MEDIUS DEAL WATCH

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"The avoidance of taxes is the only intellectual pursuit that carries any reward"

John Maynard Keynes

Pharmaceutical companies are renowned for scientific expertise and development of innovative medicines. Less well known are the boffins in the tax departments of US companies who have devised tax inversions and complex tax avoidance schemes such as the 'Double Irish with a Dutch Sandwich'. These schemes have been difficult to swallow for the US Government. The new tax legislation may relieve its indigestion. It changes taxation from worldwide to territorial, reduces headline corporation tax from 35% to 21% and allows companies to repatriate overseas cash at a tax rate of 15.5%. However it is not all good news for companies. There are proposed reductions in R&D tax breaks that could increase the cost of developing orphan drugs, limits on shifting income via transfers of intangible assets and a tax on cross border transactions that will affect supply chains. Without doubt, the complexities of the new US tax regulations will continue to make tax avoidance a rewarding intellectual pursuit.

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One of the key questions for those involved in M&A is whether the repatriation of over $100bn by the US pharma companies will lead to an increase in M&A transactions following the decline in 2017. According to a report by Reuters, an analyst at SunTrust reviewed the last repatriation tax holiday in 2004 when pharma companies repatriated more than $90bn "but there was no massive wave of M&A. Only three U.S. companies consummated deals in excess of $1 billion the following year". If history repeats itself it is unlikely that there will be a surge in pharma M&A transactions not least of all because shareholders will be seeking a share of any repatriated cash in the form of share buy backs or increased dividends. For example, Pfizer announced on 17th December that it will be increasing its quarterly dividend by 6% and the Board has authorised $10bn for share buybacks.

"Markets can remain irrational longer than you can remain solvent" *John Maynard Keynes*

Another factor working against a significant increase in M&A in 2018 is the perception that the valuations of companies are too high. The US stock market is at record levels. A survey of fund managers by Bank of America Merrill Lynch found that a net 48% of them thought equities were overvalued. High valuations have been mentioned by a number of big pharma companies including Pfizer and GSK. Companies are well aware of the evidence that most acquisitions provide more value for the seller than the buyer. Unless there is a stock market collapse next year Deal Watch (DW) expects that M&A will be driven mainly by strategic fundamentals rather than financial opportunism.

"Successful investing is anticipating the anticipations of others"

John Maynard Keynes

The point about strategic fundamentals e.g. vertical integration, is demonstrated by the biggest acquisition of 2017, CVS Health's purchase of Aetna for $77bn including debt. In the US Aetna is the third largest health insurer and CVS Health consists of a large retail pharmacy chain, walk-in clinics, home care and also acts a pharmacy benefit manager. The merger, if approved by the Competition Authorities, will provide a vertically integrated operation that will link Aetna's patient records to dispensing and purchasing of medicines. As well as synergy benefits of $750m the merger is seen as a defensive strategy, namely, "anticipating the anticipation of" Amazon's entry to the prescription medicine market.

According to a report from CNBC, Amazon has had discussions with generic companies in the US, Mylan and Sandoz. Maybe it is these discussions plus the expectation that companies like CVS and perhaps Amazon will continue to drive down medicine prices in the US that have prompted the CEO of Novartis to mention that the company may exit the oral solid dose generic market in the US. In October Novartis announced the closure of a factory in Colorado. This month Teva announced that it will reduce its workforce by 25% and close or sell a number of sites. The generics market has seen consolidation over the past few years and this seems likely to continue in 2018. Amazon has decimated book shops and record stores. If Amazon enters the pharmaceutical market it will be interesting to see how it deals with the highly regulated pharmaceutical market particularly in Europe.

