Emmanuel Dulac – President & CEO, Zealand Pharma

After 23 years, we are now building Zealand into a fully integrated independent commercial company and have the right finance, pipeline, and science in place to do so

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Zealand Pharma's Emmanuel Dulac, fresh from a first US FDA approval for the company's rescue pen for severe hypoglycaemia in people with diabetes aged 6 years and older, outlines the swift progress that the Danish biotech has made in his two and a half years as CEO. Dulac also highlights the company's bold ambitions to commercialise five products itself by 2025 and gives some words of advice to other Big Pharma execs considering making the leap to biotech.

It seems like Zealand Pharma has made rapid progress in your two and a half years as CEO, with a first new drug application (NDA) and approval, a first in-licensing, and two acquisitions. What mandate were you given upon taking the role and how far along the road to fulfilling it are you?

This two-and-a-half-year adventure has flown by! I am very happy with where we are today, having executed on our first ever filing, approval, acquisition, and in-licensing. This is a lot of 'firsts' for a company of our size and we have had to double our number of employees over this period. Another important first, which grew from one of our acquisitions, was the establishment of a commercial entity in the US.

While these achievements are remarkable in themselves, even more remarkable is the flexibility, ambition, and openness shown by our employees that made them possible. I joined a company that was very well-funded and organised due to the good work of my predecessors but, while there

was a great foundation for the next steps in our development, the transition from a monocultural R&D lab to a fully integrated global company was somewhat daunting. However, we have successfully navigated all the challenges that have been thrown up thus far and have a very healthy setup for future growth.

Zealand is now making the transition into a fully-fledged commercial-stage outfit with the US approval of Zegalogue® (dasiglucagon) injection, a rescue treatment indicated for the treatment of severe hypoglycaemia in diabetes patients age six and above. Why is this product so important and what are your expectations for it?

Zegalogue was made possible because of one major invention: chemically stable glucagon in aqueous solution. Glucagon is a peptide – actually the most unstable peptide of all – and is notoriously difficult to put into a solution without losing the efficacy of the molecule within a few minutes. The challenge was finding or modifying a molecule which has similar characteristics to natural glucagon but would be stable in solution. Zealand started working on this many years ago, as did several other Big Pharma companies, but remarkably we were the first to reach the finish line.

Because we have this chemically stable glucagon in aqueous solution, which has similar characteristics to natural glucagon, we were able to develop dasiglucagon injection for this first indication, severe hypoglycemia in people with diabetes age six years and older. We have four additional indications under study for dasiglucagon in development. This represents an important option for diabetes patients.. During their daily lives, whether due to the timing or dosing of their insulin injections, their carbohydrate intake, or the amount of exercise they are doing, these patients can suffer from severe hypoglycaemic events whereby a third party needs to rescue them. In the past, the only option was to use glucagon powder and recombine it over several steps to make an injectable solution. As you can imagine, this is not ideal in an acute situation where the patient may be unconscious and needs to be treated immediately. Moreover, most of these events happen during the night. Therefore, we developed two delivery methods, an auto-injector and a prefilled syringe. We are very pleased with the reaction from physicians so far.

Zealand bringing this product to market itself represents a significant shift from the way in which the company has traditionally operated. Why take on this risk and not try to partner or out-license as the firm has done previously?

We always had the ambition to become a fully-integrated commercial entity. The best method of maximising return on investment for years of research is by commercialising a product ourselves. Previously, the company was not really assessing what it would take to commercialise this product successfully in the US or elsewhere. However, when I came on board, I leveraged my commercial background to set a plan for launching the product after approval and successfully bringing it to market.

I made the decision to first focus on the US only and not try to tackle Europe, at least initially. Europe is a fantastic market but is very complex, with different policies, regulations, and pricing across the 27 EU member states. There is a need for people on the ground in each country to launch a product across Europe; something not yet feasible for a company of our size. In contrast, our analysis showed that we could cover around 80 percent of the USA's volume of prescribers with a small but nimble commercial team.

However, what cemented the decision to commercialise this product ourselves was the Phase IIb results for the dasiglucagon bi-hormonal artificial pancreas pump for type one diabetes management. This is the third potential indication under study for dasiglucagon, and by far the largest opportunity for both patients and shareholders. We believe that we are well positioned to realize that potential opportunity and that the best strategic path forward was to launch the first indication ourselves.

