Patent Cliffs And Drug Sales
2019 will be striking for the change pharma will see to its top-selling drugs chart (p3)

From Witty To Walmsley
Emma Walmsley has taken over the top job at GSK. What can we expect? (p4)

1Q Review
2017 has produced more new drug approvals in the EU & US compared with this time last year (p8)

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Tendering: The New Hot Topic In Pharma

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Pharmaceutical companies with maturing portfolios need to understand tendering if they want to prevent international price erosion.

Tendering is no longer only a matter for generics manufacturers to worry about. As payers increasingly turn towards tendering to get the best prices they can, companies should give more commercial focus to their older, patented medicines in order to protect margins and manage the pricing challenges that can arise from tendering.

Failure to properly understand tendering can put pressure on global prices, resulting in margin reductions, warns James Robinson, director of industry solutions for Europe at Model N, a technology company that provides pharma companies with revenue management tools. While pharma companies invest in traditional market access teams, many of them lack well developed commercial tendering teams within their organizations with the specific skills to make the most of such procurement. The price for getting it wrong can be heavy.

Generic medicines have traditionally been the target for procuring pharmaceuticals through tendering, however, this is starting to change. According to Robinson, the topic of tendering is garnering more and more interest among companies as payers increasingly use tendering to procure medicines earlier in the lifecycle, before patent expiry.

Many larger pharma firms with maturing portfolios, like AstraZeneca PLC, Pfizer Inc. or Amgen Inc., are devoting more time and energy to managing their older products, he said. "Established product divisions are popping up all over pharma," added Robinson.

He explained that as patent expiry nears, there is more likely to be increased competition within the relevant therapeutic category: "As soon as two or three options come up in the market, payers tend to switch to tendering to ultimately get the best price."

Many markets use tendering, although how much they use it compared to other methods of procurement differs. While some markets use tenders for national procurement, others use them more locally, for example different regions within Spain will issue tenders. And now Germany's big sick funds that have generally focused on negotiated contracts are also increasingly using tendering processes, Robinson said. Tendering is common in Canada, but not in the US. However, according to Robinson, the US is seeing greater use of Request for Proposal (RFP) procurement processes. "These are not as formal or as transparent as we see in tenders in Europe and elsewhere, but the introduction of RFP purchasing is driving manufacturers to invest in new processes, skills and systems to manage the bidding process they have to manage to submit these RFP responses," he said.

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from the US editor

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The last time the American Association for Cancer Research held its annual meeting in Washington, D.C., back in 2013 when cancer immunotherapy was young, the buzz was about potentially combining checkpoint inhibitors like CTLA-4 and PD-1. Four years later, immuno-oncology is featured in the mainstream news, not just the scientific press, but IO combinations are still more in the realm of research than practice.

The 2017 AACR meeting has possibly re-set the stage for IO combinations. BMS presented updated survival data for *Opdivo/Yervoy* in melanoma, but the level of benefit and high toxicity are prompting debate over who should get the combo and who should stay on monotherapy (p21). In contrast, IDO1 inhibitors stole the show with data supporting the new class as a safer partner for combination therapy (p16). Companies are moving quickly into late-stage trials in lung cancer. Research on Roche's *Tecentriq* in breast cancer (p6) and BMS' post-mortem look at Checkmate 026 for biomarkers highlight how much there is to learn about responders to IO drugs. Maybe in another four years we'll have better answers.

exclusive online content

FDA Commissioner-Nominee Gottlieb Pressed More On Drug Development Than Industry Ties
Scott Gottlieb's industry connections were expected to be a major focus of his US Senate confirmation hearing. However, our analysis of the questions asked show drug development was the top priority
http://bit.ly/2nZNFwJ

Arcturus's Differentiated RNA Technology Faces First Clinical Test In 2017
San Diego-based Arcturus Therapeutics has developed technology for the targeted delivery of RNA therapeutics, which J&Js Janssen subsidiary will evaluate for the first time in humans in a clinical trial starting as early as this year for the partners' hepatitis B drug candidate.
http://bit.ly/2nZFaln

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Patent Cliffs And Drug Sales 2016 Versus 2006, And Beyond

With pharma's tumble over the patent cliff reaching terminal velocity in 2015, a comparison of the top 10 products by global sales in 2016 with 2006 looks very different. But analysts forecast that the table will be headed by the same product – Humira – right out to 2025 despite a second impending cliff.

SUKAINA VIRJI & LUCIE ELLIS

2019 will be striking for the change the pharmaceutical sector will see to its top-selling drugs chart as a new wave of patent expiries hits. But the one thing that won't change is AbbVie Inc.'s *Humira* (adalimumab)'s status as the world's best-selling drug – this position looks safe for years to come.

Humira has been in the top 10 of best-selling drugs by global revenue since 2009, when it entered the table in tenth position with sales of $5.57bn, climbing steadily to first place in 2012 with sales of $9.61bn when Pfizer Inc.'s *Lipitor* (atorvastatin) went over the patent cliff.

In Datamonitor Healthcare's Big Pharma Outlook 2025 report, lead analyst Ali Al-Bazergan forecasts that Humira will remain at the top out to 2025, unaffected by the next patent expiry crunch in 2019. Al-Bazergan expects Humira sales of more than $11bn in 2025.

DMHC predicts that after 2015, 2019 will be the second biggest year for patent expiry resulting in $9.7bn sales deduction

Al-Bazergan predicts that after 2015, 2019 will be the second biggest year for patent expiry, resulting in $9.7bn in sales deducted from company top lines. Key patent expiries include Roche's *Avastin* and *Lucentis*, and J&J's *Velcade*.

According to Al-Bazergan, oncology will oust infectious disease in 2019 and account for the largest proportion of big pharma prescription sales by therapy area. However, a number of large product launches in the metabolic market will result in this market superseding infectious disease by 2023, owing to lucrative launches in diabetes and dyslipidemia. Al-Bazergan believes the immunology and inflammation therapy area will remain stagnant as major biosimilar threats will be offset by new innovative product launches.

Published online 6 April 2017

View Top 10 Best-Selling Drugs In 2025 here: **http://bit.ly/2ohWLHA**

2016 Versus 2006: A Decade Of Change For Best-Selling Drug League Table

RANK	PRODUCT IN 2016	COMPANY(IES)	2016 SALES ($BN)	PRODUCT IN 2006	COMPANY(IES)	2006 SALES ($BN)
1	Humira	Abbott Laboratories Inc.; AbbVie; Eisai Co. Ltd.	16.50	Lipitor	Almirall SA; Astellas Pharma Inc.; Pfizer	13.81
2	Enbrel	Amgen Inc.; Pfizer; Takeda Pharmaceutical Co. Ltd.	9.25	Advair	Almirall; GlaxoSmithKline PLC	6.18
3	Harvoni	Gilead Sciences Inc.	9.08	Plavix	Bristol-Myers Squibb Co.; Sanofi	6.06
4	Remicade	Johnson & Johnson; Merck & Co; Mitsubishi Tanabe Pharma Corp.	8.85	Epogen	Amgen; Johnson & Johnson	5.69
5	Rituxan	Chugai Pharmaceutical Co. Ltd.; Roche	7.41	Nexium	AstraZeneca	5.18
6	Revlimid	Celgene Corp.	6.97	Norvasc	Pfizer	4.87
7	Avastin	Chugai; Roche	6.89	Remicade	Johnson & Johnson; Merck & Co; Mitsubishi Tanabe Pharma	4.49
8	Herceptin	Chugai; Roche	6.89	Enbrel	Amgen; Pfizer	4.46
9	Lantus	Sanofi	6.32	Zyprexa	Eli Lilly & Co.	4.36
10	Prevnar	Pfizer	5.72	Diovan	Ipsen; Novartis AG; UCB Group	4.34

Source: Informa Pharma Intelligence's Medtrack

From Witty To Walmsley – The Priorities For GSK's New CEO

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Emma Walmsley

It's Emma Walmsley's first week at the helm of GlaxoSmithKline. What can we expect in terms of her priorities?

When Emma Walmsley was revealed as the successor to Sir Andrew Witty as CEO of GlaxoSmithKline PLC, it was clear the board had opted to secure Witty's volume-first growth strategy for the company that was launched in 2015.

But the world looks quite different in 2017 than it did in 2015. What does this mean for Walmsley and GSK?

BOOSTING REVENUE

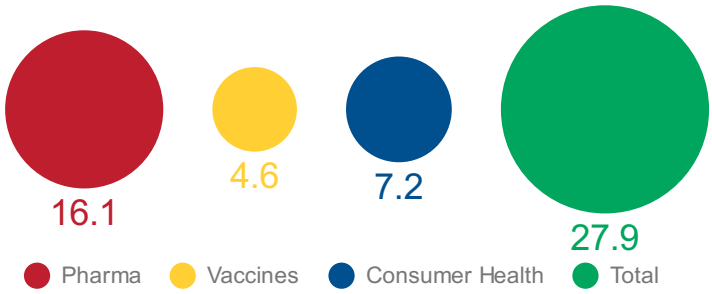
The pricing climate was cool in 2015, but the US could still be relied upon for double digit growth. In the Trump era, no such certainty remains. Walmsley's experience in boosting revenues in the consumer health arena, and her commitment to volume-based growth rather than price increases, will likely stand her in good stead here.

The departure of Abbas Hussain from the C-suite was a big blow for GSK (he left after losing out on the top job) but GSK mitigated the loss by poaching former AstraZeneca PLC exec Luke Miels and appointing him global head of pharmaceuticals. With Miels, investors got the 'fresh pair of eyes' they had been demanding during the search for Witty's replacement. They can be optimistic that the Walmsley/Miels pairing helps GSK increase revenues in those hard to reach territories.

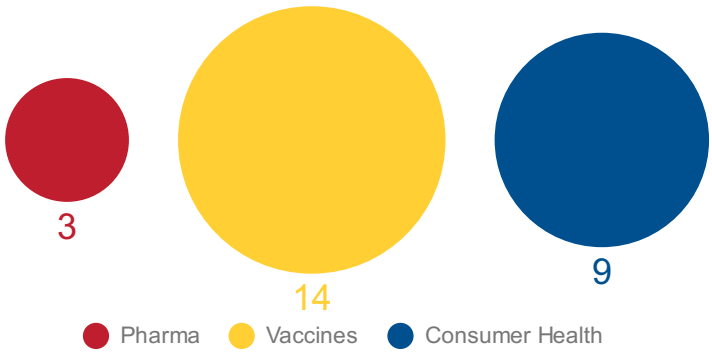
Walmsley was handed a welcome advantage last week when Mylan received a complete response letter from the US FDA on its application for a generic version of GSK's blockbuster *Advair*, likely delaying a launch by months and possibly longer. SC098479 GSK worked an interchangeable generic into its 2017 forecasts, but the boon from the FDA is only a temporary reprieve. Behind Mylan are a slew of generic rivals racing to launch their own Advair generic.

