Interview: Grace Yeh â?? Founder, President & CEO, PharmaEngine, Taiwan

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Grace Yeh,

Founder, President, and CEO of PharmaEngine, one of the most eye-catching success stories to recently emerge from Taiwanâ??s maturing biopharmaceutical sector, documents the main success factors that have allowed PharmaEngine to become the first Taiwan-based company to receive FDA approval for a locally-developed oncology treatment, as well as the promising growth options she currently envisions to ensure PharmaEngine becomes one of the most successful biotech companies in Asia.

In 2003, you founded PharmaEngine, which became on October 22nd, 2015 the first Taiwan-based company to receive FDA approval for an oncology product, the pancreatic cancer drug Onivyde®. Could you provide us with an overview of the companyâ??s main milestones that rendered this remarkable achievement possible?

In 2003, PharmaEngine began operations and in-licensed PEP02 â?? the compound that would later become Onivyde® **â??** for Asia (including Japan) from San Francisco-based Hermes Biosciences. From 2003 to 2007, we progressed in the development of this molecule from animal studies to filing an IND to Taiwan FDA and started phase I trials, which we exclusively conducted in Taiwan. The results of our phase I trials were then reviewed and accepted by both the US FDA and the EMA without having to repeat any testing in the US or in Europe before phase II, which allowed us to

accelerate our product development.

When I saw the promising data we received from the phase I, I decided to acquire the rights for the European market, in addition to the Asia rights we already held. In 2008-2009, we started a phase II trial for gastric cancer in Europe and Asia, as well as a phase II study for pancreatic cancer in the US and Taiwan, which we both completed in 2011 with very promising results.

In 2011, we licensed out PEP02 rights to Merrimack Pharmaceuticals, the US-based company that had acquired Hermes Biosciences, and jointly started a global phase III study for pancreatic cancer. A few months later, in 2012, PharmaEngine IPOd on Taiwan GreTai Securities Market, and licensed-in two new projects: PEP503 from the French biotech Nanobiotix with rights for Asia-Pacific, as well as PEP06 from Guangzhou BeBetter Medicine with worldwide rights (excluding mainland China).

In 2013, only 21 months after the beginning of our global phase III study for PEP02, we completed the enrollment of 417 patients, which allowed us to announce positive data in May 2014 â?? way earlier than expected. Our partner Merrimack then decided to license the global rights of PEP02 (excluding US and Taiwan) to Baxter, which eventually spun off its pharmaceutical branch Baxalta â?? before Shire acquired it in May 2016.

As a consequence, our current partners in this project are now Merrimack (US) and Shire (worldwide rights excluding US and Taiwan), while PharmaEngine still holds the commercial rights for Taiwan.

Could you provide insights into PharmaEngineâ??s unique business model?

There are a great variety of business models that can foster the development of ambitious biopharmaceutical companies. The â??No Research, Development Onlyâ?• (NRDO) model however seems particularly suitable to Taiwan-based biotech companies: despite the quality of its research and medical infrastructure, Taiwan remains a small country in comparison to other advanced biotech hubs in the world, while our biotech eco-system still is relatively young. In this regard, most local investors â?? especially fourteen years ago â?? were reluctant to wait for an entire R&D drug development program to come to an end before receiving their return on investment.

Looking at our business model, PharmaEngineâ??s approach actually combines a No Research Development Only (NRDO) with a Networked Pharma structure. As part of this two-fold approach, we do not hold a laboratory or a manufacturing facility, which further allowed ramping up the development of the company and crucially reducing its cost structure. We then exclusively work with contract-research and contract-manufacturing organizations (CROs and CMOs), as well as medical and research centers. Looking at the drug development process, we license-in interesting compounds at the preclinical stage and license them out again when we receive positive results for phase II trials. Historically, PharmaEngine has then never been involved in the drug discovery or marketing stages of a product development.

Following our recent successes with Onivyde$^{Â®}$, we however decided to slightly alter this approach and expand our grasp throughout the drug development process. In this regard, PharmaEngine is now involved in the lead optimization of New Chemical Entities (NCE), while we also moved downstream to handle the commercialization of Onivyde$^{Â®}$ in Taiwan.

