MEDIUS DEAL WATCH

November 2017

The harsh reality of liver disease

As we approach Christmas, with the promise of considerable overindulgence in food and drink, it is comforting to know that the pharmaceutical industry is doing its best to shield us from the potential consequences. Two companies have announced deals in the field of liver diseases, so if our livers suffer permanent damage from all the rich food and spirituous alcohol, there is light at the end of the tunnel.

Boehringer Ingelheim, which has had a busy month on the deal front (see below) announced that it has expanded its liver disease R&D programme. Boehringer Ingelheim's CardioMetabolic disease research division is focused on obesity and its consequences, including type 2 diabetes, non-alcoholic steatohepatitis (NASH), liver fibrosis and chronic kidney diseases, diabetic nephropathy and diabetic retinopathy. It has now enhanced its portfolio with the research collaboration agreement with MiNA Therapeutics, to access its small activating RNA discovery platform (saRNA) to identify and develop up to three targets for NASH and liver fibrosis. The deal comprises an undisclosed upfront payment as well as research, development and regulatory milestones amounting to €307m ($355m) and double digit royalties on sales resulting from the collaboration.

In other good news for the liver, Casebia Therapeutics, the joint venture established by CRISPR Therapeutics and Bayer to develop CRISPR-based therapeutic products, and CureVac, a company developing mRNA products, announced that Casebia has acquired rights to develop novel Cas9 mRNA constructs for use in three of its *in vivo* gene-editing programmes in liver diseases. CureVac will receive an undisclosed upfront payment and research funding, with potential development and commercial milestones and royalties on commercialised products arising from the collaboration.

The cost of *not* doing a deal

It's always important to know when to walk away from a potential deal. The price is too high. The due diligence turns up something that cannot be sorted out. The personalities on the other side suggest that post-deal alliance management might be more trouble than the deal is worth. But calculating the cost of not doing a deal is something that is rarely studied. When negotiations end, it's time to move on to the next deal and not to worry about what might have been. Of course, in a competitive situation, with more than one company seeking to acquire the same asset, the cost of not doing a deal can be more visible. Watching as the one that got away becomes highly successful can be a painful process.

The cost of **not** doing a deal is starting to become clear in the UK, as the consequences for the pharmaceuticals sector are examined in the light of the Brexit process, and the very real possibility of reaching the Brexit date **without** a deal. As well as the inevitable consequences of Brexit, such as the loss of the European Medicines Agency (EMA), the implications of the uncertainty of whether there will be a deal by the Brexit date means that companies are already spending money on contingency plans for securing their supply chains.

On the 20th November, the announcement was made that the EMA would be moving from London to Amsterdam. This much was inevitable after the triggering of Article 50, and the UK has also lost the European Banking Authority to Paris. However, given that the marketing authorisation holders (MAHs) for pharmaceutical products are regulated by the European Court of Justice (ECJ), this means that drugs where the MA is held in the UK must be transferred to an EU member state if they are to continue to be sold in the European Economic Area (EEA) post-Brexit. The EMA has recently offered guidance on the steps to be taken in order to continue to market products in the EU after 30th March 2019.

- MAHs established in the UK will need to be replaced with an MAH established in one of the remaining countries of the EEA
- A company's qualified person for pharmacovigilance (QPPV) must reside and carry out his/her tasks in an EEA member state
- The pharmacovigilance master file (PSMF) also must be located within EEA

The administrative burden of carrying out the first of these tasks alone has been estimated by the European Federation of Pharmaceutical Industries and Associations (EFPIA) as 400 man years, given that 400 centrally authorised products have the UK as a licence holder and, with multiple MAs per product, this amounts to 2,400 MAs.

In its report the EFPIA also highlights two other issues: the implications for clinical trials and for supply chains. There are presently 1,500 clinical trials ongoing in multiple EU member states where the UK is the sponsor and 50% of these trials will be ongoing at the Brexit date. Some 1,050 investigational medicinal products (IMPs) are QP-released from the UK (70% of the total).

The supply chain issues are even more critical. Some 1,300 products are batch-released in the UK for distribution in the EU and if the Brexit date is reached without an agreement or a transition deal there could be widespread disruption to the supply and distribution of medicines across Europe as the UK will be obliged to operate under World Trade Organisation (WTO) rules.