Licensor / Acquisition target	Licensee / Acquirer	Deal type*	Product /technology	Headline (upfront) $m
Aetna (US)	CVS Health (US)	Company acquisition	Health insurer acquired by PBM and retail pharmacy company	77,000
Atrium Innovations (CA)	Nestlé Health (CH)	Company acquisition	Range of nutrition and multivitamin products	2,300
Ignyta (US)	Roche (CH)	Company acquisition	Oncology product range in development incl. entrectinib, a tyrosine kinase inhibitor for NSCLC	1,700
AskAt (JP)	Arrys (US)	Licence[1]	Two pre-clinical prostaglandin E2 receptor 4 antagonists	1,200+ (ND)
Sucampo (US)	Mallinckrodt (US)	Company acquisition	Lubiprostone + orphan drug pipeline	1,200
Autifony (UK)	Boehringer Ingelheim (DE)	Option for asset purchase	Kv3.1/3.2 positive voltage gated potassium channel modulator platform incl. Phase 1b compound	737 (29)
Halozyme (US)	Alexion (US)	Licence	Subcutaneous drug delivery technology for 4 targets	680 (40)
Cell Design Labs (US)	Gilead (Kite) US	Company acquisition	Two technology platforms for engineering CAR-T cells	567 (175)
Depomed (US)	Collegium (US)	Commercialisation[2]	Nucynta (tapentadol) product range marketed in US	550+ (10)
Idorsia (CH)	Roche (CH)	Option to licence	Discovery of cancer immunotherapy compounds	460 (15)
Mitobridge (US)	Astellas (JP)	Exercise of option. Company acquisition	Technology to discover and develop novel drugs that improve mitochondrial functions	450 (225)
ReMynd (BE)	Novo Nordisk (DK)	Licence	Pre-clinical ReS39 programme to develop compounds for treatment of diabetes	411 (ND)
Genescript (Legend) (CN)	J&J (Janssen) (US)	Licence and collaboration	Phase 1 CAR-T immunotherapy for multiple myeloma	350+ (350)
Athenex (US)	Almirall (ES)	Licence to research, develop and commercialise[3]	KX2-391 (Phase 3) topical dual Src kinase and tubulin polymerisation inhibitor for actinic keratosis	275 (55)
Carmot Therapeutics (US)	Amgen (US)	Licence and collaboration	Discovery platform for small molecule drugs to treat Parkinsons and other diseases	240+ (ND)
XOMA (US)	Rezolute (US)	Licence to develop and commercialise	XOMA358 Phase 2a Mab that inhibits effects of elevated insulin	240 (18)
Idorsia (CH)	J&J (Janssen) (US)	Exercise of option. Collaboration to develop and commercialise	Aprocitentan (Phase 2) an orally active dual endothelin receptor antagonist for treatment of resistant hypertension	230
Basilea (CH)	Pfizer (US)	Extension of licence[4]	Cresemba (isavuconazole) pre-registration anti-fungal	226 (3)
Arena (US)	Everest (CN)	Licence to develop and commercialise[5]	Ralinepag and etrasimod Phase 2 for pulmonary arterial hypertension and ulcerative colitis respectively	224 (12)
Tracon (US)	Ambrx (CN)	Licence to develop and commercialise[6]	TRC 105 (carotuximab) in Phase 3 for treatment of angiosarcoma	144 (3)
Ardelyx (US)	Shanghai Fosun (CN)	Licence to develop and commercialise[7]	Tenapanor (Phase 3) for treatment of irritable bowel syndrome with constipation	125 (12)
Morphosys (DE)	I-Mab (CN)	Licence to develop and commercialise[8]	MOR202 (Phase 1/2a) Mab targeting CD38 for treatment of multiple myeloma	120 (20)
Confu (BE)	Roche (CH)	Licence to develop, manufacture and commercialise	Research collaboration G-protein coupled receptor agonists	103 (7)
vTv Therapuetics (US)	Huadong Medicine (CN)	Licence to develop, manufacture and commercialise[4]	GLP-1r agonist in Phase 2 for Type 2 diabetes	103

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1. Worldwide excl. China
2. United States
3. US and Europe including Russia
4. China and Asia Pacific
5. China, Taiwan, Hong Kong, South Korea
6. China
7. China, Taiwan, Hong Kong and Macao
8. All countries of the world except Japan, South Korea, Taiwan, China and Association of Southeast Asian Nations (ASEAN) countries

Consumer Health M&A – The industry is consolidating again

Another M&A deal driven by strategic fundamentals, in this case geographic expansion, is the acquisition of Atrium Innovations by Nestlé Health Science for $2.3bn. Nestlé Health Science is focussed on the "therapeutic role of nutrition to change the course of health management for consumers, patients, doctors and nurses". Atrium Innovations based in Canada has a range of probiotics, plant-based protein nutrition, meal replacements and multivitamin products. Some 80% of Atrium's $700m sales (10% of Nestlé Health Science – see OTC Toolbox article 6th December 2017) are in the US. The company is owned by a consortium of funds led by Permira who acquired the company in early 2014 for $1bn. The sale price of $2.3bn, assuming no further funding was provided during the four years, represents an internal rate of return of around 23% for the investors which, in this day and age, is not to be sniffed at.

Nestlé's acquisition of Atrium is the latest example of concentration in the OTC pharmaceutical market. Over the past few years Novartis has joined forces with GSK, Merck & Co has divested its OTC unit to Bayer and Boehringer Ingelheim has swapped its consumer business for Sanofi's animal health. Further major changes in the OTC pharmaceutical market are in the pipeline. Merck KGaA's consumer health business with $1bn sales is on the market and there have been comments from Pfizer recently that suggest it may sell its consumer business with sales of $3.5bn. Perrigo and Stada are said to be bidding for the Merck KGaA unit. In the meanwhile smaller companies are just as busy. For example this month, Alliance Pharma in the UK is set to acquire Vamousse, a head lice treatment, for up to $18m and Ametop, a topical anaesthetic gel, for $8m. Similarly, Recordati purchased from Bayer Consumer Health the laxative Transipeg for France with $12m sales for an undisclosed amount.

