and fund clinical trials outside of China. For any future products developed under this arrangement, they will have the rights in China, we will have the rights ex-China, and we will pay each other a reciprocal royalty of four per cent.

This partnership has a complicated structure, but in the long term it will play a significant role in the growth trajectory of Pharming. Now we have a very strong partner with abundant resources and a strong desire to develop new biological compounds; the resulting compounds will be world-class, and can be sold in the rest of the world for our joint benefit. Now, when we develop a lead, we can bring it to SIPI who will develop production and carry out the entire pre-clinical development process, and will do so using their own financial resources. Then, all we have to do on our end is organize the INDs for EMA and FDA, or even decide to contract out clinical development,

and we will get ex-China commercialization rights and long-term supply on a cost-plus basis.

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