Letter from the Editor

A wake up call for Big Pharma?

There have been many pressures on big pharmaceutical companies lately, but one thing that hasn't been discussed, at least not widely, is the entry of new players into the pharma space. Without much fanfare, Nestlé SA, the food conglomerate, is doing just that. Best known for its chocolates and breakfast cereals, Nestlé is now deepening its research into nutrition in order to discover whether the chemistry of food production can play a role in the prevention and treatment of disease. A diversified Nestlé could be serious competition for pure pharmaceutical companies.

In January 2011 Nestlé created a new company, Nestlé Health Science, to explore the area between nutrition and pharmaceuticals. Within six months, the new company had bought Prometheus Laboratories Inc of the US in order to expand its presence in the healthcare market. Prometheus is a diagnostics developer, particularly in the manufacture of diagnostics for gastrointestinal disease.

Now, in what looks like an ideal fit for Nestlé, Nestlé Health Science has entered into a joint venture with Hutchison China MediTech Ltd of Hong Kong to take a botanical drug product for inflammatory bowel disease (IBD) into Phase 3 development (please see article on pages 10 and 11).

Nestlé is taking a 50% share in the venture in exchange for an undisclosed capital commitment that will help finance the cost of the Phase 3 programme. Nestlé has the marketing rights for HMPL-004 in the US and also has access to the Shanghai company's library of traditional Chinese medicines. With Prometheus now in the Nestlé stable, the Swiss company has the perfect vehicle for marketing HMPL-004 in the US.

What does this mean for Big Pharma? In negotiating a deal with Hutchison China MediTech, Nestlé has obtained access to a late-stage botanical drug product and options on more products from the Shanghai library. If HMPL-004 is successful, Nestlé will have a route into the still incipient global market for botanical medicines that no other big company has. The US Food and Drug Administration has had a regulatory pathway for botanical medicines in place since 2004. So far only two botanical products have been approved through this route. The pathway is waiting to be exploited.

Meanwhile, by linking up with Hutchison China MediTech, a subsidiary of the giant Hutchison Whampoa Ltd of Hong Kong, Nestlé has also gained a foothold onto the Chinese market. Initially HMPL-004 will be directed at western markets. But other, future products are expected to have a wider destination.

In setting up Nestlé Health Science, Nestlé said it wanted to explore the space between traditional nutrition and pharmaceuticals. The joint venture with Hutchison China MediTech will bring it directly into the pharmaceutical arena for the first time. And Nestlé has ambitions for the future. After gastrointestinal disease, it wants to explore new therapeutic approaches in metabolic health and brain disease as well.

– By Victoria English, 13 January 2013

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Nestlé and Hutchison Whampoa

Are botanical drugs a new model for pharma?

Every once in awhile, one industry invades the space of another, particularly under pressure from advancing technology. In recent decades the sleepy telephone industry has experienced a shakeup from computer developers. With medical discovery accelerating could the food industry be about to invade the pharma industry?

A new venture between a subsidiary of Nestlé SA, the global food company, and Hutchison China MediTech Ltd, a Hong Kong-based company that is controlled by Hutchison Whampoa Ltd, has all the elements of an industry transforming deal. In late November 2012 the two companies announced the setting up of a joint venture to research and develop a pipeline of medicines and nutritional products derived from botanical plant origins. For Hutchison China MediTech, the new venture is a way to explore western demand for traditional Chinese medicines, a huge source of potential new therapies. For Nestlé Health Science, the Nestlé subsidiary, it is a chance, it says, to shape "a new industry between traditional nutrition and pharmaceuticals".

> ***"We are ready to go, looking for other indications within gastrointestinal disease"***
>
> *Christian Hogg*

The new venture is called Nutrition Science Partners Ltd. It is based in Hong Kong and the two parent companies will have equal ownership. The immediate goal is to bring a botanical drug product that is being developed by the Hutchison China MediTech subsidiary, Hutchison MediPharma, into Phase 3 development for patients with inflammatory bowel disease (IBD). The longer term objective is to research, develop, and market novel medicines and nutritional products derived from botanical plant origins. The venture will initially focus on gastrointestinal indications but may in future expand into metabolic disease and brain health.