Prescription Drugs M&A – Why license technology, why not acquire the company or take an option to do so?

Some big pharma companies continue to acquire, rather than license, technology companies where there is a complementary technology. An example of this is Gilead's acquisition of Cell Design which has two technologies for engineering CAR-T cells. This fits perfectly with Gilead's acquisition of Kite for $11.9bn in August especially as Kite already had a 12.2% share in Cell Design. This helps deal with the long term development of new cell therapies but is the market ready for these types of treatments? Apparently in the US only five patients have been treated with Yescarta, Gilead's CAR-T treatment for lymphoma, and there is a waiting list of 200 patients. This is in spite of a report at the ASH annual meeting this month that after a median 15.4 months, 42% of previously treated non-Hodgkin's lymphoma patients were still responding to the therapy and 40% continued to show complete responses. Clearly the product is very effective so the question is whether the product is not being used because of the high price of $373,000 per one-time treatment or because health insurers and hospitals have not yet put in place the procedures to deal with CAR-T. Probably it is a bit of both. However until this situation becomes clearer the uptake of Yescarta, at least in the short term, is a major risk for Gilead and equally so for Novartis' CAR-T therapy Kyrmiah priced at $475,000.

"Offer them 25 billion,
but don't make a big deal out of it."

Another example of M&A in the oncology sector is Roche's acquisition of Ignyta for $1.7bn. Ignyta has a strong pipeline with one product, entrectinib a tyrosine kinase inhibitor for NSCLC, in Phase 2 and two other products in Phase 1. The price paid by Roche was not cheap. The share price premium was over 70% for a company with annual losses of over $100m. The premium paid by Mallinckrodt for Sucampo was over 50% but it still looks like an expensive acquisition with the price of $1.2bn representing 14x 2016 EBITDA.

An alternative to acquiring a technology company is to take a licence and include an option to buy the company at a later date. Over the last several years there has been a significant increase in the number of M&A options being included in licensing deals. Some of these deals are reaching the end of the option period and are being either exercised or terminated. This month Astellas has exercised its option to acquire the US company Mitobridge for $450m. Four years' ago Astellas and Mitobridge (then Mitokyne) set up a R&D collaboration to discover and develop novel drugs that improve mitochondrial functions. At the time Astellas joined a consortium of investors who provided $45m Series A equity funding. As part of the collaboration agreement, Astellas had an option at certain points in time to acquire the company during the five year agreement. Mitobridge now has a drug for treatment of Duchenne Muscular Dystrophy in Phase 1. The 2013 collaboration deal had a headline value of $730m and stated that the buy-out price could be over $500m. In the event Astellas paid $225m upfront ($165m after adjusting for its existing stake) with a further $225m contingent on "advances in clinical programs". Looks like Astellas got a good deal.

Astellas had an option to buy the company. Another approach is to have an option to buy an asset. This is what Boehringer Ingelheim has done in the deal with Autifony. It has paid $29m upfront with a further $21m possible during the option period to acquire Autifony's Kv3.1/3.2 positive voltage gated potassium channel modulator platform including a lead compound in Phase 1b for treatment of schizophrenia. If the option is exercised a further $687m in development and pre-commercialisation milestones is payable. DW wonders if there was any connection between this deal and the resignation two days before of Boehringer's Finance Director because, according to the announcement, "it has not always been possible to reconcile divergent views and perspectives". The Finance Director leaves at the end of this month.

Licensing without options and…

This month sees a raft of new licensing agreements ranging from discovery technologies to Phase 3 products. The discovery projects are invariably licensed in by big pharma companies e.g. Novo Nordisk and Amgen. In these examples the headline values are over $200m but in neither case is the upfront disclosed probably because it is a small amount.

Building on a long standing successful relationship is always a good business development strategy for big pharma. This is what BMS has done with Ono. The development and commercialisation of Opdivo (nivolumab) for treatment of melanoma has been a great success with annual sales of around $5bn. BMS has now established a new project with Ono to develop and commercialise (except for Japan, China and SE Asia) Ono's prostaglandin E2 receptor 4 antagonist to increase the effectiveness of immuno-oncology drugs. BMS is paying $40m upfront plus undisclosed milestones. Pfizer has also built on its relationship with Basilea by extending its licence for isavuconazole to include China and Asia Pacific for $226m.

Drug delivery companies often struggle to find licensees for their technologies but Halozyme has bucked the trend. Its subcutaneous drug (sc) delivery technology has previously been licensed to seven big pharma companies including Roche who has launched sc versions of Herceptin and MabThera. This month Alexion has become the latest licensee with a deal valued at $680m (four targets at $160m each plus $40m upfront).

