TONY BRATT, NORDIC PHARMA

Graduating in Chemistry, Tony Bratt has more than 30 years' experience in the pharmaceutical industry following marketing and commercial functions through both blue-chip (e.g. Novo Nordisk) and SME companies (e.g. Elan). Mr Bratt gained a Diploma in Company Direction from the UK Institute of Directors in 2007 before starting a consultancy business in 2010 providing expertise to both client companies and investing in start-ups. In 2016, he was appointed to lead the UK & Ireland business for the Nordic Pharma group.

In this interview, Mr Bratt provides an illuminating view, from the pharmaceutical company perspective, of how the right parenteral delivery device can open up opportunities and markets for a drug product – in this case methotrexate – by enabling delivery by the patient, at home. He explains that Nordic Pharma's business model is focused on very specialised markets and how he believes drug delivery systems, and in particular the platform device concept, can play an important role in this niche product field.

Q For those of our readers who are not already familiar with the Nordic Group, I wondered if you could briefly introduce the group, its business strategy and model, its structure, and Nordic Pharma UK's place within the overall organisation?

A The Nordic Group was founded in 1995 and, as the name of the group suggests, it was originally in Scandinavia. Since then Nordic has evolved to become a pan-European business with affiliates in most of the major European countries, with reach from Portugal to Russia. The group headquarters is in Paris, as is our French affiliate, which is our largest operating group, followed by Scandinavia, and then the UK affiliate Nordic Pharma UK. So the UK affiliate is the third-largest of our operating companies.

Our business model is that we look to supply niche products, which are initiated by specialists. We are not a primary care business although, that said, our most recent product Nordimet® is often used in primary care markets but the product was not initiated there. So we look for products that are below the hurdle rate of even the mid-sized pharma companies now.

We have a strong offering to pharma companies in terms of partnering, which puts us in good stead. But from the outset we have been very much driven by products initiated by hospital specialists. We don't want to go into the mass market space and in fact over the twenty years since Nordic was founded that mass market space has declined in terms of its importance in the market.

In terms of the organisational structure, Nordic Group is a privately held company whose shareholders have a variety of interests. The Nordic Group has grown steadily over the last 20 years and is poised to grow even faster as we introduce our most exciting product to-date in Nordimet®.

Q Very recently, Nordic Pharma launched Nordimet®, a new methotrexate product presented in an auto-injector for self-injection, for the treatment of rheumatoid arthritis (RA), in the UK. Please could you tell us more about the product? How does it fit with Nordic's business model?

A Nordimet® is very important for us. It's a fascinating product. Our interest is based on having had history with methotrexate in our operating company in France, where we are distributors for another supplier. We built up experience in that space but clearly recognise some of the gaps and opportunities in that marketplace and set about developing our own franchise in which we actually have three different products available in different countries.

So we supply oral methotrexate, we supply methotrexate in a prefilled syringe or "semi-auto-injector" which meets modern safety standards in terms of retractable needles and, two weeks ago, in the UK and Ireland, we introduced Nordimet®, which is methotrexate in an auto-injector device.

In the UK we offer the prefilled syringe, which we call Zlatal, and now Nordimet®. In Ireland we have only introduced Nordimet®, and in France we offer all three products – oral, prefilled syringe and Nordimet®. So it varies across different countries.

The auto-injector behind Nordimet® is a very interesting development by SHL Group (Nacka Strand, Sweden), the designers of the device, who have really taken the evolution a long way in terms of simplicity of patient handling, healthcare professional

> "There is a second click when the injection has finished, which is unique to Nordimet®. So the patient knows when the dose has started and, crucially, when the dose has finished. The needle is of course only retracted when the dose is finished and so we think this end-of-dose click is also a really important safety feature."

"Literally only two-to-three weeks after launch, what we are experiencing in our conversations with healthcare professionals is that they believe the Nordimet® device will enable them to initiate injectable therapy where they may have otherwise failed to do so."

confidence in drug delivery, and in terms of patient safety.

There are three key messages we have about the advantages of Nordimet®. Firstly, patients with rheumatoid arthritis very often have dexterity issues and with Nordimet® there is no button to press on the device whereas the other pen device available in this marketplace requires the patient to press a button.

Secondly, Nordimet® has a compact design. All of these products have to be disposed of in cytotoxic bins and the essence of it is that you can get a lot more of our devices into a 1.5-2 L bin that you can the other products currently available. And of course the size of the device impacts on patient handling and transport.

Thirdly, and very importantly, the Nordimet® device has a unique two-click mechanism. There is a click when the formulation starts to be delivered after the pen has been pressed onto the injection site, and there is a second click when the injection has finished, which is unique to Nordimet®. So the patient and/or healthcare professional knows when the dose has started and, crucially, when the dose has finished. The needle is of course only retracted when the dose is finished and so we think this end-of-dose click is also a really important safety feature.