In an interview with *MedNous*, Christian Hogg, the Hutchison China MediTech chief executive, said the venture is an opportunity for both companies to conduct research into new products that "might end up being food for medical use or they might end up being botanical drugs". Either way, there is expected to be a market for both types of products.

The joint venture was announced on 28 November. By the end of the first quarter of 2013 the two companies expect to start a Phase 3 programme for the botanical drug product which is called HMPL-004. A botanical drug is a medicinal product that is from a natural herb. The botanical substance itself contains a relatively small number of major chemical components. The two companies have already received regulatory approvals for the Phase 3 programme which will start in the US and then expand to the European Union, Mr Hogg said.

The two companies are targeting the US and Europe as initial markets for the drug because the incidence of IBD in these regions is high. IBD includes both ulcerative colitis, an inflammation of the colon, and Crohn's disease, inflammation of the digestive tract. While the herb upon which HMPL-004 is based has been used for years in China to treat upper respiratory inflammation, it has never been used in IBD. In fact, IBD is underdiagnosed in China, the executive said. "What we were able to do is identify its IBD activity and patent its utility in the whole IBD area," he commented.

A big opportunity for the two companies is the existence of a regulatory pathway for botanical medicines that has been in place at the US Food and Drug Administration since 2004.[1] Up until quite recently, only one company, Medigene AG of Germany, had received FDA approval for a botanical drug. This was the 2006 approval of Veregen (sinecatechins), an extract, from green tea leaves which is an ointment used to treat genital warts. But on 31 December 2012, the US agency announced its second botanical approval: a drug called Fulyzaq (crofelemer) which is an extract from the red sap of the Croton lechleri plant found in the upper Amazon region of Peru, Columbia and Ecuador. The drug was approved to relieve the symptoms of diarrhoea in patients with HIV/AIDS who are taking antiretroviral therapy. Assuming the HMPL-004 Phase 3 programme is a success, the two companies will use this new pathway for registration.

HMPL-004 is an extract of the plant, Andrographis paniculata, which is a popular herbal medicine in Asia, Sweden and Chile and is believed to have both anti-inflammatory and antibiotic properties.[2] It is understood to act on multiple cellular targets in the inflammatory signal transduction pathways, including inhibiting tumour necrosis factor-alpha (TNF-alpha) and interleukin-1beta (IL-1beta). According to Hutchison China MediTech, the drug has been successfully tested in more than 400 IBD patients including those in Phase 2b trials in North America and Europe. The upcoming Phase 3 programme is expected to enroll more than 2,700 patients with ulcerative colitis and Crohn's disease.

HMPL-004 is the first drug to come out of a botanical library built up over a decade by Hutchison MediPharma Ltd, the Shanghai-based drug research and development arm of Hutchison China MediTech. The library consists of medicinal herbs that have been used in one way or another for centuries in traditional Chinese medicine. In collecting the herbs, the company collaborated with the major botanical medicine centres in the country including the Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

"We put together this library of over 1,200 herbs, then spent five years with our team of in-house chemists breaking them down on a molecular level," Mr Hogg commented.

The result is a library of more than 50,000 fractions, all of which have been carefully characterised. The company has also built up chemistry, biology and pharmacology teams around the library so that it is capable of doing integrated drug research and development- and regulatory affairs. "We are ready to go, looking for other indications within gastrointestinal disease," Mr Hogg commented.

While the initial objective of the joint venture with Nestle is to register and commercialise HMPL-004, Nestle also has an option to develop botanical drugs for other indications. According to Luis Cantarell, chief executive of Nestlé Health Science, Nestlé will evaluate the possibility of expanding into metabolic health and brain health. Nestlé's financial commitment to the venture hasn't been disclosed. But Panmure Gordon analyst Savvas Neophytou said the Swiss company most likely is paying for access to the botanical drug technology in tranches – similar to a traditional venture capital investment. Meanwhile – and importantly – the venture has assigned marketing rights in the US for HMPL-004 to Nestlé Health Science, Mr Cantarell told *MedNous* in an email.