2016 GSK Group Revenues & Growth

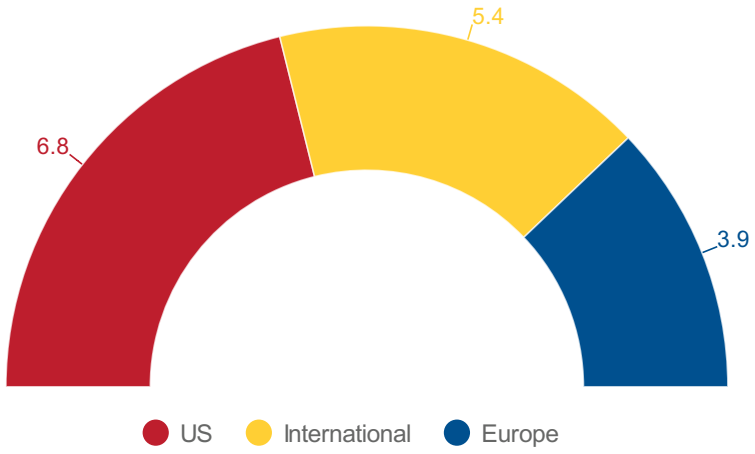
Revenue (£bn)



Reported Growth CED (%)

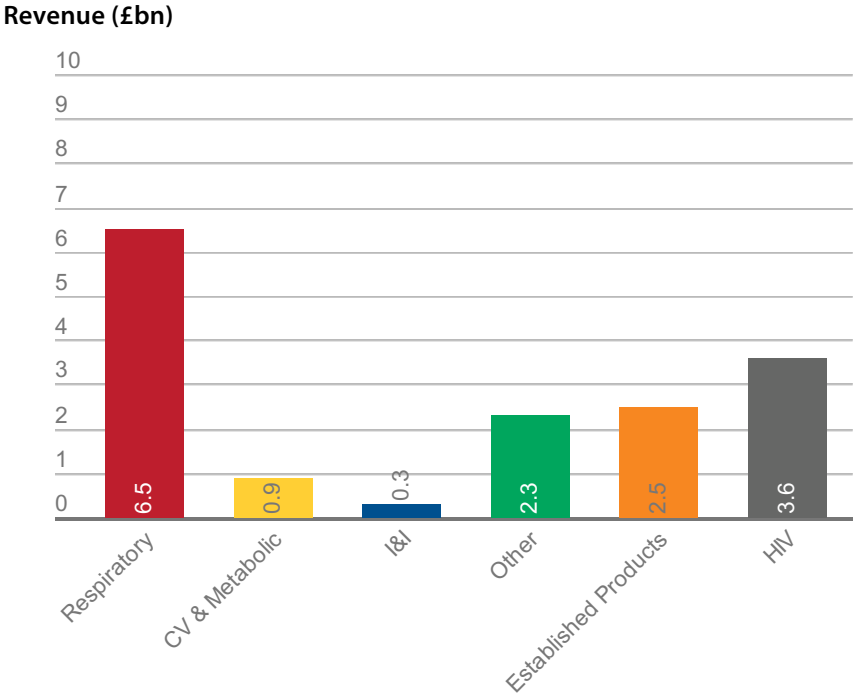


GSK's Pharmaceutical Revenues By Region In 2016



Total pharma revenue: £16.1bn

2016 GSK Pharmaceutical Revenues By Therapy Area (£bn)



R&D PRODUCTIVITY

Investors have repeatedly pointed to Walmsley's lack of pharma credentials as a disadvantage of her appointment. She joined GSK in 2010 following a 17-year career at L'Oréal. However, a former career as a Heinz executive hasn't harmed Novartis CEO Joe Jimenez. Increasing R&D efficiency has proved challenging for all of big pharma, no matter the background of their top executive. GSK tried to boost R&D by creating its Centres of Excellence in Drug Discovery and linking scientists' incentives closer to commercial milestones. "Neither of these initiatives has proven as successful as was hoped," point out Societe Generale analysts in a March 22 research note. They suggest GSK needs more "creative tension" through "raising competition between internal R&D and its external biotech companies" for GSK's investment dollars. Walmsley's relationship with GSK's respected head of R&D, Patrick Vallance, will be crucial here.

NEW LAUNCHES

GSK is expected to secure approval for two major products in 2017. It has filed its *Shingrix* shingles vaccine, which will compete with Merck & Co. Inc.'s *Zostavax*, and a once-daily closed triple combination therapy for COPD. Both are slated as potential blockbusters, and Walmsley will need to get the launches exactly right to win over investors.

But this isn't the most important challenge. Around 25 drugs are set to deliver crucial data over the next few years, and it will be up to Walmsley and her team to pick the winners. Not quite a baptism of fire, but Walmsley will need to hit the ground running to ensure GSK's pipeline delivers its potential. And here is where she can really make her mark at GSK. As the SocGen analysts point out: "Given how low the stock market's expectations are for GSK's pharma business, in our view, executing well here is the way to maximize returns for shareholders."

> GSK needs more 'creative tension' through 'raising competition between internal R&D and its external biotechs'

Pharmaceutical sales grew 3% in 2016 to £16.1bn. GSK said this reflected the continued good performance of new HIV products *Tivicay* and *Triumeq*, which had combined sales for the year of £2.7bn, up 82%. Total respiratory sales grew 2%, with the continued decline in *Seretide/Advair* sales offset by growth in the rest of the portfolio. New respiratory products generated sales of £1.05bn. The Vaccines business grew 14% to £4.6bn. This included Meningitis vaccines *Bexsero* and *Menveo* (from the Novartis asset swap), which had combined sales of almost £600m (+96%), and flu vaccines sales of £414m (+38%). Consumer Healthcare grew 9% to £7.2bn with good contributions to growth from a number of brands including *Sensodyne*, *Voltaren* and *Panadol* as well as growth from *Flonase OTC*.

**I&I covers GSK's immunology and inflammation therapies. Financial data from GSK's 2016 annual report.*

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Roche's Tecentriq Shows Survival In Triple-Negative Breast Cancer

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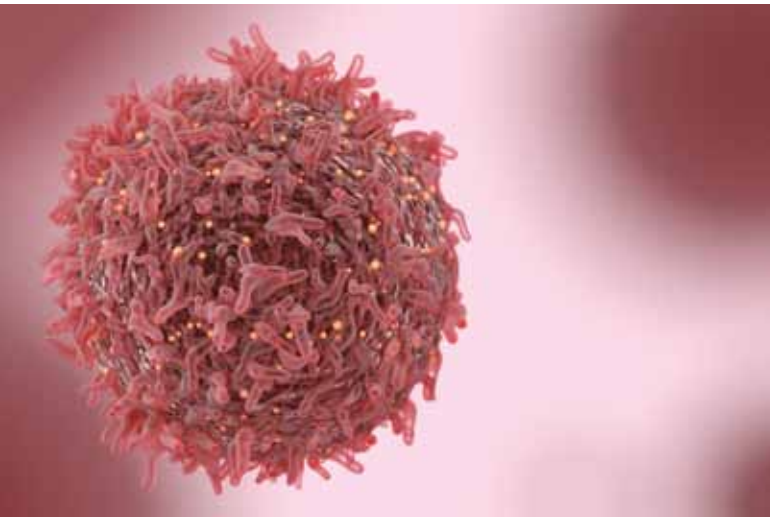
Treatment with Tecentriq helped some patients with aggressive metastatic triple-negative breast cancer to live significantly longer, those that responded to treatment, according to data presented at AACR.

Despite a positive outcome for some patients with metastatic triple-negative breast cancer (TNBC) treated with Roche's PD-L1 inhibitor *Tecentriq*, the study shows that questions about why some patients respond to treatment while others do not continue to challenge the immuno-oncology field.



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Roche claimed to be the first to report positive survival in patients with TNBC with data presented at the American Association for Cancer Research annual meeting in Washington, D.C. April 3.

The Phase I study showed patients treated with Tecentriq (atezolizumab) who responded to the treatment lived significantly longer compared to those who did not respond. The company presented Phase Ib data last year in the same patients showing positive overall response and objective response rates to treatment with Tecentriq in combination with Celgene Corp.'s chemotherapy *Abraxane* (paclitaxel-protein bound), but not survival data.

Study leader Peter Schmid, director of St. Bartholomew's Breast Centre at St. Bartholomew's Hospital and Barts Cancer Institute in London, said the most significant finding of the study was the difference in survival between responders and non-responders. All of the responders were alive after one year, while the one-year survival rate for non-responders was only 38%.

"Another noteworthy finding is that metastatic TNBC patients treated with atezolizumab had a prolonged median duration of response of 21 months, which is substantially longer than what has been seen with any other treatment to date for this patient population," Schmid said in a statement. The company is currently enrolling patients in a Phase III trial further exploring the combination in first-line metastatic TNBC patients, and is also running several earlier-stage studies testing a range of different combinations. Tecentriq was the third PD-1/L1 inhibitor to reach the market when it was approved last year, first for bladder cancer and then for metastatic non-small cell lung cancer in patients whose disease has progressed during or following platinum-containing chemotherapy.

Roche is competing against Merck & Co. Inc., Bristol-Myers Squibb Co., Pfizer Inc. and others not yet on the market to expand the indications for their respective immune checkpoint inhibitors to more patients. Merck is studying *Keytruda* (pembrolizumab) in combination with chemotherapy in a Phase III study in neoadjuvant TNBC, while Bristol also appears to be testing *Opdivo* (nivolumab) in TNBC patients, according to clinicaltrials.gov.

TNBC represents an important indication because while the aggressive cancer appears in only a small subpopulation of breast cancer patients, there are few treatment options for these patients beyond surgery and chemotherapy. Some 10% to 20% of breast cancer is believed to be TNBC, according to Roche.

The study presented at AACR enrolled 112 evaluable patients. Nineteen received Tecentriq as first-line treatment and 93 had received at least two or more therapies. Patients' tumors were also evaluated for the presence of PD-L1 protein on the immune cells inside the tumor, a potential biomarker for efficacy, though physicians and drug makers are still trying to figure out how best to apply it to treatment. The study categorized patients in two cohorts by PD-L1 status: those with PD-L1 on fewer than 5% of immune cells and those with PD-L1 on 5% or more.

> 'Metastatic TNBC patients treated with atezolizumab had a prolonged median duration of response of 21 months'

There has been significant debate in the industry about how best to study patients by PD-L1 status in clinical trials. Per RECIST criteria, 11 patients responded to treatment, representing an overall response rate of 10% (including complete and partial responses). Of the 11 RECIST responders, five received Tecentriq as a first-line treatment and nine had disease with high PD-L1 expression.

For responders, overall response rates were 100% at one year and two years, while overall survival rates for non-responders was 33% and 11% at one year and two years, respectively.

"It will be down to other ongoing and future studies to further improve on these treatment outcomes by optimizing treatment regimens and combinations for this hard-to-treat group of patents," Schmid said.

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CONTINUED FROM COVER

TRANSPARENCY & LEAKAGE

The big thing that companies need to understand about tenders is that they are very transparent. Payers openly set out their requirements and the criteria that companies need to fulfill to win, but they also make transparent the prices that companies put forward. This means that any discounts or rebates are no longer confidential. Setting out net prices is uncomfortable for industry because of the fear that these prices will be used in other markets to set prices locally through international reference pricing.

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'You win or you lose, there is no negotiation, so you put in your best price'

National boundaries around pricing are falling away in other ways too, Robinson said. He pointed to consolidation among payers in the retail channel and rafts of mergers and mega mergers, for example, between Walgreens and Boots. This means that these organizations are more frequently buying medicines not just for hundreds of pharmacies in one country, but for many more pharmacies across several countries. In addition, big healthcare providers, like Bupa, operate across multiple countries.

