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Mark Lotter, founder and CEO of Nuance Biotech, explains why he decided to return to the China market to establish Nuance Biotech, two years after his retirement. He also shares the rationale behind their three-track business model, their exciting portfolio of products, and their ambitions to expand into the Asia-Pacific region, as well as highlights their mission to bring innovative compounds into the market to meet the needs of patients in China.

Mark, after an extensive career with stints in both Big Pharma as well as biotech in South Africa and China, you retired in December 2012 â?? before deciding to establish Nuance Biotech in January 2015! What brought you out of retirement?

Nuance Biotech is actually the second company I have co-founded; the first was a commercial venture called NovaMed Pharmaceuticals, founded in 2005 as a contract service organisation service provider for MNCs in China. NovaMed was subsequently acquired by SciClone Pharmaceuticals in 2011. For Nuance Biotech, my motivation was to build a platform for innovation in China. We initially planned to start with an R&D unit before migrating to a commercial platform.

My decision to return to China was spurred by the changes I could see taking place in China in 2014 and 2015. Traditionally, the bulk of Big Pharma MNCsâ?? portfolios in China were off-patent

originator products (OPOs), also known as legacy products. These represented at least 70 percent in a number of MNC revenues in China, while the contributions of innovative medicines to the overall revenues were rather insignificant. By 2015, and even as early as 2014, however, we could see the market shifting to focus more and more on innovative products and therapies, particularly in oncology and immunology. At the same time, it was clear that pricing post expiry of patents would come under pressure in favour of generics. This positive development within the Chinese pharmaceutical industry was the main driving factor behind the establishment of Nuance Biotech.

What have been some key milestones for Nuance in the past four years?

Firstly, we have successfully raised three rounds of funding. We have two Tier 1 investors: Matrix Partners and C-Bridge Capital, the latter of which is the largest healthcare-specific fund in China.

Secondly, in terms of our portfolio, we have completed multiple transactions, including the licensing of four R&D assets. Two of them, both novel oral small-molecule cancer drugs, are Phase 2 ready. We have also in-licensed a billion-dollar product (Exparel$^{Â®}$, an opioid-free product for post-surgery pain control) from US-based Pacira Pharmaceuticals to commercialize in China. In addition, we have acquired Niferex$^{Â®}$, an iron deficiency product, from UCB. This acquisition has transformed the company from a CSO model to a fully-fledged pharmaceutical company in China.

More excitingly, we have launched our first oncology product, Treanda$^{Â®}$. This launch represents an important milestone in the company and one which will serve the future commercial needs from both the Nuance pipeline as well as other oncology assets.

In recent news, we have also won a major award in Shenzhen (Shenzhen government award) for a cancer therapeutic we have in-licensed, that can stimulate both B and T cell responses simultaneously, for the second-most innovative project out of over 900 projects evaluated. This was done in partnership with a European company, TYG Oncology.

Why did the China market need a company like Nuance back in January 2015 â?? and with the significant changes within the market today, can Nuance still meet these needs?

While the Chinese pharma landscape has developed very rapidly over the past few years, we still see a split within the industry between very commercial-based and very R&D-based companies, with very little movement or synergies between the two groups. Realistically speaking, for many of the new R&D-focused biotech start-ups that have sprung up in the past few years, they would not transition into commercial-stage companies, for a number of reasons including i.e. M&A, licensing, clinical trial failures, and so on.

We think a balance could â?? and should â?? be established, which is essentially the premise of the MNC model, after all. Building short-, medium- and long-term revenues and portfolios prospects is key to build a long term and sustainable business model for China. We wanted to build a fully integrated entity without necessarily going through the pains and risks of undertaking long-term capital investments into R&D and manufacturing facilities whilst building a world-class commercial engine. This is all underpinned by building a leading regulatory and clinical trial presence in both China and South Africa. This is a very different model compared to what most companies are doing in China today is R&D and CSO like models.

With regards to the short-term prospects, we look to capture revenue that already exists in China â?? i.e. products already approved and in the market. Here Nuance has built a leading commercial and market access team designed to cover the leading cities and hospitals across China. In order to expand its commercial footprint in China the company has recently added a novel and first in class Open Commercial Platform. This is a novel commercial and academic platform for pharmaceuticals, which aims to link leading drugs and leading agents nationwide in those areas where the company does not have a physical presence. An MNC like compliance platform underpins its commercial efforts in China with a strong focus on medical education, an area which requires more attention by companies going forward. I can share more on this later.