What are the crucial skills needed to make a success of this kind of innovative business model?

First and foremost, this approach requires very strong competences in project evaluation. Considering the growing but still limited size of our company, we can only afford to simultaneously handle a small number of projects. This also implies that we couldnâ??t afford to fail too often; as a

consequence, project evaluation and our capacity to assess the development potential of a given molecule over a decade is absolutely crucial. In this regard, we also need to hold a deep and extensive knowledge of the global oncology market, assess the needs of patients and the healthcare community in all strategic geographies as well as anticipate their evolution for the next ten years.

In the meantime, the importance of business skills should not be overlooked either. Like many of my counterparts within Taiwanâ??s biotech sector, I spent quite some time of my career working in a laboratory as a research scientist. However, I transitioned to preclinical development, project management and corporate development during the latter part of my career. In 2008-2009, PharmaEngine experienced difficult times during the global financial crisis. At that time, we almost exhausted the USD20 million raised from our first round of financing, one of our major investors bailed out of their commitment in 2008. This sudden decision left PharmaEngine in limbo, while we were working on two phase II trials for OnivydeÂ®. I then decided to invest personal funds in the company to ensure that we could complete these crucial trials forward.

Finally, collaboration holds a central importance in our networked pharma model. Being able to identify and jointly work with the best oncology experts in the world has been absolutely critical to the development of OnivydeÂ®, while the absence of in-house research and manufacturing capacities forced us to be extremely selective when choosing our service providers and other commercial partners.

In this regard, I deeply regret that our government officials today still hold the traditional thinking that biotech companies should conduct manufacturing activities in Taiwan. For the sake of our local, R&D-driven industry, I believe governmentâ??s attention should be primarily centered on the value PharmaEngine has generated for our shareholders and local economy, without forgetting domestic and patients worldwide may be able to access a life-changing treatment we managed to develop, thanks to this business model. Although we donâ??t hold our own laboratory, I would also highlight that we work with both local and international CROs and CMOs, which also contributes to support employment in Taiwan.

OnivydeÂ® currently is marketed as a pancreatic cancer treatment, which stands as an interesting niche market because this disease had no standard of care for patients who have progressed on first-line gemcitabine-based therapy. How do you plan to further optimize Onivydeâ??s life cycle?

In partnerships with Merrimack and Shire, we have already been advancing clinical trials for other indications. We are currently working on a phase II trial for front-line pancreatic cancer, and we expect to get some results in 2017 to design the phase III trial. Furthermore, we plan to start a global, multi-center phase III trial in 2017 for small cell lung cancer (second-line).

In addition to these two new indications, we also have started phase I studies for Ewingâ??s sarcoma (pediatric bone tumor), brain cancer (recurrent glioma, CED) and metastatic breast cancer, and expect to receive preliminary data before the end of 2016.

Finally, we started in 2015 a phase II study for second-line colorectal cancer and a Phase I study for second-line colorectal cancer (with anti-EGFR) in 2016. We also currently envision potential development for OnivydeÂ® as a combination backbone with targeted therapies and immuno-oncology therapies.

In March 2016, Onivyde was included in the guidelines of the National Cancer Comprehensive Network (NCCN), an alliance of the worldâ??s leading cancer centers, as a Category 1 Treatment Option for pancreatic cancer. Given this important recognition, how have US sales been evolving since the product reached the US market?

Merrimack launched Onivyde in the US four days after it was granted market approval by the US FDA. Since then, net product revenues in the US have been rapidly increasing from USD4.3 M in Q4 2015 to USD14.5 million in Q3 2016. They consider ~18,500 potential post-gemcitabine patients in the US are eligible to receive treatment of Onivyde plus 5-FU/LV for around USD43,000 per patient, which means potential US peak sales of post-gemcitabine pancreatic cancer could amount to USD800 million.

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Looking at our return on investment, we licensed-in PEP02 in 2003 for USD3 million and licensed it out for USD220 million of milestone payments as well as tiered royalty payment based on the net sales in Europe and Asia. In 2015, Merrimack licensed out the ex-US and ex-Taiwan rights of Onivyde$^{Â®}$ to Baxalta (before it was acquired by Shire) for USD 970 million.