This all means that it is more and more difficult to charge these entities different prices in different countries. "This is causing issues because you can't price fence and say I will sell for this in country X and sell for that in country Y because [the organizations] are buying across multiple countries," Robinson said. This is a headache for pharmaceutical companies and their country affiliates, which must tread carefully so they do not set new, lower price levels. "It's about understanding where the potential risks are. If you are dealing with a group purchasing organization and are about to bid locally, you need to know what other tenders that they have put out in other countries," he said.

Procurers within these organizations are very sophisticated and are quick to pick up lower bids put forward in other parts of their network, Robinson noted. They are just as quick to demand that lower price in other markets.

Robinson warned that without the right skills, country affiliates can often be very reactive and go all out to win a tender with overzealous discounts. Indeed, this type of procurement system encourages such behavior. "You win or you lose, there is no negotiation, so you put in your best price, … you are afraid of what the competition is going to do, so you over compensate and you go in even lower," he said. "It's not surprising to see massive amounts of margin to be given away because the companies fear they are not being competitive."

Nevertheless, it does not have to be a race to the bottom, Robinson maintained. Some companies put the roles and controls involved in tendering at a regional or even global level. The people in these roles work with country affiliates to ensure that all parts of the company are acting as one entity to protect margin overall. "It's about having a regional, and to some extent, a global view about where your prices have been pegged through tendering … so you are not setting new and lower price floors that will impact and ripple across different markets."

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What Is Tendering?

Tendering is a transparent process through which purchasers (public or private organizations within healthcare systems, including hospitals, pharmacies, drug plans or health insurers) buy pharmaceuticals by asking for bids from competing pharmaceutical companies. The company that offers the most attractive bid, in line with pre-defined criteria, such as low price, is then awarded a contract to supply the product to the purchaser. This differs from confidential contracts negotiated directly between the purchaser and supplier.

Sucampo's Vtesse Acquisition

In search of a new direction since shelving cobiprostone last summer, Sucampo acquires Cydan-backed startup and Niemann-Pick disease candidate VTS-270, now in a pivotal Phase IIb/III study.

Troubled Sucampo Pharmaceuticals Inc. is placing a $200m wager on the potential of bringing the first drug therapy for the rare disorder Niemann-Pick Disease Type C1 (NPC-1) to market, announcing a cash-and-stock buyout of privately held Vtesse Inc. and its pivotal-stage VTS-270 on April 3.

Sucampo has been struggling since it decided to shelve its lead pipeline candidate, cobiprostone, last July following clinical disappointments in oral mucositis and gastroesophageal reflux disease, and called the deal "an excellent strategic fit." A fully enrolled, global Phase IIb/III study of VTS-270 – a mixture of 2-hydroxypropyl-beta-cyclodextrins (HPβCD) – is expected to report out by mid-2018. The drug was in-licensed by Vtesse from the National Institutes of Health in 2015, and has FDA breakthrough therapy designation.

The US FDA and the European Medicines Agency previously assured Vtesse that the ongoing trial of VTS-270 – if successful – will be sufficient for review and potential approval. Preclinical and Phase I/II data have already demonstrated clinically significant benefit, as measured by specific disease outcomes and extended survival seen in animal models, including data from a retrospective analysis against a matching natural history cohort. In addition, safety experience to date supports chronic treatment, Sucampo indicated.

During an April 3 investor call, Sucampo CEO Peter Greenleaf said VTS-270 will complement its gastrointestinal drug *Amitiza* (lubiprostone), which is approved in four different constipation settings and in Phase III for pediatric functional constipation. NPC-1 is often first diagnosed in pediatric patients.

joseph.haas@informa.com, 3 April 2017

Approvals, Successes and Setbacks

As public companies prepare to present their financial reports for the first quarter of 2017, Scrip has gathered the stats on drug approvals for the first three months, as well as highlights of the biggest trial success and most disappointing clinical setbacks of this year so far.

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2017 has, in just three months, already produced more new drug approvals in Europe and the US compared with the same time point last year. This year so far has also revealed positive efficacy signs for some of 2017's most promising new drugs, as well as clinical setbacks for high profile, late-stage novel drugs in development.

As the first quarter reporting season approaches, *Scrip* takes a look at the highlights of the year to date.

NEW DRUG APPROVALS

First up, celebration of a successful first quarter that has upped the number of new drug approvals compared to last year.

As of March 23, 2017, the European Medicines Agency's scientific committee, the CHMP, had granted positive opinions for 20 market authorization applications (MAAs) and 10 extensions of therapeutic indications for this year, compared to 19 MAA and 12 label extension nods in the same period 2016.

Meanwhile, in both the first quarter of 2016 and 2017, the CHMP granted no negative opinions. This is likely due to increased transparency from the regulatory agency, which is providing insight to companies earlier in the application process on the data required for a positive recommendation. In the first quarter of 2017, three companies withdrew applications in Europe in contrast with just one application withdrawal in the same period last year.

Across the pond, in the first three months of 2017, the US FDA granted a total of 29 NDA and BLA approvals compared with only 19 positive decisions over the same period in 2016. These totals are not exclusive to filings for new active substances but are labeled on the FDA's database as 'original new drug applications'.

2016 was an unusually slow year for novel drug approvals with the FDA granting market approval for just 28 products classed as new active substances throughout the full year. Already in 2017 things are looking up and in February internal analysis from the Pink Sheet showed that the FDA had more than 40 submission reviews lined up for products classed as new molecular entities or novel biologics.

DATA TRIUMPHS

In terms of clinical data triumphs, the first quarter has been fairly quiet. However, a few late-stage trials have stood out for products that have the potential alter the standard of care within their respective treatment paradigms.

News in February that AstraZeneca PLC's *Lynparza* (olaparib) works better than standard of care chemotherapy in treating a group of patients with HER2-negative metastatic breast cancer harboring germline BRCA1 or BRCA2 mutations lifted hopes for the first-in-class drug. Lynparza is already approved in the US for ovarian cancer, but the extra indication is an added boost for the product and for AstraZeneca's overall DNA Damage Repair portfolio.

Lynparza showed a significant and clinically meaningful improvement in progression-free survival in patients with germline BRCA mutated breast cancer in its Phase III OLYMPIAD trial comparing the PARP-inhibitor – taken in tablet form of 300mg twice daily – to physician's choice of a standard of care chemotherapy. The trial data will likely be presented at the American Society for Clinical Oncology's annual meeting in June this year.

Around the same time as Lynparza's Phase III success, Celgene Corp.'s ozanimod also cleared its first Phase III hurdle in multiple sclerosis. Investors are keeping their eyes on Celgene's sphingosine-1 phosphate (S1P) receptor modulator because it has the potential to be a blockbuster product outside of the company's hematology franchise. This would further diversify revenue beyond Celgene's multiple myeloma backbone therapy *Revlimid* (lenalidomide) and would give its immunology and inflammation franchise a significant boost. More detailed data from the Phase III SUNBEAM trial – which has initially shown ozanimod to be better than the standard of care interferon treatment for MS on three different efficacy measures – will be presented later this year, most likely at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in October.

In March, during the American Academy of Dermatology's annual meeting, held in Orlando, Florida, Johnson & Johnson reported positive results for its IL-23 inhibitor guselkumab against AbbVie Inc.'s anti-tumor necrosis factor drug *Humira* (adalimumab) in the VOYAGE-2 psoriasis study. VOYAGE-2 is the second positive Phase III head-to-head study in this indication, following VOYAGE-1.

Importantly, while other interleukin inhibitors have been tested against Amgen Inc.'s anti-TNF *Enbrel* (etanercept) they have not been pitted against the world's best-selling biologic Humira, which some clinicians view as the higher bar.

Guselkumab is positioned to follow-on from J&J's successful *Stelara* (ustekinumab), which inhibits both IL-12 and Il-23. J&J also presented results from the Phase III NAVIGATE study at the meeting, which the company said shows patients can be safely and effectively switched from Stelara to guselkumab, with superior results.

Also in March, the first look at Phase III data for Chi-Med (Hutchison China MediTech Ltd.)'s new highly selective VEGF inhibitor fruquintinib showed encouraging efficacy on both primary and secondary endpoints in third-line colorectal cancer. These data are expected to be used to file the product in China by mid-year, with a possible launch in 2018.

CLINICAL FAILURES

But there have been failures too. Starting off the year with a bang, Inotek Pharmaceuticals Corp.'s stock took a big hit on Jan. 3 after its lead product trabodenoson failed in a Phase III trial in glaucoma patients.

The first of Inotek's Phase III studies, known as MATrX-1, missed its primary endpoint, causing the Massachusetts-based company's stock to drop more than 71%. Inotek executives at the time pointed to a stronger than expected placebo response as one explanation for the failure of the first-in-class, highly selective adenosine mimetic, which targets the A1 subreceptor.

The top-line data from the MATrX-1 study in 303 patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT) and an IOP ≥24 mmHg and ≤34 mmHg revealed that it did not achieve its primary endpoint of superiority in reduction of intraocular pressure (IOP) compared with placebo at all 12 time points tested over three months of treatment (at four time points during each of these days: 8AM, 10AM, 12PM and 4PM on days 28, 42 and 84).

Later in Jan. Israeli firm Alcobra Ltd. also stumbled when its attention deficit hyperactivity disorder (ADHD) therapy missed the primary endpoint in a second Phase III trial, known as the MEASURE study, in adult patients. Alcobra's metadoxine extended-release (MDX) product was already walking a tightrope as a potential new therapeutic approach for adult ADHD and this Phase III clinical trial miss prompted the biotech to shutter the program and consider strategic alternatives.

While MDX – a 5HT2b antagonist – would have been a new mechanism of action for ADHD, the drug had already been placed on a clinical hold by the FDA in Sept. 2016. A total of 283 patients had been enrolled in the MEASURE study at the time of the FDA hold, meaning each patient had at least one efficacy assessment for the primary endpoint conducted post-randomization. Roughly 180 patients had completed the trial.

Alcobra is now considering ex-US development of MDX for Fragile X syndrome. Because Fragile X is an orphan indication, the hurdle for safety concerns might be lower, CEO Yaron Daniely said at the time.

1Q 2017 also rubbed salt into Eli Lilly & Co.'s wounds regarding its failed Alzheimer's disease therapy solanezumab. The big pharma was forced to end its EXPEDITION PRO trial for solanezumab in prodromal Alzheimer's disease due to the product's high-profile failure in other late-stage Alzheimer's trials. Finally, Lundbeck Inc. added to the vast graveyard of failed Alzheimer's drugs in the first quarter after its compound idalopirdine, a 5HT6 antagonist, failed to show efficacy in late-stage studies.

Lundbeck and its partner Otsuka Pharmaceutical Co. Ltd. announced the failure of the Phase III STARBEAM and STARBRIGHT studies of idalopirdine in moderate to severe Alzheimer's disease on Feb. 8, saying at the time that the data do not support a regulatory approval. Idalopirdine had already failed in the Phase III STARSHINE study in September 2016.

COMING SOON...