Zealand has an ambitious plan to commercialise five products by 2025; what is your strategy on that front?

For now, we are focusing all our commercialisation resources and efforts into the US. That is true across all dasiglucagon development programs, as well as for our two rare disease candidates. The first investigational rare disease candidate is dasiglucagon, which is being studied in congenital hyperinsulinism, while the second is a long acting GLP-2 agonist, glepaglutide, a different molecule, is being investigated as a potential treatment option for short bowel syndrome (SBS). However, SBS is more of a rare condition than a rare disease, suffered by patients who have recently had surgery to remove part of their intestines.

These rare diseases and conditions are not limited to the US and the patients who suffer from them often have severely limited treatment options. Therefore, we will consider expanding to the rest of the world with these therapies.

Zealand has a historic footprint in Denmark, but an increasing focus on the US. In that sense, why does it make sense to continue to base operations out of Denmark rather than pack up shop and move to Boston or the Bay Area?

Firstly, Denmark is where our R&D base is and I am a firm believer that amazing research requires stability. History has shown that mergers and acquisitions which force research groups to move to a different state, or even country, can be very destructive to value. Researchers – unlike commercial teams – are not necessarily the easiest group to move and tend not to sign up to being moved around. Additionally, research is a long-term investment and individual projects take a period of several years.

Looking at Denmark specifically, there is huge know-how around the increasingly hot field of peptide-based medicines here. Much of the significant progress being made, and the drugs being developed in metabolism and obesity, are today coming through peptide-based innovation, not least at Zealand. We are now a world-renowned biotech in peptide medicines, both on the chemistry and formulation sides, because we have been able to innovate in these critical development areas. Additionally, we are now advancing oral peptides and there is enormous untapped potential in the field. The development goal of these peptides is to have high potency – meaning only small volumes are needed – and high selectivity. Adding these oral peptides to our development portfolio helps create an incredible platform from which to develop pipeline product candidates.

While our research and operations remain in Denmark, we wanted to establish a strong US presence in advance of the US commercial launch of Zegalogue. And our US team is based in Boston, which provides us with access to the talent and capital that make the city such an important life sciences hub.

Having spent time in both Basel and Boston, how would you compare the life science innovation ecosystem in Copenhagen to those more globally renowned hubs?

There is definitely a huge dynamic in this region, which is now perhaps the most active in Europe. We see a good combination of the right science, leadership, financing, and entrepreneurial spirit. However, it is still much smaller than Boston, where there are large amounts of financing being funnelled into science. While this is of course broadly positive, one downside is that for many years

anything and everything could be financed in Boston, and the market cap of very early-stage companies could soar to hundreds of millions of dollars overnight.

There is much more conservatism and risk adversity here in Europe, where it can be challenging to raise enough money and develop a multi-million-dollar market cap. However, when a European company reaches that level, it tends to have proven its worth and shown that it has what it takes to succeed. Zealand is 23 years old and today has a market cap of around USD 1.2 to 1.5 billion, which reflects our endurance, resilience, and great science.

How well financed is the company in terms of being able to fulfil its ambitious launch plans up to 2025?

This is a constant effort for all biotechs. Even US biotechs need to ensure that they have long-term financial support. At Zealand, we are lucky to have amazing long-term investors who believe in our science and the team, but we are always on the lookout for extra funding sources, given our rich pipeline. We have made the decision not to cut down on research to fund short-term commercial aims and we want to keep advancing. By 2025, when we aim to have five commercialised drugs, we still want to have an abundant pipeline full of promising compounds.

Zealand has struck clinical and preclinical license collaborations with Boehringer Ingelheim and Alexion respectively; how do you see the company's partnership model evolving?

Partnerships are an essential part of our strategy. When I came on board, I was struck by the potential of peptides and instructed our discovery team to focus on broadly bringing peptide-based drugs forward across all therapeutic areas. Money is precious – especially for a company which at that time was not yet generating revenue – and so I set the mandate of being productive. We did not want to try and produce drugs for very specific therapeutic areas, rather the aim was to produce *something*. At that point, we can then make the decision to either take ownership of the molecule ourselves, if it helps consolidate our existing pipeline and presence, or find a partner if it does not.