Overall, PharmaEngine is eligible to receive up to USD266.5 million (including $46.5 million sublicense revenue) plus tiered royalty for Onivyde$^{Â®}$, which we already received USD73.5 million from the licensing agreement. As part of the license agreements, Merrimack and Shire are also financially responsible for the clinical trials of the aforementioned new indications we are currently exploring, even for the trials conducted in Taiwan.

Another exciting product in PharmaEngineâ??s pipeline is PEP503. Why are the recent developments for this product that make you confident it can become the new success-story of PharmaEngine?

Nanobiotix, a Paris-based, 50-employee spin-off from the State University of New York (SUNY) approached us in 2011 regarding the licensing of PEP503 (NBTXR3), a nanoparticle formulation of hafnium oxide crystal for the local treatment of tumors that enhance the efficacy of radiotherapy.

In August 2012, we signed an exclusive license agreement for the Asia-Pacific region when the molecule was about to start the phase I trial. Nanobiotix is now eligible to receive USD57 million and up to double-digit royalty payments, while so far we have already paid USD3 million to our Paris-based partner.

As this product is considered a medical device in many countries, Nanobiotix already filed a CE marking application in August 2016. Receiving positive results from our ongoing pivotal (phase II/III) study will then be the last step needed before actually bringing this product to the market. Our current pivotal study, which targets patients with soft tissue sarcoma of the extremity and trunk wall, is about to finish the enrollment of 156 evaluable patients within the upcoming months, and we expect to receive final data by H2 2017.

In the meantime, PharmaEngine is expanding the clinical applications of this product to rectal and head & neck cancers (phase I/II study), with data expected by 2018/2019. Finally, preclinical data also showed that PEP503 with radiation actively stimulates the host immune system to attack tumor cells, which could also offer promising development options in the near future.

To what extent has your recent success with Onivyde$^{Â®}$ changed the perception of the global industry vis-Ã -vis PharmaEngine?

We are now in the good position to receive an impressive and ever-increasing number of propositions from small to large biopharmaceutical companies. Our attractiveness has been increasing rapidly since 2014 because we now hold a successful track record that proves we can deliver on our promises, while we remain a small structure in comparison to big pharma companies.

This aspect is particularly critical for other small partners that may be interested to license-out some of their early-stage compounds. To the contrary of big pharmas, we cannot afford to invest substantial resources to a project that is a potential game-changer: we are then extremely selective in projects, but also even more committed to its development. By partnering with us, chances are largely reduced for smaller companies to see the development of their projects being suddenly deprioritized.

In the upcoming years, we want to remain focus on oncology and solid tumor therapies, because we found that hematologic cancer has become a very competitive field for a relatively small company like PharmaEngine.

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What would be your advice to other biopharmaceutical entrepreneurs in Taiwan and globally?

In our industry, all decisions should be based on science. From the preclinical stage to market entry, entrepreneurs must stick to their vision and ignore the numerous short-term temptations that may arise â?? especially now that funding is more abundant than a decade ago.

In 2008, when PharmaEngine was experiencing financial difficulties, some industry observers advised me to leverage our drug development expertise to become a CRO, which would imply to abandon the rights we hold onto our compounds. Despite our difficulties, I refused to divert from the vision I had and took the risk to fully believe in the development potential of our company.

As CEO and Founder of the company, what is your vision for PharmaEngine?

From Day 1, we have been stating we want to become one of the most successful biopharmaceutical companies in Asia for new drug development. I believe that PharmaEngine is just at the starting point of its history and the future looks particularly bright and exciting. We have already managed to build a reputable team comprising international experts, while we now hold the financial resources to invest in very promising projects. Overall, we have been accumulating extensive experience in drug development for more than 13 years. This expertise makes us an ever more attractive partner from both scientific and commercial perspectives.

I also want to ensure that PharmaEngine becomes a long-standing company, which will continue to work towards consolidating our international positioning as a thriving, ambitious and science-based company in order to bring value to our society. In the grand scheme of things, my vision of success for PharmaEngine goes way beyond our financial results: our fundamental objective has always been to provide patients and healthcare professionals with game-changing oncology therapies.

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