It's not all doom and gloom. Looking ahead to the second quarter, Celgene expects to report top-line results from a second Phase III study for ozanimod, known as RADIANCE. Meanwhile, Neurotrope Inc.'s novel bryostatin treatment for Alzheimer's, AstraZeneca's durvalumab in bladder cancer and Actelion Pharmaceuticals Ltd.'s antibiotic cadazolid are among a raft of therapies scheduled for major data read-outs or approval decisions in 2Q 2017.

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Longtime Genzyme Holdout Meeker Passes Reigns To Sibold

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Bill Sibold will take over the leadership of Sanofi's Cambridge-based Genzyme group as the unit begins the important launch of Dupixent. Meeker ends his career at Genzyme after 23 years.

The longtime head of Sanofi's Genzyme unit, David Meeker, will step down and be succeeded by Bill Sibold as the Cambridge, Mass.-based group embarks on an important transition with the launch of *Dupixent* (dupilumab). Sanofi announced Apr. 5 that Sibold will take the reigns as executive vice president of Sanofi Genzyme after working to prepare for the launch of Dupixent as the head of Sanofi Genzyme's Global Multiple Sclerosis, Oncology and Immunology organization.

The announcement sets the stage for a significant leadership change since Meeker helped to build Genzyme over his 23-year career at the company. He held leadership roles at Genzyme when it was an independent rare disease company, prior to the acquisition by Sanofi in 2011.

Meeker took on the role of overseeing the unit under the ownership of Sanofi from founder and CEO Henri Termeer after the acquisition.

But Genzyme has changed considerably from the rare disease specialist it was then, laser focused on selling enzyme replacement flagships like *Cerezyme* (imiglucerase) and *Fabrazyme* (agalsidase beta) for ultra-rare genetic diseases.

The unit morphed into a broader specialty care platform under the leadership of Sanofi CEO Olivier Brandicourt. In addition to the rare disease drugs and multiple sclerosis drugs *Lemtrada* (alemtuzumab) and *Aubagio* (teriflunomide), Brandicourt shifted responsibility for oncology and immunology under the Genzyme umbrella.

The leadership transition appears in line with the broadening responsibility of the organization. Genzyme's main near-term priority will be executing on a top-notch launch for Dupixent, given the big commercial opportunity for the drug for the treatment of atopic dermatitis and the investment behind it.

Prior to joining Genzyme in 2011, Sibold worked as chief commercial officer of Avanir Pharmaceuticals Inc. and worked in commercial operations for Biogen Inc.

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Leo Pharma To Compete With Big Pharma

Denmark's specialty dermatology company, Leo Pharma, has globalized its infrastructure and is now investing in its internally and externally sourced product pipeline to help it compete with big pharma companies keen to move into the therapeutic area.

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Leo Pharma AS is hoping a second-half 2017 launch of the new psoriasis therapy, *Kyntheum* (brodalumab) in Europe will add to its range of therapies for the condition, from topical ointments for mild disease to a systemic biologic for severe disease. The specialty dermatology company also expects its Phase IIb investigational atopic dermatitis therapy, tralokinumab, to become one of the leaders in a burgeoning atopic dermatitis sector.

Brodalumab, an interleukin-17 targeted monoclonal antibody, was licensed from AstraZeneca PLC for marketing in Europe, and is a key future product for Copenhagen, Denmark-headquartered Leo Pharma, which expects to expand its biologic offerings in the future, and to head off competition from several big pharma companies that have moved into the dermatology field.

The brodalumb deal is "our first step into marketing a biologic therapy, but won't be our last", commented Leo Pharma CEO and President Gitte Aabo in an interview with *Scrip* as the company announced its 2016 annual results on Apr. 3. In fact, the company is working on six early stage dermatological biologics under its Nov. 2016 collaboration with MorphoSys AG.

Despite a black box warning on an association with suicidal ideation and behavior being added to the product's label when AstraZeneca's US brodalumab licensee, Valeant Pharmaceuticals International Inc., gained approval for the product, as *Siliq*, in February, Leo executives pointed to the clinical data on brodalumab as one of the factors that made the company optimistic about its future.

The reason why Leo became interested in brodalumab was its efficacy data, said the company's head of global research and development, Kim Kjoeller. "In a clinical trial, around 50% of patients achieved PASI 100, a completely clear skin, and brodalumab also has a quick onset of action," he added. The compound is undergoing regulatory review for patients with moderate to severe plaque psoriasis.

Leo has for many years faced competition from TNF-inhibitors in psoriasis, and this will continue in the future from Phase III compounds like Sun Pharmaceutical Industries Ltd./Almirall SA's IL-23 inhibitor tildrakizumab. But it now also faces competition from newer therapies in another key dermatology sector, atopic dermatitis, where big pharma Sanofi and its partner Regeneron Pharmaceuticals Inc. have just received US approval for the IL-4/IL-13 inhibitor *Dupixent* (dupilumab) to treat the condition.

Leo has acquired the global rights to the IL-13 blocker, tralokinumab, also from AstraZeneca, and it is expected to enter Phase III in the treatment of atopic dermatitis in the second quarter of 2017. Leo expects the atopic dermatitis market to develop along the same lines as the psoriasis market, with numerous agents and companies, but with Leo having products that cover patients with mild, moderate and severe disease.

Top-line Phase IIb results have shown that at week 12, the two higher doses of tralokinumab tested were associated with a significant improvement from baseline in the EASI score (eczema area and severity index). Leo is also developing a topical JAK inhibitor, LP0133, licensed from Japan Tobacco Inc. in 2014, for use in the condition, and also in chronic hand eczema, which is a "difficult patient group to help and one with a high unmet need," Kjoeller said.

"LP0133 is being moved forward into Phase IIb and should enter Phase III in two years' time, and potentially giving us a full offering in mild, moderate and severe atopic dermatitis, and later in other indications including hand eczema," the company executive added.

In a third dermatological sub-sector, Leo's marketed actinic keratosis therapy, *Picato* (ingenol mebutate), has not lived up to the company's expectations (sales in 2016 declined by 11% compared with the previous year, following a change to the US label), but the US approval of ingenol disoxate, a new treatment for actinic keratosis, is on track for 2018, Kjoeller continued. There is an unmet need for a product that will treat large areas of skin, and ingenol disoxate should offer that possibility, he reported. The product's development in Europe is behind that in the US.

The company also has in development an oral long-acting PDE4 inhibitor, LP0058, about to enter Phase IIa in psoriasis patients. "There is growing excitement in the dermatology field, and more innovation than we have seen in many years," Kjoeller concluded.

GLOBAL PRESENCE

"For Leo going forward, we want to strengthen our global presence, perhaps with further acquisitions, but we also want to invest heavily in Phase III programs to bring new treatments to the market," Aabo remarked.

Over the past decade, Leo has grown its global reach – it is the leading player in dermatology in China for example, having entered the market in 2008 – and has a presence in more than 100 countries. Sales in international markets grew by 39% during 2016, compared with a 13% sales growth in Europe and a 16% growth in the US.

But it is also facing increasing generic competition to some of its mainstay topical psoriasis products, and Aabo noted that in 2016, the company "faced significant pricing pressure in the US and Europe."

Business development deals were a key feature of Leo's progress in 2016, with the acquisition of Astellas Pharma Inc.'s dermatology portfolio adding to the products licensed from AstraZeneca and the research collaboration with MorphoSys.

"We integrated the Astellas portfolio more efficiently than we originally thought," noted Aabo, adding that "integrating a large portfolio has now become a core competence of the company, and has increased our appetite for marking another acquisition along the same lines in the future." The sales of the acquired products were behind a 19% increase in revenues in 2016 to reach DKK9.8bn ($1.4bn), and an 11% increase in EBITDA to reach DKK1.3bn.

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Jardiance Joy Boosts Boehringer Ingelheim

Boehringer Ingelheim GMBH reported 56.1% currency-adjusted growth in its diabetes business in 2016, and from 2017 the early lead in the use of diabetes medication for cardiovascular indications that it and partner Eli Lilly & Co. have established looks likely to help drive continued expansion. The family-owned German company revealed that total global sales of the SGLT-2 inhibitor *Jardiance* (empagliflozin) were €433m in 2016, with combination product *Synjardy* (empagliflozin plus metformin) booking €25m. This leaves Boehringer and Lilly's product still firmly in third place behind AstraZeneca PLC's *Farxiga/Forxiga* (dapagliflozin) and Johnson & Johnson's *Invokana* (canagliflozin) in terms of global sales, but 2017 could see it narrowing the gap following its label expansion in the US in December 2016 to cover cardiovascular death risk reduction among patients with type 2 diabetes and pre-existing cardiovascular conditions. The product's European label was also updated in January 2017 to include the cardiovascular risk reduction data. Recently released real-world data analysis from patients taking Farxiga and Invokana as well as Jardiance suggest that the cardiovascular risk reduction is a class effect. Boehringer Ingelheim executives believe this is not necessarily bad news for Jardiance but rather that it could help convince physicians and payers of the product's benefit without undermining its standing versus other drugs in the class.

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Allergan Sees Hope In Poor Botox Depression Data

Allergan PLC has left analysts scratching their (fore)heads over its decision to investigate *Botox* (onabotulinum toxin A) in Phase III for major depressive disorder (MDD), despite less than stellar Phase II data and little clarity on how it might work in this setting. Evercore ISI analyst Umer Raffat offered a rather cynical opinion. He suggested in an emailed statement on Apr. 5 that the decision might be more to do with not jeopardizing near-term off-label use of Botox in depression, with Allergan prepared to "let a Phase III go on for years to come". Following on from a couple of small external studies suggesting the use of Botox was effective in treating MDD, Allergan conducted its own, larger trial involving 258 women with MDD. Allergan tested two doses of Botox, 30U and 50U, against placebo over a duration of up to 24 weeks. The primary endpoint was at week six. The cosmetic use of Botox in the facial region usually involves injections of 20U-24U of Botox. In the Phase II depression trial, neither dose met the primary endpoint, although the smaller 30U dose came close. The 30U dose demonstrated "numerically superior efficacy" in Montgomery-Asberg Depression Rating Scale (MADRS) total score compared to placebo, said Allergan. The treatment difference for 30U was -4.2 at three weeks (p=0.005); -3.7 at week six (p=0.053) and -3.6 at week nine (p=0.049). The 50U dose did not demonstrate superior efficacy over placebo at week three, six or nine, said Allergan. The lack of a dose response has intrigued Datamonitor Healthcare analysts. "It is possible that Botox wouldn't display a proper dose-response curve because of how its mechanism translates into a potential antidepressant effect," commented lead analyst Daniel Chancellor. There is negligible information available about how Botox might achieve an anti-depressant effect (other than improving cosmetic appearance). "I would only ever see this as mixed cosmetic-therapeutic use, rather than a purely therapeutic indication," he added.

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Paratek Sees Broad Potential For Omadacycline

Paratek Pharmaceuticals Inc. believes its antibiotic omadacycline, which it will submit for US FDA approval in the first quarter of 2018, has broad potential against a variety of pathogens and patient populations based on the drug's second successful Phase III clinical trial. Boston-based Paratek reported on April 3 that its broad spectrum oral and intravenous antibiotic proved its non-inferiority to moxifloxacin in the treatment of community-acquired bacterial pneumonia (CABP), including the Phase III OPTIC trial's separate primary endpoints for FDA and European Medicines Agency (EMA) approvals. The company will submit a new drug application (NDA) to the FDA as soon as the first quarter of 2018 and it will submit a marketing authorization application (MAA) to the EMA later in 2018. Thanks to a Qualified Infectious Disease Product (QIDP) designation from the FDA, the omadacycline NDA will be subject to a slightly shortened eight-month review period and the drug will have five additional years of patent exclusivity. Omadacycline previously was non-inferior to the generic Pfizer Inc. antibiotic *Zyvox* (linezolid) in a Phase III trial comparing the two drugs in the treatment of acute bacterial skin and skin structure infections (ABSSSI) in June 2016. The company now will speak with ex-US and other types of prospective partners about commercialization, which executives said last year they would do when they had the Phase III results in both skin infections and pneumonia.