…licensing with options

In the same way that M&A is being driven partly by exercise of options, so too is licensing. Idorsia has been involved in two option deals this month. The first is a $460m cancer immunotherapy discovery project with Roche. Roche pays $15m upfront and $35m if the option is exercised. The second is the exercise of an option arising from the acquisition earlier this year of Actelion by J&J (Janssen). Prior to the acquisition, Actelion's R&D unit was set up as a spin-out company called Idorsia managed by Actelion's founder. As part of the acquisition deal, Janssen was given an option to license from Idorsia aprocitentan, a treatment for resistant hypertension in Phase 2. The study completed in May and Janssen has now exercised the option for $230m. Idorsia and Janssen will jointly share development costs but Janssen has worldwide commercialisation rights paying royalties of 20% (up to $0.5bn sales), 30% (on sales between $0.5bn and 2bn) and 35% (on sales over $2bn). Wow!

Perhaps royalties of 20% to 35% are not so uncommon, at least where the licensor has co-funded development. For example in the early 2016 deal with Gilead for filgotinib for the treatment of inflammatory indications such as RA and Crohn's disease, Galapagos agreed to pay 20% of the development costs and had an option to co-promote the product. This month Galapagos has decided to opt-in to co-promote the product in the big 5 European countries plus Benelux. In the co-promotion countries there will be a profit share but in other countries Gilead will pay Galapagos tiered royalties of 20% to 30%, not much different to the rates being paid by Janssen to Idorsia.

"The difficulty lies not so much in developing new ideas as escaping from old ones"

John Maynard Keynes

Licensing out by small and mid-sized companies is a bit of a lottery especially to big pharma companies who are prone to change strategy or priorities on development and commercialisation of in-licensed products. Of course the lottery also applies to medium or small companies who may have insufficient expertise or resources or financial problems.

A case study of the licensing out lottery is Grünenthal's tapentadol sold as Nucynta in the US. This was originally licensed to J&J, a big pharma partner with expertise in pain for the US, Canada and Japan where Grünenthal did not have a marketing presence. J&J was a good choice of partner for Grünenthal. The product was launched in the US in 2008. In 2015 J&J decided to divest its US licence rights to Depomed for $1.05bn. Depomed was a smaller company with a portfolio of pain products so it appeared to be a reasonable replacement commercialisation partner for Nucynta. However Depomed had to borrow over $0.5bn to pay J&J which increased its finance costs by over $60m per annum. This pushed Depomed into a loss and by the end of 2016 Depomed had a net loss of $89m on sales of $456m. With continued losses in 2017, the management was changed and the new CEO adopted a new strategy.

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This month Depomed announced a reduction in staff and a transfer of Nucynta commercialisation rights to Collegium, a small company with sales of around $30m. In 2016 Nucynta had annual sales of $281m representing 60% (!) of Depomed's total sales. Collegium will pay a small ($10m) upfront plus a royalty of 58% on annual sales up to $233m, 25% between $233m and $258m and 17.5% over $250m subject to a minimum of $135m per year for the first four years. Nucynta sales are slowly declining so Depomed is unlikely to earn more than the minimum royalty in the next four years. However the Collegium deal is part of a company restructuring so the reduction in costs may help Depomed reduce its debt and interest payments.

More importantly, given the changes of commercialisation partner Grünenthal has endured over the past 10 years, is this latest change a good deal for Grünenthal? Well according to Grünenthal's press release "Grünenthal concluded and agreed that transferring Nucynta to Collegium would be the best option. This agreement should give Grünenthal a more committed partner and provides a pre-agreed fixed minimum royalty income stream over the next few years, if the partner performs within a given range of revenue achievements". Presumably Grünenthal had little choice but to accept the Depomed / Collegium deal but in doing so it has agreed to reduce royalties by $3.2m if sales drop to $220m per annum and gets an incremental $1.2m if sales reach $240m. Another issue is whether Depomed will continue to develop another Grünenthal product, cebranopadol, acquired in late 2015.

This case study demonstrates some of the difficulties mid-sized companies face licensing out products in major markets. The difficulty is not so much in finding new partners as escaping from old ones.

Conclusion

In looking at deals each month certain patterns start to emerge. This month there are three:

- Out of the 24 deals in December's DW Table, excluding the top 2, 13 or 59% of the product innovators, licensors or acquisition targets, are US based companies.
- Five of the six European licensor companies are spin-outs.
- Out-licensing to China is becoming increasingly important. Five out of the 22 deals are out-licenses to Chinese companies for territories including China.

The message, at least from this month, is that if you are in-licensing new products go to the US or to European spin-out companies and if you are out-licensing go to China.

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