The medium-term prospects focus on finding IP is already launched in other international markets and that is relevant to China but that has not been filed within China as yet. For instance, you have multiple mid-sized international players with novel and differentiated brands that are still not present in China. There are a number of novel and exciting compounds in different parts of the world which offer material opportunity in entering the China market. For many of these companies, these innovative products the next logical step for the IP holders might be to enter Europe or other developed markets with China not being targeted. Given this Nuance seeks to in-license them, thereby affording them the opportunity to enter the worldâ??s second-largest market. The upside for us targeting these compounds is that there are no medical or scientific risks associated with these products since they have already been successfully launched in other countries. Since setting up the company, the company has now been carved into two legal entities â?? Nuance Pharma (which is responsible for the short and medium terms assets) and Nuance Biotech (which is the companyâ??s R&D arm). The â??Nuance Pharmaâ?? entity, which is headquartered in Shanghai and has eight more regional offices across China, comprising around 400 people in total. The size of the team is predicted to grow rapidly in 2020 as additional commercial stage assets are added to the company portfolio.

The long-term aspect is looking at the ability to take our own compounds through clinical development, typically from late-stage Phase 2 onwards. This is our R&D business, which is now referred to as Nuance Biotech. We recently relocated this to Shenzhen (Guangdong province), in line with the Chinese governmentâ??s efforts to promote the economic development of the whole Guangdong-Hong Kong-Macau Greater Bay Area. For our in-house R&D efforts, we intend to home in on areas where we believe we can generate sufficient value and also attract reasonable attention if we are successful. We have attracted a number of leading overseas returnees as well as immunology PhDs trained at the University of Cambridge in the UK (Dr Ni Jian), for instance.

Indeed, you have stated the objective to develop your Open Commercial Platform into the single largest and most comprehensive industry platform in China by 2020. What value will this bring?

The biggest challenge for pharma companies in China is to achieve the right commercial footprint across China. Even top MNCs like AstraZeneca, with 16,000 employees, still do not manage to cover the entire market of 1.4 billion people. Local companies have traditionally used sales agents and distributors to commercialise and distribute their products. However, the recent introduction of the Two-Invoice system in China has challenged this agent model. The other challenge the traditional agent model faces is compliance â?? which, as you can imagine, is a significant concern for MNCs.

For any company, based on your ability to cover China, you have to look at a two-tier model. For key institutions, cities and geographies, you would want to cover directly through your own sales

organization, and for all other areas, you would look to leverage existing structures in China in order to expand your footprint.

However, once they segment the market, they would still need to find a professional, well-organized and educated group of commercial people to deliver their strategy. As far as we could see, there is nothing available on the China market which ensures both an education and compliance-based approach as required by MNC companiesâ?? which is why we have launched our Open Commercial Platform to provide companies with the ability to select, educate and most importantly, perform quality control on third-party promotion. This requires significant technology advances, building in the relevant compliance controls whilst ensuring MNC like the commercialisation of brands, the core focus being that of academic pronation â?? both at a disease and brand level.

The combined approach of a dedicated commercial team, as well as access to the commercial platform, allows for Nuance to cover the China market as would larger MNC in China.

With the increasingly competitive biotech landscape in China, what is Nuanceâ??s positioning against the early-stage Chinese biotechs like Zai Lab, Hua Medicine and Innovent, who also see in-licensing the China rights of global assets as a BD strategy?

Many current Biotech units in China are either partnering with MNC R&D assets (these have been de-prioritized or divested for different reasons) or developing their own R&D projects.

Given that our primary objective is to secure both innovative and China-specific compounds for China, our starting point is different. We have opted to focus on smaller-sized companies with a direct link to universities, such as the case of Celleron, an Oxford University spin-out. Our fundamental belief is that truly novel innovation lies within the domain of academia or where there are strong links to academia.

Over time the company will seek to also build its own R&D capabilities but for now itâ??s based on a licensing model.

How do locals perceive a â??foreignâ?? company like Nuance?

The nationality is a minor element â?? it is about your company having a combination of local and foreign experience. I have also been in China for a long time and have established a track record, level of experience and knowledge as well as a network of industry contacts, which potentially makes local partners more comfortable in partnering with Nuance in China. My initial experience, having helped the AstraZeneca affiliate in China scale its commercial operations, launch new products (Iressa) and attract core talent to the company has also proved tremendously useful in both building the company and partnering with other international companies.

Furthermore, I have spent more than twenty-five years in Big Pharma, including with Aspen (South Africa and Europe) as well as AstraZeneca in both South Africa and China, so I understand the overall sector both in China and abroad. Understanding the needs and concerns of foreign companies wishing to enter China is important and something we as a company view as a competitive advantage. Having the backing of international tier 1 investors is also something that has helped foreign-based companies see value in partnering with Nuance in China.

From what we understand, Nuance has a unique joint focus on China and South Africa. Can you explain how this is a competitive advantage?

Our operations in South Africa are purely focused on clinical development because the commercial market in South Market is still relatively small. In China, you can typically only recruit Chinese patients. The benefits of having clinical operations in South Africa include the lower cost of clinical development and the ability to capture a larger patient pool from diverse ethnic groups, including Caucasian and African subsets, providing clinical data that could be used for global filings.