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Can Pharma Keep Up With The Challenges Of Digital Healthcare?

By Kevin Grogan & Lubna Ahmed

The digital revolution is transforming the world of healthcare, which is awash with new technologies and floods of data. Pharma companies are beginning now to focus on harnessing these advances in their businesses, from mining genomic data to identify new drug targets, to establishing the most appropriate patients for targeted and personalised treatment, and creating tracking systems to monitor clinical trials in real time.

That there are opportunities is not in doubt, however the sector realises its models have to change in order to capture these. Ali Parsa, chief executive of UK digital healthcare provider Babylon, believes that pharma as a whole "needs some reengineering" given that its operating model has not really changed for decades. This new territory also triggers questions about the challenges that come with digital health including data privacy, security, patient behavior, and rules and regulations.

In this feature Scrip, in partnership with international law firm CMS, gets the perspectives of leading industry players, including AstraZeneca, Novartis and Qualcomm on the inevitable coming of digitized healthcare and discusses the key challenges they will face.

Digital integral to healthcare

AstraZeneca's pharmaceutical project director, Matthew Bonam, notes that "it is hard to believe that the use of digital will not become an integral part of healthcare delivery", saying "there are many potential benefits including enabling patients to self-manage their conditions, providing a more complete picture of a patient's current and future health status to healthcare professionals to support decision-making.

"These technologies, and the data they generate, have the potential to revolutionise care, identifying 'at risk' patients earlier and supporting more cost-effective management for populations and improved outcomes for the individuals".

Pharma doing enough to embrace the digital age?

Yet there is still a feeling that pharma has been moving too slowly and is only reluctantly embracing the digital age. Healthcare "is one of the last remaining sectors of our economy and our society that is yet to go fully digital" says Qualcomm's chief medical officer Jim Mault, adding that "the way we deliver healthcare hasn't changed for 100 years. When we write someone a prescription, we say take x mg of x medication, but why is every human being getting the same dose of x?

Do you really think everyone will respond the same? With digital health, what we will see is personalised care, intelligent care".

Indeed, while the traditional business model has taken a bashing and many observers believe that the days of the blockbuster are over, a glance at the sales figures of AbbVie's anti-inflammatory drug Humira (adalimumab) and Gilead Sciences' hepatitis C big-sellers Sovaldi (sofosbuvir) and Harvoni (ledipasvir and sofosbuvir) suggests the old ways are still effective and perhaps explain a reluctance to change.

Pharma should not fear disruption

Nevertheless Novartis' global head of digital medicine, Amy Landucci, suggests pharma should not be afraid when technology disrupts its current ecosystem. Indeed when the Swiss major was looking to reach out in to this upcoming space, it became aware that technology and digital medicines were already up and running and would continue to fundamentally change how healthcare is delivered.

In deciding how best to gain a foothold in this space, it soon became clear that partnerships with tech-savvy companies would be the way to go. "We are not looking to build capabilities in our company but we are looking for companies to partner with," Landucci said.

Partnerships best path to take

Christopher James, professor of biomedical engineering at Warwick University, says: "If you consider the fact that technology can be lighter, smaller, harmless and dissolvable, then I think it's only natural that pharma asks for help in personalising medication and healthcare".

Novartis, with the full backing of chief executive Joe Jimenez, has inked a number of digital pacts. It was an early investor in Proteus Digital Health, best known for its ingestible sensor, or 'chip-in-a-pill, which could send a patient or a doctor alerts when it's swallowed (however Proteus' investigational digital pill, which is designed to measure adherence to Otsuka's antipsychotic Abilify (aripiprazole), has run into regulatory problems).

Novartis has also set up a $100 million joint investment fund with the mobile chip giant Qualcomm which provides cash for early-stage tech companies. The partners are also developing a smart inhaler that is designed to improve adherence by detecting usage in patients who are using the Swiss major's portfolio of chronic obstructive pulmonary disease treatments. The connected version of Novartis' Breezhaler is expected to be launched in 2019.

Respiratory ripe for digital deals

The respiratory area is a prime example of drug developers linking up with digital healthcare groups to help personalise their offerings and improve their gathering of real-world data. In 2016 Boehringer Ingelheim teamed up with Qualcomm to improve patient adherence in chronic obstructive pulmonary disease by developing a fully-integrated data-capturing module for Respimat - Boehringer Ingelheim's platform inhaler.

The firms say it will allow physicians to remotely monitor patient outcomes, help patients better follow their treatment plans and so decrease healthcare costs and hospitalisations associated with COPD, as well as the number of avoidable deaths.

AstraZeneca is another group looking at pacts in the respiratory area. It has signed a 10-year supply agreement with Adherium to access the latter's platform which consists of a cloud-based server that collects data gathered by Adherium's Smartinhaler - a device that can be clipped onto any prescribed inhaler to treat asthma or COPD.

Beyond respiratory

Though respiratory is one disease area in which companies are digitally active, the potential of this technology does not stop there. Babylon's CEO Parsa says the company has been in discussion with a pharma company around the digital expertise it can offer them. Through Babylon's app individuals can track physiological parameters by taking blood tests and having results including iron levels and vitamin levels sent directly to the app on a digital device. Parsa believes that this sort of technology can aid patients in keeping track of vitals when taking a certain medication.

"This digitisation has to happen, the healthcare system is so broken and dysfunctional it's a scary notion for it to not change – the problem is; it's just not changing fast enough."

Equally, in its collaboration with Qualcomm, Novartis is using the company's 2net platform as a basis for its clinical trials. Jim Mault points out that if one was to be carrying out a clinical trial on a drug for heart disease, blood pressure is a parameter that would need to be measured. In the past a nurse would have to be sent out to physically take participants' blood pressure. However, with technology such as the 2net platform, participants can be given a blood pressure

meter allowing them to take readings themselves that are then saved instantly on the cloud.

Safe and secure

As a highly regulated industry though, pharma does have its concerns about digital healthcare and they are valid ones. As companies begin to grapple with great blocks of data, it is clear that privacy and security become increasingly more important.

AstraZeneca's Bonam says "there are issues which need to be carefully addressed. Issues such as data privacy and security, along with the use of the data for further research, all need to be managed well by the providers and consumers alike. It is also critical that providers deliver digital health tools with the same level of rigour in design, development and evaluation that would be expected of any healthcare intervention".

Pharma must take care to pick the right partner

Choosing which company to team up with thus requires a rigorous approach. Carina Healy, a partner at the multinational law firm CMS, who acts for a range of biotech, speciality pharma, medical device and medical technology companies, says that "partnering with tech companies that know pretty much everything there is to know about data would appear to be straightforward," she says.

However she advises caution as tech companies "may not be as used to dealing with compliance". Their starting point is to see "what they can do with data but [they] don't always understand the privacy aspect of it or how that data might be regulated".

For patients, privacy is paramount

Pharma needs to think through all the issues right from the beginning to ensure patient privacy is protected and to guarantee that secure processes are in place so its systems are not vulnerable to hacking. As Healey notes, "all the challenges surrounding data protection and security are manageable if they are thought about in advance and if appropriate processes are put into place". Patients are very happy to partner with pharma and offer up their data if they believe it is being used to benefit science and innovation, Healy says. However, that partnership is based on trust which collapses very quickly if patients believe their privacy is being compromised.

Transparency and consent are crucial. Quintiles' head of digital health acceleration, John Reites, says that "people are concerned about their security, privacy and what they're giving up, the only way we can change this is by a very open opt-in consent." He believes that when it comes to participation in clinical trials in particular, if there is a digital element to it, patients need to know what data they are giving up, what data will be collected, why it is being collected, the purpose for it and how long it's going to be stored.

Regulation no excuse to do nothing

So is it possible for an industry as strictly regulated as pharma to go above and beyond in something as limitless as digital health? GlaxoSmithKline's head of global multi-channel marketing platform, AJ Ploszay, believes that being a highly regulated industry is no excuse for pharma not to embrace this innovation. What he questions is the industry's ability to build up multiple new commercial models at the same time.

With the arrival of technology, consumers are more demanding about new ways to receive information and services, and Ploszay believes that the real challenge here is whether pharma can shape its strategy to adapt to these new capabilities. When asked if a firm can act in a highly regulated industry and still be digital, he says: "I don't buy into that argument because I could give you examples of countless financial service companies that have the ability to be digital and they are as regulated as the pharmaceutical industry – GSK and other companies are already showing it can be done in an ethical, compliant manner and there is a pocket of brilliance."

Qualcomm's Mault is also wary of those who push the privacy argument too much: "When you get a prescription filled, they will have a record with your name on it and the medication you're taking. All that stuff is on a database, in lots of different places – so you're already facing it, whether you know it or not."

He goes on to say "you have already been exposed for a long time to the risk of someone hacking into your information – you're already exposed to risks that exist. The problem is you're not getting any of the benefits – the benefits that could save your life."

Mault argues that "this digital evolution is bringing a whole different model of care that everyone will need to adapt to and though there will be bumps and frustration, it needs to happen. When you start talking about whether you want your health information digital or somewhere on a piece of paper – it's an unfortunate level of concern right now, because it's not rational when you look at the facts."

Change just not fast enough

"This digitisation has to happen, the healthcare system is so broken and dysfunctional it's a scary notion for it to not change – the problem is; it's just not changing fast enough."

CMS Cameron McKenna's Healy also believes that the privacy argument should not stall digital progress. While digital health is perceived as a relatively new concept, data protection has been around a very long time and there are directives at a European level that lay out standards for companies handling personal data across all sectors, not just pharmaceuticals and healthcare.

She concludes by saying that "the companies who will do well in big data are those who are ahead of the game and have worked out how to deal with data protection, how to get the right consent, how to put the right security process in places and how to give their customers confidence in those processes."

As Trump Meets Xi, Will Trade Dynamics Change?

As U.S. president Donald Trump meets his Chinese counterpart Xi Jinping at his Florida resort, the first U.S-China presidential summit between the two leaders, trade and market access will be at the center of the talks. President Trump has expressed his intention to center the discussion on trade issues, during his election campaign; Trump has repeatedly called upon China to reduce trade surplus. The current administration will likely to push hard on market access for American companies, noted one expert. Already, trade groups including the U.S Chamber of Commerce have complained that access barriers deter further investment in China. Meanwhile, China in a major shift, has outlined its ambitious plan to become an innovation-driven economy, and in its Manufacturing 2015 Plan, the government lists biotech as one of key areas for innovation breakthroughs. Given recent regulatory changes by China FDA to encourage new drug innovation, and increasing price erosions to off-patent originator products, multinational firms may have fewer options but to increase their R&D investment in China. Johnson & Johnson CEO Alex Gorsky, visiting China in March to attend the annual China Development Forum, said the U.S. healthcare giant is to invest hundreds of millions in R&D in China. Gorsky estimated the investment to reach $500m in the coming years. "China in many ways helps to set the pace," he told the audience during a panel discussion on March 18. The company, positioned for the change, has established its Asia Pacific regional innovation center in Shanghai. The move indicates that China is an essential component to Johnson & Johnson's strategy for future innovation, said the CEO in a later interview with state-owned media People's Daily. U.S. drug maker Eli Lilly & Co., has also been active in China via local partnerships.