In the Boehringer Ingelheim, Alexion, and now AstraZeneca deals we had huge assets that are now proving to be exactly as good as we first thought, but there was a need to partner with leaders in their fields who have the ability to realize the full value of the product. We made the strategic

decision to partner in these instances. For example, for the program we out-licensed to Alexion, we would face a very strong competitor (in Alexion itself) if we brought the product to market as Zealand. If everything went well, the best we could hope for would be around a 20 percent market share, and it would require a lot of effort to expand across the world. However, by partnering with Alexion, this product will have access to 100+ countries and 100 percent of the market; the financial comparison is no-brainer.

In terms of upcoming partnerships, we are now stepping into the obesity field, which is very large and where partnerships are crucial. The assets we are advancing are simply revolutionary and have nothing to do with the obesity products of the last 20-30 years. Like hypertension in the 80s and 90s, class after class of new products are coming through. Today, almost every hypertension patient can control his or her disease through combination therapies and different dosing, which is the direction in which the obesity field is also moving.

The past issue with treating obesity was compliance and the blame was put on the patients. However, this low compliance rate is natural, given the low effectiveness and significant side effects of existing treatments. In the compounds we are now advancing, we are seeing encouraging results in the early clinical trials. If patients see that their treatments are paying off, then they are more likely to stick to them.

COVID-19 created unique challenges for all healthcare stakeholders, although it seems like the last 19 months have been quite productive for Zealand. What was your experience of managing through this period and are there any lessons to be taken from it?

Culturally, we were well set up to deal with COVID. When the pandemic hit, our teams had the clear short-term goal of ensuring that all the patients in our clinical studies were able to continue to access our treatments for their own sakes and so that the quality of the studies and data generated would not be impacted. Additionally, we continued to run experiments in our labs throughout the pandemic.

Initially, the focus was on crisis management; dealing with an unplanned crisis and attempting to fix a very specific issue. However, we were also able to execute on longer-term plans – such as the acquisition and integration of Valeritas – during this challenging period. This was a company that had filed for bankruptcy, and the acquisition had to be done within a legally set timeframe, which made things difficult.

Another challenge of COVID was the slowdown in clinical trial recruitment, caused by patients' reluctance or inability to go to hospitals. However, thanks to our global presence, when Europe shut down, we continued to recruit patients in the US. Then, when the US shut down, Europe was regaining steam, so we were able to redirect resources there to maintain consistent recruitment of patients.

Overall, we were able to maintain transparency, set short-term executable goals and keep our teams engaged and focused, which allowed Zealand to weather the COVID storm. There is a certain level of pride, as a smaller company, in being able to show the rest of the world that we are able to deal well with these sorts of challenges.

Having taken the plunge of moving from a career in Big Pharma to head up a biotech, what has your experience been thus far and would you recommend it to others in your position?

It works for some, but not others. You must be at ease with a level of ambiguity to work in a biotech, which some executives very quickly tire of, given the fact that 20 to 30 percent of their agenda is constantly being changed, necessitating rapid adaptation.

However, people with Big Pharma experience can make a huge difference in smaller companies, because they have seen what good looks like and can easily apply time-tested principles around governance and structure which quickly lead to results. The well-organised way of working in larger companies pays off much more in a smaller structure with the agility to make decisions quickly and fix problems. If sufficient experience is brought from outside into small companies, they can be turned into fantastic, productive machines.

What is your final message to our international audience, some of whom are potential partners or collaborators, on behalf of Zealand Pharma?

After 23 years, we are now building Zealand into a fully integrated independent commercial company and have the right finance, pipeline, and science in place to do so. Our investors are in it for the long-term and have backed us solidly so far and we have a great board of directors in place who support our ambitious vision.

However, achieving such a vision will require bringing even more outstanding talent on board. Talented people should pay close attention to Zealand because there is a lot more to us than first

meets the eye. Each of our programs could be the basis for individual companies in their own right, which gives us a unique chance to execute our strategy and prove to the world that we are a fantastic company in the making.

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