In anticipation, major companies such as Eisai and AstraZeneca are already duplicating their testing and approval procedures, and GSK has announced it will activate contingency plans from the end of 2017. Whether the ongoing Brexit negotiations result in an agreement or a transition deal to smooth these problems, a lot of money is being spent to avert the potential consequences of no deal.

By contrast, the report in the Financial Times of an announcement by Merck & Co of an estimated £1bn ($1.3m) investment in a research facility in London, and by Qiagen of a "hundreds of £m investment" in Manchester brought a little cheer to the UK's pharmaceutical industry.

Platform deals

Platform deals are always popular – they provide the opportunity to access innovative technology for a relatively attractive upfront cost with the big money heavily weighted towards a successful outcome. Paying out when you have a successful product to fund the payouts is a lot less painful than paying upfront with no certainty of success. But this month we have an unusual number of platform deals in the top 20 deals, with Zymeworks, Peptidream and Cue Biopharma all agreeing deals valued at over $100m, with Johnson & Johnson, Bayer and Merck & Co, respectively. While much of the elevated numbers are, clearly, "Biodollars", Johnson & Johnson has paid a $50m upfront fee to develop up to six bispecific antibodies from Zymeworks' Azymetric™ and EFECT™ platforms, with the remainder of the $1,452m total deal in milestone and success payments. Peptidream and Cue Biopharma did not disclose the upfront fees received, but the total value of the deals, at $1.1bn and $374m respectively is substantial.

Acquisitions continue to decline

For some time now, Medius has noted that corporate acquisitions are in decline. And this month's statistics bear that out – only one company acquisition was announced; that of Ocera Therapeutics by Mallincrodt. All the other five purchases in the Top 20 were partial acquisitions, with buyers acquiring a division of a company or making a minority investment. Even the acquisition of the Stelic Institute by Mitsubishi Tanabe was preceded by Stelic splitting itself into two parts, with Mitsubishi Tanabe acquiring the gastro-intestinal assets alone.

High Scoring Teams from Big Pharma

Three companies have been particularly busy in November, with AstraZeneca signing five deals and Bayer and Boehringer Ingelheim signing three each. AstraZeneca has agreed deals with CN Bioinnovations (R&D agreement in infectious diseases / oncology), with Moderna Therapeutics (co-development agreement in heart disease), G1 Therapeutics (development agreement in non-small cell lung cancer) and with PhaseBio (development of a reversal agent for ticagrelor/Brilinta). However the most significant deal appears to be the creation of a joint venture in China, Dizal Pharmaceutical. AstraZeneca has rolled the scientific and technical capabilities of its Innovation Center China (ICC) into the joint venture, which also gained exclusive rights to develop and commercialise three preclinical products in AstraZeneca's pipeline. The other partner in the Dizal Pharmaceutical joint venture is China's Future Industry Investment Fund (FIIF) which will be contributing funding and expertise in establishing strategic partnerships in China. The deal has been valued at $265m.