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Alkermes Brushes Off IP Pressures To Look to Potential Blockbuster Vivitrol

Alkermes PLC has come out just about evens from a couple of recent US court rulings on IP protection involving other companies that potentially also affect the Ireland-headquartered specialty company. And with its marketed products showing progress, Alkermes expects total revenues, including royalties and product sales, to increase by 20% in 2017, led by the addiction therapy, *Vivitrol* (naltrexone). Alkermes manufactures Acorda Therapeutics Inc.'s multiple sclerosis therapy *Ampyra* (dalfampridine) and receives royalties on sales, but a US district court has just ruled that four of Acorda's US patents on the drug are invalid because of obviousness, leaving Acorda with IP protection only until 2018. Acorda says it will appeal the decision, but is already making job cuts to blunt the effects of the ruling.Balancing that negative news, the US PTO has just ruled that another company, Biogen, can retain its '514 patent on the MS therapy, *Tecfidera* (dimethyl fumarate), preventing the launch of generics in 2021 that would likely have stymied Alkermes sales of its Tecfidera follow-on product, ALKS-8700 (monomethyl fumarate). Alkermes will maintain modest royalties from the ex-US sales of Ampyra, but those from the US will decline by around $85m a year from mid-2018 onwards, estimates analysts at Jefferies. Credit Suisse analysts believe around 85% of Alkermes' Ampyra royalties of around $155m could be at risk from 2018 onwards. Investors initially marked Alkermes shares down by 7% on the intellectual property news to $57.05 on March 31. But there may be growing sentiment that Alkermes' marketed long-acting addiction therapy, Vivitrol is an under-appreciated asset. All three compounds are in Phase III clinical studies.

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Merck Blocked In Adding CV Claim For Januvia

Merck & Co. Inc.'s diabetes franchise took a major blow Apr. 7 when the firm announced that its supplemental new drug application to add a cardiovascular outcomes claim to the labels for *Januvia* (sitagliptin) and *Janumet* (sitagliptin/metformin) received a complete response letter. The New Jersey pharma offered no details on the CRL, other than to say it is reviewing the letter and will discuss "next steps" with the US FDA. Merck hopes to add a CV safety claim to all of its sitagliptin-containing diabetes drugs based on findings from the 14,671-patient TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) study. The company unveiled data during the American Diabetes Association conference in 2015 that showed in patients with type 2 diabetes and established cardiovascular disease, its dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin demonstrated non-inferiority to placebo for outcomes such as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for non-stable angina. It's an important claim for Januvia as Merck wants the drug to compete against the more effective sodium-glucose cotransporter 2 (SGLT-2) and glucagon-like peptide-1 receptor (GLP-1) classes, which either have or are working on cardiovascular safety claims. Like all diabetes medicines, the sitagliptin products are under significant pricing pressure in the US as well. Leerink "modestly" decreased its expectations for Januvia/Janumet last year, although it noted there were "relatively strong script trends."

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IDO Emerges As Clean Combo Partner, Rising Star At AACR

Clean safety profile for combination of IDO inhibitors with anti-PD-1 agents in early studies presented at the American Association for Cancer Research meeting contrasts with the toxicity-laden CTLA-4/PD-1 regimen in Bristol's Phase III CheckMate 067 study.

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New early data on IDO inhibitors from NewLink Genetics Corp. and Bristol-Myers Squibb Co. reinforce the image of the class as a safe combination partner that can enhance efficacy of PD-1 inhibitors in cancer treatment.

PD-1 immunotherapy has had an enormous impact, but only about one-third of cancer patients respond to the drugs as single agents and some tumor types don't respond at all. Bristol has invested heavily in the combination of its PD-1 inhibitor *Opdivo* (nivolumab) in combination with its CTLA-4 inhibitor *Yervoy* (ipilimumab), which is already approved for melanoma with development ongoing in multiple tumor types, but Yervoy is associated with severe toxicities.

Inhibitors of indoleamine 2,3-dioxygenase 1 (IDO1) have emerged at the head of the next wave of immuno-oncology, especially because of their potential to be successfully paired with PD-1 inhibitors.

"We are still waiting for the big wave to break in terms of novel combinations. The vast majority of combinations being investigated in trials currently in the immuno-oncology space are PD-1 antibody based," commented Keith Flaherty, director of developmental therapeutics at Massachusetts General Hospital, in an interview at the American Association for Cancer Research (AACR) meeting.

Incyte Corp.'s epacadostat is the most advanced IDO inhibitor in development. After early data were reported for the drug in combination with Merck & Co. Inc.'s PD-1 inhibitor *Keytruda* (pembrolizumab) in melanoma, the combination jumped straight to Phase III for that indication.

Data for two other IDO inhibitors – NewLink's indoximod and Bristol's BMY-986205, which was acquired from Flexus Biosciences Inc. – were presented on Apr. 4 at the AACR meeting in Washington D.C. and give the class even more momentum.

Indoximod is in Phase I or I/II for melanoma, brain cancer, breast cancer, pancreatic cancer and acute myeloid leukemia.

Keith Flaherty

In an interim analysis of the Phase II NLG2103 study, which included patients with harder-to-treat ocular melanoma, the combination of indoximod taken twice daily with Keytruda demonstrated an objective response rate (ORR) of 52% overall in 60 patients (including a complete response of 10%) and a 59% ORR (CR 12%) when patients with ocular melanoma were excluded, researchers reported at the AACR meeting (see table). NewLink noted in a statement about the data that some trials of other IDO inhibitors have not included patients with ocular melanoma.

The most common adverse events were fatigue, headache and nausea. Importantly, investigators reported that the rate of severe adverse events was very low in the study, with only 3 (5%) Grade 3 events (see table below).

NewLink's CEO Chuck Link told *Scrip* that the company intends to start a large randomized trial in 2017 and that the patient population for this trial in advanced melanoma will be similar to the patient population in the interim Phase II study released at the AACR meeting.

That next trial will be essential confirmation of these early signals. Commenting on the IDO data in an interview at the AACR meeting, Mass General's Flaherty cautioned that "judging provisional promising results for several dozen patients can be a hazardous enterprise." A signal could be missed or conversely, there could be an "erratic overestimation of efficacy," and it is important to have larger numbers of patients treated and randomized data to have confidence, he added.

On the other hand, the data, though uncontrolled, reinforce the idea that this is a uniquely promising combination that continues to produce results that are above expectations for PD-1 antibodies alone, Flaherty said. Furthermore, he said, the IDO class looks very clean on safety and any augmentation in efficacy would be "pure upside."

The market reacted to the data differently, sending the NewLink stock down by 10% to a close of $20.79, presumably due to comparison with a very small combination study of Merck's epacadostat. Merck

Indoximod With Keytruda: Phase II Interim Results

ENDPOINT	ALL PATIENTS (N=60)	CUTANEOUS/NON-OCULAR (N=51)
Objective response rate	31 (52%)	30 (59%)
Complete response rate	6 (10%)	6 (12%)
Partial response rate	25 (42%)	24 (47%)
Stable disease	13 (22%)	11 (22%)

Source: Presented by Y. Zakharia, AACR 2017

Phase II Interim Safety Analysis Of NewLink's Indoximod With Merck's Keytruda (n=60)

ADVERSE EVENT	ANY GRADE	GRADE ≤ 2	GRADE 3
Fatigue	36 (60%)	35 (58%)	1(2%)
Headache	20 (33%)	20 (33%)	0
Nausea	19 (32%)	19 (32%)	0
Arthralgia	17 (28%)	17 (28%)	0
Diarrhea	17 (28%)	16 (26%)	1 (2%)
Pruritis	16 (26%)	16 (26%)	0
Rash	14 (23%)	13 (21%)	1 (2%)
Cough	13 (21%)	13 (21%)	0

Source: Presented by Y. Zakharia, AACR 2017

announced in October 2016 that in the Phase I ECHO-202 study of epacadostat twice daily with Keytruda in 19 melanoma patients, the objective response rate was 58% and the complete response rate was 26%. Previously, in June 2014, the combination of epacadostat with Yervoy demonstrated an ORR of 41.7% and a CR of 8.3% in a Phase I/II study of 12 melanoma patients.

The early toxicity profile of indoximod/Keytruda compares favorably to that of Bristol's Yervoy/Opdivo combination in the same indication. In updated results from the CheckMate 067 study in frontline melanoma presented at the AACR meeting on Apr. 3, the Yervoy/Opdivo combo was associated with a 58.5% rate of Grade 3/4 adverse events compared to 21% for Opdivo alone.

Flaherty believes that the severe toxicities and modest efficacy – the combination's 64% two-year survival rate in CheckMate 067 wasn't much higher than Opdivo alone at 59% – mean that the Yervoy/Opdivo combination is a less attractive treatment option and that melanoma patients may opt for Opdivo monotherapy or a trial of a novel combination including a PD-1 therapy instead.

The most important test for the combination will be lung cancer, where Bristol has fallen behind Merck's Keytruda/chemo combo.

The Opdivo/Yervoy combination also saw a setback with the failure of the failure of the CheckMate 143 study, announced Apr. 3, which tested the duo against Roche's *Avastin* (bevacizumab) in glioblastoma, a notoriously difficult tumor type. Results will be presented at the World Federation of Neuro-Oncology Societies meeting in Zurich on May 7.

PROMISING IDO INHIBITOR

While heavily invested in the combination of Opdivo and Yervoy, Bristol has also been exploring many other targets, including IDO, having obtained an IDO development program through the acquisition of Flexus for $800m upfront in February 2015.

> 'We are still waiting for the big wave to break in terms of novel combos. Currently, the majority of combos investigated are PD-1 antibody based'

Bristol presented safety and tolerability data for BMS-986205 (F001287) with and without Opdivo in a Phase I/IIa dose-ranging study of previously treated advanced malignancies at the AACR meeting. The trial tested seven once-daily doses (25 mg, 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, 800 mg) in eight tumor types (cervical, diffuse large B-cell lymphoma, melanoma, non-small cell lung cancer, squamous cell head and neck, bladder, pancreatic, and renal cell carcinoma).

The University of Toronto's Lillian Siu reported that the drug was well tolerated when tested as a monotherapy and in combination with Opdivo (see table). The most common treatment-related adverse events included decreased appetite and diarrhea.

In an Apr. 4 note, Barclays analyst Geoffrey Meacham described Bristol's pharmacodynamic and safety data as promising, "albeit in populations less likely to be clinically responsive initially."

The Phase I/IIa data for '205 as a monotherapy and in combination with Opdivo appear good overall up through the 200 mg dose, granted the number of evaluable patients was small for each dose, Meacham commented.

Bristol is now studying BMS-986205 in multiple tumor types in Study 003, a Phase I/II trial.