Q **Patient centricity and the move to self-injection at home are incredibly important themes in the parenteral delivery industry today and it seems Nordimet® is a great example of a product that, if it required administration in a clinical setting by a healthcare professional, simply would not be viable, yet thanks to delivery device innovations it is perfectly feasible to develop it for self-injection at home and it is therefore a very viable product.**

A It's a once a week delivery and so, yes, the burden on the system would be unsustainable. It is very much a patient-at-home self-injection system. If you look at the alignment with the anti-TNF (tumour necrosis factor inhibitor) space, it fits very well. The first generations of anti-TNF products were infused and patients had to literally go in – be it weekly, fortnightly, monthly – to have their anti-TNF treatment, which is used alongside methotrexate. And of course those products with time have moved to patient self-administration with ever increasingly improved pen devices.

So we're following that trend and really it's not unique to here. I was fortunate enough in the 1980s to work at Novo Nordisk when the NovoPen insulin pen was introduced – the very first pen, which was designed by Bang & Olufsen. We are now thirty years on and these devices are more standardised but there are always improvements – as demonstrated by Nordimet®.

Q **What are Nordimet®'s advantages in terms of benefits for the patient, and also commercially speaking? Methotrexate is effective orally and is widely available in oral dosage forms. What are the advantages of parenteral administration of methotrexate? To what extent does the auto-injector remove barriers to acceptance of the parenteral version?**

A Looking to Ireland provides a good example to answer this. In Ireland at the moment, apart from Nordimet®, they are still using a prefilled syringe to deliver methotrexate. Nordimet® will be the first methotrexate auto-injector in the Irish market. Literally only two-to-three weeks after launch, what we are experiencing in our conversations with healthcare professionals is that they believe the Nordimet® device will enable them to initiate injectable therapy where they may have otherwise failed to do so because of patients not being comfortable using a syringe device where the needle is on show. With Nordimet®, of course, the needle is always hidden, and it is protected after the injection meaning there is no risk of accidental needlestick injury.

Injecting the product enables a higher plasma level of methotrexate than can be achieved with oral. If you could deliver enough oral methotrexate to achieve high enough plasma levels to gain the required clinical effect, then of course you would always go for the oral route rather than any parenteral route. The issue though is that the side-effect profile of oral methotrexate, delivered in such doses, for many patients is just unsustainable. It is not uncommon for some patients, particularly younger patients, to have a very severe reaction even becoming nauseous at the sight of methotrexate tablets, before they have taken their dose.

So I think, for healthcare professionals, yes in an ideal world if we could deliver oral methotrexate safely in some form of protected oral delivery system which would cut down the GI side-effect profile, that would be great. It doesn't exist though and none of the drug delivery houses have successfully managed to overcome that barrier. So parenteral – for achieving the right dose – has to remain the way forward.

The other question is, once patients are on methotrexate as the gold standard of DMARD therapy, how long can you keep them on methotrexate with the right clinical effect before moving up to a biologic where you face significant changes in drug acquisition costs? The right delivery device can enable healthcare professionals to keep patients on higher doses for longer – and this is what they are aiming to achieve by having an injectable methotrexate product that they and their patients are confident with.

If with Nordimet® we can expand the window for injectable methotrexate by either pushing down on oral or up onto biologics, then we believe that this will of course be good for us commercially

"If you could deliver enough oral methotrexate to achieve high enough plasma levels to gain the required clinical effect, then of course you would always go for the oral route rather than any parenteral route. The issue though is that the side-effect profile of oral methotrexate, delivered in such doses, for many patients is just unsustainable."

"Products that are small in terms of revenue can still provide a great deal of support for healthcare professionals in treating specific patients. Nordic fulfils a really important role in these areas where large companies cannot operate because it is not worth their while. This is where we think Nordic, as we become more focused, will become more established as we unify pan-European brands."

by having the right product available at the right time but, more importantly, it could enable healthcare professionals to have a greater window of use for this kind of agent than they have had in the past. If patient convenience improves, compliance can also be improved and therefore efficacy of disease management.

Q Please could you tell us more about the selection of the delivery device for Nordimet®? Was it developed in-house or by a third party?

A Whilst I was not directly involved in this process, what I can tell you is that right from the start, having had the experience of working in France (where our corporate headquarters is) for the competitor product, we knew the space very well indeed. We recognised that there was an opportunity to address some of the issues both with the standard prefilled syringe version and with the pen device that, at that time three or four years ago, would shortly be coming to market.

Nordic Group set about scouring the world really to find the optimal device, which could also be assembled in our manufacturing company in Sweden, QPharma. Where would you want to go if you wanted an injection device for once weekly self-administration of a cytotoxic agent? We have to remember that it's not all that long ago that these products were made up by galenic compounding pharmacists with all the challenges that this entails.

We wanted to make sure that we took this product as far as we could as an organisation for the best patient acceptability and patient safety, and for the confidence of the healthcare professional in terms of safe, full-dose delivery of a cytotoxic agent.

The device that was eventually selected, SHL's Molly, really stood out. It ticked the following boxes:

- We didn't want a button to press because our customers and the market told us that this is difficult for RA patients.
- We wanted a compact device because we knew that the bigger the device is, the more intimidating it can be, particularly if it's a patient's first injection.
- The innovative double-click mechanism meant that we could say with absolute 100% confidence to healthcare professionals, your patients will know that the drug has been delivered because they can see, hear and feel when it has worked.