For instance, given global competition the fields of immunology and oncology today, patient recruitment within the Caucasian subset is difficult in Europe and the US, but in South Africa, we are able to access that pool relatively more easily.

South Africa also offers a unique phase 1 capability and with many companies already having migrated to Australia or phase 1, the capacity and costs in South Africa are proving to be attractive.

On another note, looking at the Chinese industry, many Big Pharma executives like you have left to start their own companies in China. How do you expect this to impact the overall pharma and biotech industry in China?

To date, most of the migration of executives from MNCâ??s to start up is in the R&D space although more recently one is seeing a migration of commercial executives into Chinese based start-ups.

The issue of start upâ??s will continue to be challenging and will be most influenced by the companiesâ?? ability to fund its operations in China. The vast majority of new biotech companies in China are currently focused on the biologics segment, mainly looking at immunology and oncology. This means the space is growing increasingly competitive and we can expect to see only a few winners emerge â?? first to market is key as we have seen in the PD-1 market.

However, the addition of start-ups, both R&D and commercial to the overall industry development is positive for the market. In addition to attracting talent â?? both foreign and local â?? these companies will ensure the addition of new compounds, technologies, thinking and business models to China, all of which will materially add to the development and growth of the sector.

The recent changes to the regulatory and commercial sectors have resulted in a level of disruption and opportunity for start-ups to enter and prosper. In a time of change China will present a level of opportunity to allow smaller, more flexible and agile start-ups to enter and innovate. Large and well-established companies might be on the receiving end of many of these changes and their DNA and size make it difficult for them to respond in a timely and appropriate manner.

What have these changes meant for Nuance?

We have focused on what we think would be best from a commercial perspective. We are not only new launch status and market share; we just want to focus on critical unmet medical needs and areas that require solutions in China. This can be both disease-specific and pricing-related opportunities.

For example, we know that the incidence of colorectal cancer has continued to increase in China. In addition, many patients are diagnosed at a very late stage â?? versus other countries i.e. Japan. In

addition, many of these patients look to be treated in key centres in major cities like Shanghai and Beijing â?? this would require them and them families to travel and fund treatment and all the associated costs â?? this is both expensive and challenging. Allowing for oral interventions would allow for patients to be treated on an out-patient basis versus that of traditional hospital-based treatments which require hospitalization.

In addition to being China-specific, we are also expanding our strategy to the Asia-Pacific region, where we see more similarities than differences in the market from a disease and product profile point of view. The main reason is risk mitigation. Being in a single market with a defined portfolio is risky. The Asia Pacific markets continue to represent synanon opportunity in growth whilst ensuring making policy and pricing risks of that being in China only. Another reason is leverage of business development transactions â?? Nuance seeks to expand the territory in its BD activities to include Asia Pac, thereby assisting the company build a firtree pipeline in these markets as well.

Nuance would be among the first China-based companies to build an Asia-Pacific footprint. Many companies have yet to discover the value and potential of the region. The entire Asia-Pacific healthcare market is currently of similar size to that of China (in many TAâ??s), and in some respects, even bigger! The regulatory and market access process is less complex which would allow for earlier commercial traction than in China.

We have different approaches in mind when seeking to enter AP â?? these include acquisition to partnering. We could work with companies with a similar business model to ours, or rely on the usual approaches licensing, partnerships and even acquisitions.

From your extensive experience in the China market with Big Pharma companies like AstraZeneca as well as your own companies, what are the most common misunderstandings or misconceptions about the China market that persist today?

Firstly, that doing business in China is less expensive than in more developed markets â?? this is no longer true. You pay a premium for almost anything in the sector whether that is getting your product registered, recruiting quality people or building infrastructure. Creating something independently in China is expensive and takes time. This together with the delayed time of registering products and the complex market access process makes the ROI model challenging. In order to build a profitable and sustainable business one needs to excel on all fronts â?? in order to do this the right people and correct levels of investment are required.

Secondly, the constant fear of IP infringement. This is something big Pharma has dealt with and frankly have shown the confidence and commitment to commit to building a presence in China. I want to emphasize: companies that are prudent when they file in China will receive more than sufficient IP protection.

Looking ahead, where would you like to see Nuance Biotech in three years?

Growth will be driven via a novel and unique BD, regulatory/medical and commercial capability in China. The second growth lever will be through the companies ambitions to geographically expand into Asia Pac.

Going forward Nuance hopes to offer companies not already present or those not optimally represented in China a differentiated and unique route to enter or grow in China. The Nuance team

has a strong track record in commercially scaling assets as is in evidence in the time spent by the team members in AZ & other MNCâ??s, and more recently the acquisition from UCB.

In summary, Nuance will be an Asia Pac based company, headquartered in China, with a mix of commercial-stage, regulatory stage and development stage assets in its core targeted TAâ??s. The growth will be underpinned by a strong team, good systems and an MNC compliance platform.

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