Nestlé Health Science

There is little doubt that Nestlé, known for generations for its chocolates and consumables, wants to build a business in healthcare. In January 2011, the parent company set up Nestlé Health Science SA in Vevey, Switzerland to develop personalised treatments for disease based on nutrition. Simultaneously it set up an institute of health sciences on the campus of the Swiss Federal Institute of Technology in Lausanne. One of the remits of the institute is to establish genomic, proteomic and metabolic platforms for studying the way cells function in both healthy and diseased tissues.

In addition, the institute will look for ways to modify disease mechanisms through nutrition. In the email, Mr Cantarell said that the company is looking to develop "scientifically validated botanical-based solutions" for disease. These could be "medicines/drugs and nutrition products". Driving the research is the company's belief that the delivery of healthcare in the future will involve both disease prevention and new ways to mitigate the effect of chronic conditions.

Within months of its founding, Nestlé Health Science announced the acquisition, in May 2011, of Prometheus Laboratories Inc, a US producer of gastrointestinal diagnostics. Nestlé Health Science is expected to use Prometheus to commercialise HMPL-004 in the US. Thus far, there aren't any plans to develop a specific diagnostic for the botanical drug, but this can't be ruled out in the future, according to Mr Hogg.

The engine behind the botanical drug project, Hutchison MediPharma, is one of three business units held by Hutchison China MediTech. Hutchison Whampoa owns 71% of Hutchison China MediTech, while 29% is traded on the Alternative Investment Market (AIM) in London. In the first half year ended 30 June 2012, Hutchison China MediTech had group sales of $102.9 million and a net profit, before discontinued operations, of $2.5 million. MediPharma was loss-making, but in the 2012 first half, its loss narrowed from the previous year. Like research intensive biopharma companies elsewhere, MediPharma is mitigating its research and development costs with licensing deals. The agreement with Nestlé, which is essentially a licensing deal, is the first in the botanical drug arena. In late 2011, the company also secured a licensing deal with AstraZeneca Plc for a small-molecule drug directed at cancer. This deal brought in an immediate $20 million in cash with the promise of up to $120 million later, upon the successful achievement of clinical development and first-sale milestones.

Hutchison MediPharma was founded in 2002 with the aim of modernising and globalising traditional Chinese medicines. In 2005, management decided to broaden the scope of the company by introducing a small-molecule discovery and development programme. Mr Hogg calls the small-molecule programme the "second pillar" of MediPharma's R&D business. "We have developed a portfolio of small-molecule oncology programmes and immunology programmes, many of which are in the clinic in China, because the opportunities in China in oncology are enormous," he commented.

Since 2005, MediPharma has entered into collaborations with Merck KGaA, Eli Lilly and Company and Johnson & Johnson Inc. The deal with AstraZeneca gives the UK company rights to a drug called Volitinib which is an inhibitor of the c-Met receptor tyrosine kinase. The molecule was discovered and developed in China by MediPharma. Under the agreement, MediPharma will lead development in China while AstraZeneca will manage development elsewhere. AstraZeneca plans to develop the drug as a single agent treatment as well as a combination therapy. The possible therapeutic indications include gastric cancer and non-small cell lung cancer as well as other cancers with aberrant c-Met signaling, according to the UK company.

Conclusion

It would not be an exaggeration to say that the pharmaceutical industry is changing rapidly. Not too long ago, it would have been very unusual for a pharmaceutical multinational to go to the developing world to both source and exploit a major cancer indication. This is now happening. It would also have been hard to imagine a traditional Chinese medicine gaining approval from the US Food and Drug Administration. This is now a possibility. Furthermore, it would have been inconceivable that a food company, famous for chocolates, could pioneer new treatments for chronic disease. This too is a possibility.

References:

1. 'Guidance for Industry, Botanical Drug Products', Food and Drug Administration, Center for Drug Evaluation and Research, June 2004.

2. Cohen, R and Harrell, L, *Gastroenterology & Hepatology*, 14 January 2011.

This article was written and researched by the editors of *MedNous* and based on two interviews with Christian Hogg, CEO of Hutchison China MediTech Ltd and an email exchange with Luis Cantarell, CEO of Nestle Health Science.