In terms of what we wanted to achieve for patients, it came down to these three key elements.

Q From the point of view of a pharma company focused on developing cost-effective specialist, niche and orphan products, there is a constant dynamic, when looking at new product opportunities, between seeking out new molecules or, as was the case with Nordimet®, seeking out new ways to add real value to existing molecules. Could you talk about this from Nordic's point of view?

A It's a fascinating dynamic because taking an established generic molecule and innovating with device can be a very successful business strategy. If you look back to the insulin and growth hormone markets before the advent of biosimilars or analogues, then insulin was insulin and growth hormone was growth hormone, but if you had a superior device to add differential, then you gained an advantage in the marketplace.

So on one hand, it is possible, and Novo Nordisk did it extremely well, to put up enormous barriers to competitors encroaching on your market using manufacturing technology and also devices. However of course on the other hand this is not as robust, early in the lifecycle, as having a patentable new molecular entity. Having said that, if you manage the lifecycle successfully including by the use of delivery devices, you don't face the traditional generic exposure at the loss of exclusivity and your business model can run for longer.

These are the kinds of tensions you're looking at and Nordic has been down both routes. Every asset has to be treated on its own merits but there is usually a reason why they have missed that Phase I / Phase II "mop-up" by big- and mid-pharma and you have to be extremely careful about moving into areas where you may have only one single asset. Franchise identity is really important in specialised areas and becomes more important with new chemical entities.

There are times when we have been innovative in different ways. For example, we have a pan-European haematology product called Nordic Aprotinin, which used to be called Trasylol. The marketing authorisation was suspended by the EMA in the late 2000s but Nordic continued to supply it in the UK at the request of the MHRA as an unlicensed medicine and it has recently been re-introduced and the marketing authorisation brought back by the EMA. This is an instance of a very small company being able to maintain a niche product, working in partnership with the regulator, because it was adding clinical value.

Those kinds of products that are small in terms of revenue can still provide a great deal of support for healthcare professionals in treating specific patients. Nordic fulfils a really important role in these areas where large companies cannot operate because it is not worth their while. This is where we think Nordic, as we become more focused, will become more established as we unify pan-European brands.

We can go to the US, go to Asia, go to Eastern Europe and say to organisations, if you have an asset that is worth potentially €20-30 million, don't even bother trying to talk to large pharma companies as it is way below their hurdle rate, whereas we have stretched from Portugal to Russia and an asset of €20-30 million would potentially be of interest to us and we are equipped to support healthcare professionals by bringing it to market.

I believe a unique strength of Nordic is that whilst being able to focus on niche products we also have that true pan-European footprint. It is possible to go and find a small family-owned pharma business in France, one in Germany, another in Italy. But if you want one single partner across Europe who has that scale but can also handle small

specialist products, I cannot think of another company, other than Nordic.

Q Finally, in an ideal world where anything is possible (within reason!) what would you like to see coming out of the drug delivery sector over the coming years – in terms of innovative technologies or indeed innovative ways of working and doing business – that would really help Nordic achieve its objectives?

A Broadly speaking, we want to continue being as successful as possible in the spaces in which we operate.

The drug delivery environment – historically – had sought big market opportunities to apply their technologies. Particularly on oral dosage forms, thinking back to companies like Alza and Elan, there were huge cardiovascular franchises in global primary care markets and it was all about developing modified-release dosage forms for different products – to minimise dosing frequency, evergreen the product, and potentially reduce the side-effect profile.

In terms of what we would like the drug delivery sector to bring to the table if we imagine that anything is possible, we touched on it earlier. Across all of our core areas we have established molecules with different risk-benefit profiles and different side-effect profiles.

Let's stick to rheumatology, as mentioned previously if someone could develop a patentable oral formulation of methotrexate you can dose up to 25 mg with no GI side effects, that would be a very welcome product – by healthcare professionals and their patients. For us, we would love to be able to get hold of something like that because it would enable us to become a more established partner with our healthcare professionals. Being in a position to provide an offering that covers the entire therapeutic platform means that it becomes a more adult-to-adult conversation. Rather than simply saying to customers, "Our product is better than theirs", we are able to say "We have the entire range, what is best for your patient?"

Beyond improving the oral product, we continue to see significant innovation in rheumatology in developing new chemical entities, such as the area of interleukin 17 inhibitors. But whilst this level of innovation continues I still believe we can look at products that come earlier in the treatment paradigm – like methotrexate, but there are other DMARDS too – where we can enhance the drug delivery mechanism to give healthcare professionals and their patients more choice.

Unfortunately, these products are not always the most attractive, financially, for drug delivery firms because, in contrast to the blockbuster oral cardiac therapy markets we just mentioned, these are the smaller products, and that is the dilemma.

Mr Tony Bratt
General Manager
E: info@nordicpharma.co.uk
T: +44 0118 207 9160
F: +44 0118 207 9161

Nordic Pharma Ltd
Unit 3 Commerce Park
Brunel Road
Theale, Berkshire
RG7 4AB
United Kingdom

www.nordicpharma.co.uk