Interview: John London – CEO, Nuvo Pharmaceuticals, Canada



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John London, CEO at Nuvo Pharmaceuticals Inc., explains how he and his partners turned the Canadian company from insolvency into a profitable enterprise with FDA approved products that are being marketed around the world. He further talks opportunities in the topical pain management market and how Nuvo Pharmaceuticals will enhance its portfolio by acquiring more products, while continuing to bring its own products to various markets around the world.

John, when you and your partners took over management of Nuvo Pharmaceuticals in 2005, the company had no FDA approved product, approximately CAD 50 million (USD 39 million) in debt and two weeks of cash Under your leadership, Nuvo has obtained four FDA approvals and now has over CAD 17 million (USD 13 million) in cash and no debt. What are your secrets to success?

Really no secrets – just hard work and tenacity I guess. In 2005, Nuvo Pharmaceuticals was effectively an insolvent company, so our first steps were to raise money and restructure our debt. We were able to raise some survival money in a fairly difficult equity financing. We then settled part of our debt by meeting with our creditors and convincing them to trust in Nuvo Pharmaceuticals' new management team but to accept significantly less than what they were owed in full settlement. We also were able to get a major creditor to convert his debt to equity. Shortly thereafter, we changed the name of the company to Nuvo Research in an effort to escape the tarnished image that it was suffering from. Once we got the company back onto more solid

financial footing, we turned to the business issues that were plaguing the company; most importantly, we worked hard to address the FDA's issues relating to original Pennsaid® and in particular focused on completing a phase III study that we knew was a prerequisite to FDA approval.

Nuvo's main product at the time was Pennsaid®. When we first took over Nuvo in a proxy fight we discovered that the FDA had issued a non-approvable letter for Pennsaid® that had never been disclosed. The letter indicated that a complicated, expensive five arm clinical study was needed in order to achieve approval. As we were definitely lacking deep expertise in clinical drug development, we hired as a consultant, a former FDA director, Dr. Lee Simon—who ironically had authored the non-approvable letter when he was FDA director of its pain group. We completed the clinical study on the understanding that if the results were positive, they would meet the expectations of the FDA and Pennsaid® would be approved for marketing in the US. Once the study was complete, we were encouraged by the results which were spectacularly positive on all counts.

In mid-2006, we submitted the clinical study results to the FDA as part of our response to the non-approvable letter, fully expecting Pennsaid to be approved as we were confident we had addressed all of the FDA's clinical issues. We understood that any pharm tox safety issues had been previously satisfactorily addressed. However, at the end of 2006, we were surprised to receive not an approval but an approvable letter that raised safety concerns about the topical use of one of the excipient in Pennsaid®, dimethyl sulfoxide (DMSO),

We quickly got over our frustration and disappointment and set about proving that DMSO was indeed safe when used as a topical excipient. We again hired a former FDA director as a consultant—this time Dr. Jonathan Wilkin the recently retired brilliant head of the FDA dermatology division and an expert in topical product efficacy and safety—. Jonathan helped us decipher the FDA letter and determine what studies we needed to conduct to respond to the FDA's issues. It took us the better part of three years, millions of dollars and 12 more safety studies to finally satisfy the FDA of the safety of DMSO. Today, Dr. Wilkin believes that DNSO is likely the most studied topical excipient in the history of the FDA.

The field of topical pain products addressing osteoarthritis and related conditions is still considered to be a niche market. What opportunities does it present for Nuvo Pharmaceuticals?

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Our two main products, Pennsaid® and Pennsaid 2%® are nonsteroidal anti-inflammatory drugs or NSAIDs. While there are many NSAIDs on the market, they are mostly orally administered. They are quite effective in pain control, including for conditions such as osteoarthritis. However, they do come with a series of more than unpleasant side-effects. The main serious side effect is gastro-intestinal bleeding. In the USA, there are 15,000 deaths from gastrointestinal bleeds related to oral NSAID medication every year. A raised risk for cardio-vascular incidents is also a side-effect of oral NSAIDs.

These side-effects are in large part significantly reduced when Pennsaid® or Pennsaid 2%® is applied topically. Both Pennsaid and Pennsaid 2% act locally, not systemically by carrying the active drug, diclofenac, through the skin to the affected joint. We know from studies that the systemic exposure of diclofenac in Pennsaid® and Pennsaid 2%®, is much lower compared to its oral administration by taking a pill. Yet, we have demonstrated in two placebo controlled clinical studies that Pennsaid® achieves equivalent efficacy to oral diclofenac treatment in osteoarthritis of the knee.

In Europe, the market for topical pain relief products is already well developed, many of the products are over the counter products rather than prescription products and competition is significant. In North America, our society is still somewhat averse to topical treatments, although we have seen this trend slowly reversing. More and more people are realizing that in order to fight pain in one joint, there is no need to expose one’s entire body to the drug.

In the USA, NSAID topical products are prescription medication, and the competition is significantly less. Besides Pennsaid® and Pennsaid 2%®, there is only one other FDA approved topical NSAID for the treatment of osteoarthritis, Novartis’ Voltaren® Gel. Voltaren® Gel went generic in 2016, and we are not aware of any new significant competitors that are close to FDA approval and to entering the American market.