The company noted that the IDO1 inhibitor is one of 21 oncology compounds in clinical development and that the company is studying combinations across multiple tumors. "We continue to be committed to the Opdivo/Yervoy combination, and our work to develop IDO adds an additional novel mechanism to potentially help patients with unmet need," Bristol told *Scrip*.

Bristol has also been teaming up with Incyte to test Opdivo with the IDO inhibitor epacadostat. On April 2, the companies announced an expansion of their partnership, with plans to launch two new registrational studies of the Opdivo/epacadostat combination – one in first-line non-small cell lung cancer (all levels of PD-L1 expression) and one in first-line head and neck cancer. The companies are also planning to add relapsed refractory melanoma cohorts to a Phase I/II study of epacadostat and Opdivo.

"While '205 generally showed the desired characteristics, we see the commercial logic behind the decision to proceed into Phase III with Incyte's epcadostat as the dose escalation and expansion studies for '205 remain ongoing," Barclays Meacham commented.

The expansion of Bristol and Incyte's partnership followed on the heels of a March 31 announcement by Merck and Incyte to start registrational studies in new tumor types. The announcement clarified that in addition to melanoma, Merck and Incyte are planning six additional pivotal trials, two in non-small cell lung cancer, one in first-line kidney cancer, one in squamous cell cancer of the head and neck and two in bladder cancer (first-line and second-line).

Published online 4 April 2017

View table showing Phase I/II Data For Bristol's BMS-986205: Treatment-Related Adverse Events here: **http://bit.ly/2nTJK3v**

Biopharma Leaders Call For Diversity Drive

An open letter signed by key figures in UK biopharma, calls on industry leaders, HR and recruitment organizations to increase diversity in sector boardrooms and C-suites, by facilitating the path of women and minorities to the top. The letter came out of a recent meeting on BioPharma Boardroom Diversity hosted by MedCity (the hub for the UK's London-Cambridge-Oxford life sciences cluster) and the life sciences executive recruitment firm Liftstream.

THE LETTER

Biopharma Boards Can't Afford To Ignore The Power And Benefit Of Diversity

The societal, financial and ethical benefits of diversity at senior levels in business are known and obvious. But for life sciences companies, typically small and lean organisations, protecting the bottom line and short-term pressures and concerns have tended to take priority over the types of inclusion initiatives that larger corporates have the time and resources to pursue.

But a growing body of evidence shows that diversity in life sciences across the sector has a tangible impact on share price performance and returns. Research from executive search company Liftstream has confirmed that in recently floated companies, those with a mix of genders on boards delivered an average 19% increase in share price, compared with a 9% decrease from all male boards. This is a message that anyone on the Board of, or in a leadership role of, a public company, can no longer afford to ignore.

Although it has made progress on diversity, the biopharma industry still lags behind other sectors in the representation of women and minorities at Board level. The Liftstream study reported that today women occupy just 10% of biopharma board positions, 98% of Chair positions and 92% of CEO roles are occupied by men. Liftstream suggests that to achieve the demonstrated benefits of diversity, companies need to reach what it defines as "critical mass", a 30% representation of women at board level. Based on current appointment trends, this is unlikely to take place before 2036.

Historically, men dominated the pipeline of science in academia. Today, the UK's Higher Education Statistics Agency shows that 69% of medical, technology and 77% of veterinary science students are female. The pipeline of young talent is full. But there are structural challenges and roadblocks in the industry perpetuated by the current model of venture capital, specifically in the period post IPO. Data suggests that the male dominance of venture capital is impacting the ability of talented women to break through into board roles.

So, while the benefits of diversity and inclusion at board level are generally accepted and, more importantly, supported by data, the path of progress remains challenging and requires collective dialogue and action. The signatories to this letter reject tokenistic appointments and quotas, that we believe to be counterproductive and essentially missing the point. Diversity begets diversity, and this will be achieved through a set of approaches that support the entire system with the common goal of improving performance and delivering better outcomes.

Firstly, we need to ensure strong committed advocacy and sponsorship from the top. Board members should be seeking out fresh, diverse talent, to support and recommend for opportunities, whilst raising their visibility within the organisation. It is important that men and women in a position of influence work together on this, as a women-for-women approach is at best slow, and at worst simply does not work. We also need more mentors to make sure talented people are 'board-ready', and a decision-making process that is transparent, fair and truly meritocratic.

HR and recruitment services must work harder to encourage and promote diverse candidates, not only for boards, but also into C-Suite positions, to deliver a sustainable flow of talent and a robust pipeline.

Finally, we must ensure that the cultures at the top of our organisations and across our sector are open and welcoming so that people feel wanted and needed, and able to contribute, instead of asking "do I belong here?". Strong leadership and good governance impact the behaviours of organisations. They will attract a new diverse set of people who want to make a difference for our industry and thus feel able to compete for positions of power and influence.

The life sciences enjoy active and engaged industry bodies and collaborative partnerships across the system and we welcome a broad-based dialogue and response. We came together for the Board Meeting on BioPharma Boardroom Diversity recently, and we are calling on companies large and small, investors, and trade bodies, to work together to ensure the UK life sciences sector will grow and flourish based upon the talents of men and women who seek to ensure better options for patients and a world-leading, vibrant healthcare system.

Annalisa Jenkins, CEO, Dimension Therapeutics Inc
Jo Pisani, UK pharma & life sciences consulting leader, PwC
Karl Simpson, CEO, Liftstream
Denise Scots-Knight, CEO, Mereo BioPharma
Kate Bingham, Managing Partner, SV Life Sciences
Sarah Haywood, CEO, MedCity

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Piramal Plans To Scale Up In Critical Care

Piramal Enterprises Ltd. (PEL), the diversified Indian healthcare to financial services group and active M&A participant, plans to deploy a "blended" strategy to expand its critical care business, including in-licensing products in the near-to-medium term. Peter DeYoung CEO of Piramal Critical Care outlined four key prongs of the company's growth strategy, including building on the core inhalation anesthetics business, steering the upcoming launch and commercialization of desflurane in the US successfully, and transitioning and integrating the recent acquisitions from Janssen Pharmaceutica NV and Mallinckrodt LLC. Organic growth – developing and launching its own products – is also proposed, though DeYoung noted that time horizons for that could be longer. Earlier this year, PEL acquired a portfolio of intrathecal spasticity and pain management drugs from Mallinckrodt – products that complement its expanding critical care business especially in the US. The deal marked the Piramal group's seventh pharmaceutical acquisition in the last 24 months and the second buy on the trot for the critical care unit. In October 2016, Piramal acquired five anesthesia and pain management injectable products from Janssen.

anju.ghangurde@informa.com, 6 April 2017

Astellas' Cash For Ogeda's Women's Health Drug

The founders and investors of the privately owned Belgian biotech Ogeda SA will be flush with up to €800m following the sale of the company to Astellas Pharma Inc., one of the first pharma companies to express an interest in the biotech during its earlier development stage. However, the Belgian firm is only likely to retain operations for around a year in its home country post-acquisition. The Japanese company is paying €500m upfront for Ogeda – which used to be a pharma services business (known as Eurofins Scientific) before it made the transition into drug discovery and development – as well as milestone payments of up to €300m based on attainment of certain clinical development and regulatory milestones for lead compound fezolinetant. Upon completion of the deal, Ogeda will become a wholly owned subsidiary of Astellas. The transaction is subject to certain conditions, but Astellas expects the deal to contribute to its late stage pipeline and mid-to-long term growth. Astellas has committed to maintain Belgian Ogeda operations in place for minimum one year before it is likely to move development to one of its own sites. Ogeda's chief financial officer Ruth Devenyns told *Scrip* in a previous interview about the company's pipeline goals that the firm was seeking financing to advance its products. However, she noted at the time that "if the right partner with suitable capabilities comes along" Ogeda would be interested in a buyout.

lucie.ellis@informa.com, 3 April 2017

Nabriva's Approach To Antibiotic Stewardship

Nabriva Therapeutics AG plans to buck conventional thinking for antibiotic stewardship with the commercialization strategy for lefamulin, a potential first-in-class pleuromutilin antibiotic in development for community-acquired bacterial pneumonia. The company is aiming to position the antibiotic as a first-line option to treat CABP, rather than as an antibiotic to be held in reserve for only the sickest patients. The strategy is precisely in-line with the over-arching theme of antibiotic stewardship, because of the targeted nature of lefamulin, according to CEO Colin Broom. "We think we have a very, very strong case and medical argument to use lefamulin up front, particularly for patients [that physicians] are concerned about," Broom said in an interview. Nabriva sees a first-line opportunity for the novel antibiotic, because it is not a broad-spectrum antibiotic, but a narrower antibiotic that addresses pathogens found in lung infections.

jessica.merrill@informa.com, 5 April 2017

Novartis Lubris In-Licensing Deal

Continuing its search for ophthalmic drivers, Novartis AG has in-licensed a recombinant human lubricin from Lμbris BioPharma which it hopes will become a solution for dry eye, a condition with high unmet medical need that affects more than 344 million patients globally. The in-licensing arrangement for the product, dubbed ECF843, was announced Apr. 6 and gives the Swiss drug maker commercial rights to it outside the European market. No financial details were given by the duo. Originally identified in joints, lubricin is also found on the ocular surface as well as other body tissues. It is the most lubricating and anti-adhesive molecule in the human body and has natural anti-inflammatory properties, according to Boston, MA-based Lμbris. Novartis added that lubricin is an endogenous glycoprotein expressed in areas of high shear stress and friction including the tear film where it binds to and protects tissues of the ocular surface, the assumed mechanism that ECF843 addresses. Earlier this year, Novartis combined its retina medicines business with the Alcon pharmaceuticals business of Alcon, in which it acquired a majority interest in 2010; together they are now operating as one ophthalmology-focused division of Novartis Pharmaceuticals. Novartis' in-licensing pact with Lubris is its second ophthalmology-related deal in recent months.

sten.stovall@informa.com, 6 April 2017

Bristol's CheckMate 067 Revives Debate On Rationing Yervoy/Opdivo

Yervoy/Opdivo combo proves significant survival benefit over Yervoy alone in Phase III frontline melanoma study, but is on par with Opdivo alone in patients with higher PD-L1 expression.

EMILY HAYES emily.hayes@informa.com

Survival data for Bristol-Myers Squibb Co.'s *Yervoy/Opdivo* combination in the CheckMate 067 study in frontline melanoma reinforce the regimen's potency, but also revive a debate about whether the regimen should be reserved for select subsets of patients, with others getting enough benefit from Opdivo alone or other treatment options.

The combination of *Yervoy* (ipilimumab), a CTLA-4 inhibitor, and *Opdivo* (nivolumab), a PD-1 inhibitor, received accelerated approval from the FDA in frontline metastatic melanoma in October 2015 based on an improvement in the trial's co-primary endpoint of progression-fee survival. Approval was conditional on demonstrating a survival benefit in the study.

Combination use of Opdivo/Yervoy for melanoma has not been a major commercial focus, as the opportunity is dwarfed by the potential for combinations in lung cancer, but Bristol has cited the stabilization of Yervoy sales as a sign of steady use of the combination in melanoma.

CheckMate 067 randomized patients to three arms: Yervoy/Opdivo, Opdivo or Yervoy. But the study was only powered to compare Yervoy/Opdivo to Yervoy and Opdivo to Yervoy. It was not powered to test the combination against Opdivo alone, though exploratory analyses were performed for this comparison. Patients in the monotherapy arms were permitted to crossover to combination treatment, making it difficult to show a benefit in overall survival.