Licensor/Target| Licensee / Acquirer	Deal type	Product /technology	Headline $m
Loxo Oncology | Bayer	Licence to develop and commercialise	Selective TRK inhibitors lanotrectinib and LOXO-195	1,550
ZymeWorks | J&J	Licence to research, develop, commercialise	Up to 6 bispecific antibodies using Azymetric™ and EFECT™ platforms	1,452
PeptiDream| Bayer	Drug discovery collaboration	Peptide Discovery Platform System for targets in oncology and cardiology	1,110
Principia Biopharma | Sanofi	Licence	Bruton's tyrosine kinase (BTK) inhibitor PRN2246 for multiple sclerosis and other CNS conditions	805
Halyard Health | Owens & Minor	Acquisition of division	Surgical and infection prevention products	710
Unichem Laboratories*| Torrent Pharmaceuticals	Acquisition of brands and manufacturing plant	120 brands of OTC, especially in cardiology, diabetes, gastrointestinal and CNS	557
Cue Biopharma | Merck & Co	Research collaboration and licence	CUE Biologics™ platform for development of biologics to selectively modulate T-cell subsets	374
MiNA Therapeutics | Boehringer Ingelheim	Collaboration & licensing agreement	Up to 3 targets for NASH and fibrotic liver disease from small activating RNA (saRNA) platform	355
The Medicines Company| Melinta	Acquisition of division	Marketed antibiotics including meropenem, Minocin, Orbactiv & others	270
Future Industry Investment Fund | AstraZeneca	Joint venture – Dizal Pharmaceutical	3 preclinical AZ products to be developed by Dizal, in oncology, cardiovascular and metabolic disease; independent R&D	265
Alkermes | Biogen	Licence to develop and commercialise	ALKS8700 – monomethyl fumarate (MMF) molecule for multiple sclerosis	228
Sawai America**| Sumitomo	Minority acquisition	20% of Upsher-Smith (acquired by Sawai in April 2017) – generics	211
Ionis Pharmaceuticals| Dynacure	Licence	IONIS-DNM2-2.5Rx (Dyn101), an antisense drug targeting dynamin 2 for the treatment of centronuclear myopathy (CNM)	210
Ardelyx*** | Kyowa Hakko Kirin	Licence	Oral NHE3 inhibitor, tenapanor, for cardiorenal diseases	160
Ocera Therapeutics| Mallinckrodt	Acquisition	Company, including OCR-002 (an ammonia scavenger) for hepatic encephalopathy	117
Vascular Biogenics***| NanoCarrier	Licence to commercialise	VBL-111, dual mechanism biologic in glioblastoma, thyroid and ovarian cancers, based on VTS™ platform	115
Stelic Institute | Mitsubishi Tanabe	Acquisition	Gastro-intestinal operations; STNM01 (siRNA inhibitor of carbohydrate sulfotransferase 15) for ulcerative colitis	105
Portal Instruments| Takeda	Collaboration for development & commercialisation	Needle-free injection device for biologics; for use in Entyvio® (vedolizumab), a mAb to treat ulcerative colitis or Crohn's disease and other products	100
Becton Dickinson | Merit Medical Systems	Product line acquisition	Soft tissue core needle biopsy product line and Bard's Aspira® tunneled home drainage catheters and accessories	100
Oncolytics Biotech**** | Adlai Nortye	Licence to develop and commercialise	REOLYSIN®, an intravenously delivered immuno-oncolytic virus	86.6

KEY: All deals global unless otherwise stated:

* India only
** US only
*** Japan only
**** China, Hong Kong, Macau, Singapore, South Korea and Taiwan

Catharine Staughton

supports Medius clients in various aspects of business development, particularly in product forecasting, the financial structuring of licensing deals and all aspects of finance. Catharine gained her financial experience at Robert Fleming (now part of JP Morgan), and her business development experience at Medeva and Antisoma.

As noted earlier, Bayer has two deals in November's Top 20 – indeed, it has two deals in November's Top 3. As well as the deals with Peptidream ($1,100m) and Loxo Oncology ($1,550m) Bayer has signed a deal with Compugen for process development manufacturing to produce COM902 for future use in clinical trials.

In addition to its deal in liver diseases Boehringer Ingelheim has agreed a deal with the Chinese company, HitGen, which announced a drug discovery research collaboration to identify novel small molecule leads using HitGen's DNA-encoded library design platform. The third deal, with the US company CellSight Technologies, is a strategic collaboration to develop a non-invasive technology for monitoring anti-tumor T-Cell activation based on Positron Emission Tomography (PET).

And finally...

BioMarin has agreed to sell the Rare Pediatric Disease Priority Review Voucher (PRV) it obtained in April of this year for a lump sum payment of $125m. PRVs are a mechanism to reward investment in rare paediatric or in tropical diseases and are awarded on FDA approval. BioMarin gained the voucher when Brineura® was approved for the treatment of patients with a form of Batten disease. The name of the purchaser has not been announced, but it is now entitled to a priority review, where the FDA aims to complete and act on the review within six months instead of the standard ten month period. Fourteen PRVs have been awarded (since 2009) and, as they are fully transferrable have a market value.
Seven PRVs have been sold, for figures between $67.5m and $350m, a very substantial sum for a product that, at best, brings forward a product's approval by four months.

And to all our clients – we wish you the compliments of the season and good wishes for 2018.

DEAL WATCH

medius associates

Tel: +44 (0) 20 8654 6040