Our strategy has been and still is to rely on solid local commercial partners for the distribution of Pennsaid® and Pennsaid 2%® in international territories. We have fared well with this strategy, not only in the USA, but also in Greece where Pennsaid® goes head on head with Voltaren®. Thanks to our distributor in the USA, Horizon Pharma, we have also done very well in competition against Voltaren® in the US market.

Is Nuvo Pharmaceuticals pursuing concrete plans to bring Pennsaid 2%® to Canada?

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Pennsaid 2%® is a significant improvement over original Pennsaid®. Pennsaid 2%® comes in a gel-form, metered dose pump bottle while Pennsaid® is a liquid solution that requires the patient to count drops into his or her hand before application to the affected joint. Most importantly, Pennsaid 2%® requires application only twice per day and not four times a day which is the dosing regimen for original Pennsaid® and for Voltaren® Gel. Currently Pennsaid 2%® is sold only in the USA. Our strategy is to make Pennsaid 2%® a global brand and available to patients in Canada and around the world.

The FDA approval we have for Pennsaid 2%® dates back to a time when we were operating with a different distributor in the USA. This distributor was responsible for the sales of Pennsaid® and agreed to complete the development of Pennsaid 2%® by conducting and paying for two knee osteoarthritis phase III studies, each with a cost of approximately 20 to 30 million USD. When the sales of Pennsaid® did not go as they had hoped, our distributor cancelled the studies which resulted in Nuvo suing them and eventually getting the US product rights back. We were pleasantly surprised that our then distributor was able to obtain US approval for Pennsaid 2%® with a phase II study that we had never intended to be a pivotal study

From Nuvo Pharmaceutical’s perspective we were pleased that Pennsaid 2%® had achieved FDA approval, however, we were left without the phase III data that we had anticipated and was required by health agencies in some other markets around the world to support marketing approval of Pennsaid 2%®. While many countries will rely on our FDA approval as the basis for their local market authorizations, Canada, many European countries and Australia were insistent that a fresh phase III clinical study of Pennsaid 2%® was required.

Unfortunately, Health Canada was not ready to accept the same approach and data the FDA did, and both Health Canada and the MHRA (Medicines and Healthcare Products Regulatory Agency) of the United Kingdom indicated that they needed another clinical study to support approval. With their agreement, we conducted two phase III ankle sprain studies in acute pain, something we had not done before. While these studies brought in reasonable results, they were not statistically significant and do not support an acute pain indication.

In collaboration with our scientists and consultants, we have gone back to the drawing board and are hoping to persuade Health Canada and European regulatory authorities that the extensive body of evidence that we have to support the safety and efficacy of Pennsaid® and Pennsaid 2%®, should support a Pennsaid 2%® approval for the treatment of osteoarthritis. We will be seeking scientific advice from select regulatory authorities on the correct pathway forward which we expect to receive by the end of the first quarter of 2018.

We are in advanced discussions with international partners who have the ability to sell Pennsaid 2%® in their respective territories without a new study and expect to complete licensing arrangements with them this year and throughout 2018. We currently have partners in place for Greece, Italy, the United Kingdom, the USA, Canada and in India, Sri Lanka, Bangladesh and Nepal where our partner, Sayre Pharmaceuticals is about to apply for regulatory approval.

Can you tell us more about the recent enhancement of your production plant in Varennes, Quebec?

Currently, the plant outside of Montréal is operating at 25 to 30 percent of its capacity only, which is why we are actively looking to acquire or in-licensing products that we can manufacture to more fully utilize its capacity. The types of products we are interested in are those in our field of expertise, which tend to be topical products. We therefore see potential in creams, gels, lotions and solutions that can be used in the areas of pain management, dermatology and some women's health areas.

What makes Nuvo Pharmaceuticals the partner of choice?

We are not only interested in global or territorial rights to products that we can in-license or acquire, but want to secure manufacturing rights for those products as well.

I think that Nuvo has proven that we are capable of achieving our goals. We are making money with our flagship product approved and selling only to the USA. Much of the margin from new products and sales will drop to our bottom line. We have a great balance sheet with over CAD 17 million (USD 13 million) of cash and no debt so we certainly have the financial capability to acquire more products.

Pennsaid 2%® has enormous potential, and we are eager to entrust and out-license its rights to partners throughout the world. If they succeed through increasing sales, Nuvo Pharmaceuticals will succeed through royalties and manufacturing margins.

As an entrepreneur yourself, what advice would you give to young Canadian entrepreneurs, just about to launch their company?

For whatever reason, Canada seems to not be as entrepreneurial as some other places in the world, especially in the biotech sector, where US startups are prevalent. However, Canadian investors understand the value of solid balance sheets and profit but sometimes don't have the internal scientific band width to handicap the risk and reward equation of drug development. The USA for their part have the specialized and sophisticated exclusively life sciences investment funds

that can wrap their minds around the science and therefore fund biotech startups.

I guess the message that I would relay is “Just go for it!” You do not want to miss out on the excitement and experience of forging your own way. I would also suggest, when you need advice, do not shy away from asking help from world class experts, no matter how far you deem them out of your league. It might come as a surprise how many are glad to help with advice, having once stood in the same place as young entrepreneurs stand today. Be prepared and bold when asking for financial support. If you are able to articulate the opportunity for investors together with an honest and knowledgeable assessment of the risks and rewards, you will be well on your way to starting a potentially interesting and exciting venture.

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