The combination met the co-primary endpoint of improved overall survival (OS) compared to Yervoy in the study, Bristol reported April 3 at the American Association for Cancer Research (AACR) annual meeting in Washington D.C.

In an Apr. 3 note, Barclays analyst Geoff Meacham noted that the survival improvement in CheckMate 067 was highly statistically significant and concluded that the positive overall survival data from the study should offset concerns about the Opdivo/Yervoy regimen's accelerated approval.

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"We are encouraged that the Opdivo and Yervoy combination is showing a meaningful OS benefit, particularly given the potential for crossovers to muddle the results," Meacham said.

The positive outcome is clearly good news, but the data prompted questions about whether the difference between the combination and Opdivo alone was big enough to justify combination treatment, at great expense, and whether patients could be more appropriately selected based on subset data.

Survival results were statistically similar for the combination and Opdivo monotherapy in BRAF wild-type patients and in patients with more than 5% of PD-L1 expression.

Questions about whether the benefits of the combination will be worth the costs and toxicities compared to Opdivo alone came up in past data releases.

'MODESTLY HIGHER' SURVIVAL

Results reflecting follow-up of 28 months in CheckMate 067 were presented at the AACR meeting by James Larkin, a consultant medical oncologist at The Royal Marsden Hospital in London.

Median overall survival was not reached in the Yervoy/Opdivo and Opdivo arms, versus 20 months for Yervoy. The combination and Opdivo monotherapy arms both demonstrated a statistically significant reduction in the risk of death, by 45% and 37%, respectively. In an exploratory analysis, the combo also had a numerical improvement in OS compared to Opdivo, with a 12% reduction in risk.

At the two-year mark, median OS was 64% for the combination versus 59% for Opdivo monotherapy and 45% for Yervoy alone.

The two-year OS rate for the combination was only "modestly higher" than Opdivo monotherapy, though both were well above Yervoy monotherapy, Meacham noted.

"Consequently, given that the regimen had a Grade 3/4 adverse event rate of 58% vs. 21% for Opdivo monotherapy (and 28% for Yervoy), we suspect the debate will move to the relative risk/reward profile. However, we would also note though that as physician experience with the regimen increases and the side effect profile becomes better characterized, we anticipate that adoption of the regimen will continue," the analyst concluded.

CONTINUED ON PAGE 22

CONTINUED FROM PAGE 21

Larkin noted that the vast majority of events resolved within three to four weeks. In the combination arm, the adverse event rate caused 40% of patients to drop out, primarily in the combination phase, but even drop-outs benefited from treatment in terms of response.

GUIDANCE FROM SUBSETS

After the presentation of results at the AACR meeting, Larkin was asked whether the subset results should guide treatment.

The data are not definitive regarding use in patients with BRAF mutations, who can benefit from targeted therapies. In patients who were BRAF-wild type, OS was not reached in the combination and nivo groups and was 18.5 months for Yervoy. In an exploratory analysis of the combination compared to Opdivo in this subset, the hazard ratio was 0.97 in the combination's favor, not a statistically significant result.

In BRAF-mutant patients, the median OS was not reached for Yervoy/Opdivo or Opdivo alone and was 24.6 months for Yervoy. The hazard ratio in the exploratory analysis comparing the combination to Opdivo was numerically better at 0.71 but was not statistically significant. In the real world, these patients have the option of taking a BRAF inhibitor with a MEK inhibitor in the frontline setting; optimal sequencing of targeted vs. immunotherapy in this population has still not been determined.

In other cancer settings, most notably lung cancer, PD-L1 expression levels are used to identify patients most likely to respond to treatment – although this has not been relied on in melanoma.

In the quarter of trial participants who had PD-L1 expression over 5%, the combination looked very similar to Opdivo (hazard ratio 1.05) though the response rate was numerically higher. The combination looked better than Opdivo monotherapy for those with less than 5% expression (hazard ratio 0.84).

Larkin said that the subset data are intriguing, but was reluctant to say they could be used to guide treatment. The role of PD-L1 as a biomarker is still not yet really understood, he noted during a press briefing.

The role of the Yervoy/Opdivo combination in BRAF-mutant patients is also complicated by the question of whether this subset should instead be receiving a BRAF inhibitor and MEK inhibitor upfront rather than immunotherapy.

Larkin explained to *Scrip* that in his opinion, there are still not enough data to steer BRAF-mutant patients to the targeted BRAF/MEK combination instead of the immunotherapy combination. Studies are ongoing of different sequencing approaches and could provide answers in the future.

Larkin said that in his practice, he reviews aspects of treatments with patients and lets them make a decision. BRAF and MEK inhibitors are oral, whereas the PD-1 and CTLA-4 immunotherapies are given by intravenous infusion. The BRAF/MEK combination may be given continuously, whereas the Yervoy/Opdivo combination often causes severe side effects, resulting in early discontinuation in about one-third of patients.

The clinician said that once he reviews all of these details, patients usually are ready to make a choice.

"It's a sequencing question. It's not really a question of which is better… it's a question what is the strategy going to be in that patient to maximize control of disease, survival and quality of life," Larkin said.

Going forward, a major research focus will be developing biologically rational combinations for individual patients and trying to reduce toxicity, while maintaining efficacy, he added.

Michael Atkins, deputy director of the Georgetown-Lombardi Comprehensive Cancer Center in Washington, D.C., commented to *Scrip* that in his opinion the results in CheckMate 067 are good enough to support recommending the combination over Opdivo alone for many patients, particularly those who are PD-L1-negative or BRAF-positive.

The toxicities are manageable for experienced clinicians and the treatment is over faster, Atkins said.

The CheckMate 067 study doesn't address the question of whether an immunotherapy combination is better than BRAF/MEK upfront in BRAF-mutant patients – the National Cancer Institute-sponsored EA6134 study of sequential combinations will help answer that question, but CheckMate 067 supports the use of the combination in BRAF-mutant patients, he said.

Published online 3 April 2017

View CheckMate 067 Results here: **http://bit.ly/2pla3AM**

Teva's Austedo To Compete With Generic Rival

FDA approved Teva's Austedo (deutetrabenazine) for chorea associated with Huntington's disease, with a warning on depression and suicidality similar to generic Xenazine, but other parts of the labeling points to advantages.

Shutterstock: Oravan Pattarawimonchai

Teva Pharmaceutical Industries Ltd. secured FDA approval of *Austedo* (deutetrabenazine) April 3, and the drug appears to have a competitive price and label to compete against an older generically-available medicine, Lundbeck Inc.'s *Xenazine* (tetrabenazine). Austedo will be available to patients in two to three weeks, Teva said.

Austedo is a deuterated version of the VMAT2 inhibitor Xenazine and the promise of the drug – which Teva gained with the $3.5bn acquisition of Auspex Pharmaceuticals Inc. in 2015 – is that the technology would yield an improved pharmacokinetic profile, and as a result, benefits over the older drug like improved safety, less frequent dosing and improved tolerability.

Few of the 35,000 or so Huntington's patients in the US are treated with Xenazine because of the drug's side effects like depression, somnolence and suicide. And neither Xenazine nor Austedo treat the underlying condition or the progression of the debilitating neurodegenerative condition, but they can improve chorea, the involuntary random twisting movements associated with the disease.

As it turns out, Austedo was approved with the same black box warning on risk of depression and suicide carried by Xenazine, but the labeling does point to important differences between the two drugs.

jessica.merrill@informa.com, 4 April 2017

Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage, Phase III clinical trial developments for the more than 10,000 drug candidates under active research worldwide. To see changes to the progress of product candidates further back in the development pipeline, and a table of the week's product approvals, please visit our Pipeline Watch webpage at scrip.pharmamedtechbi.com.

CLICK

Visit the Pipeline Watch webpage at scrip.pharmamedtechbi.com for all the week's changes to the industry's R&D pipeline

Selected clinical trial developments for the week 31 March – 6 April 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
GlaxoSmithKline PLC	*Nucala* (mepolizumab)	eosinophilic asthma	MUSCA; in the Apr. 5, 2017 online issue of *The Lancet Respiratory Medicine*.
Chiesi Farmaceutici SPA	CHF 5993 (extrafine beclomethasone, formoterol and glycopyrronium)	chronic obstructive pulmonary disease	TRINITY; in the Apr. 3, 2017 online issue of *The Lancet*.
Novo Nordisk AS	semaglutide	type 2 diabetes	SUSTAIN 2; in the Apr. 3 2017 online issue of *The Lancet Diabetes And Endocrinology*.
Updated Phase III Results			
Trevena Inc.	*Olinvo* (oliceridine)	acute pain	APOLLO-1, -2; positive data vs. iv morphine.
Bristol-Myers Squibb Co.	*Opdivo* (nivolumab) plus *Yervoy* (ipilimumab)	glioblastoma multiforme	CheckMate-143; did not improve overall survival versus bevacizumab.
Bristol-Myers Squibb Co.	Opdivo (nivolumab) plus Yervoy (ipilimumab)	melanoma	CheckMate-067; improved overall survival.
Peregrine Pharmaceuticals Inc.	bavituximab	non-small cell lung cancer (NSCLC)	SUNRISE; supportive of certain combination trials.
Phase III Interim/Top-line Results			
Roche	*Alecensa* (alectinib)	ALK-positive NSCLC	ALUR; significantly improved PFS.
Sumitomo Dainippon Pharma Co. Ltd.	*Trerief* (zonisamide)	Parkinson's disease with Lewy Body dementia	Met the primary endpoint, indication filed in Japan.
Paratek Pharmaceuticals Inc.	omadacycline	community-acquired pneumonia	OPTIC; second positive study for approval .
Phase III Announced			
Corbus Pharmaceuticals Holdings Inc.	anabasum	systemic sclerosis	In diffuse cutaneous disease .
Bristol-Myers Squibb Co./ Incyte Corp.	epacadostat plus nivolumab	first-line NSCLC, first-line head and neck cancer	A IDO1 inhibitor with a PD-1 inhibitor .
Updated Phase II Results			
Medigene AG	dendritic cell vaccine	acute myeloid leukemia	Clinical benefit in small group of patients.
Genexine Inc.	GX-H9, twice-monthly	short stature	Encouraging results.
Spark Therapeutics Inc./Pfizer Inc.	SPK-9001 gene therapy	hemophilia B	Consistent and sustained Factor IX levels.
Karyopharm Therapeutics Inc.	selinexor	diffuse aggressive lymphoma	SADAL; durable and prolonged responses.
NewLink Genetics Corp.	indoximod plus *Keytruda*	advanced melanoma	Robust response rates with the IDO pathway inhibitor.
Immunomedics Inc.	sacituzumab govitecan	small cell lung cancer	Active with manageable toxicity.
Puma Biotechnology Inc.	neratinib	HER-2, -3 mutant solid tumors	SUMMIT; clinical responses in some subgroups.
Bayer AG	copanlisib	indolent non-Hodgkin's lymphoma	CHRONOS-1; met objective response rate endpoint.

Source: Biomedtracker

Sanofi has appointed ***Bill Sibold*** executive vice president Sanofi Genzyme and member of the executive committee – effective July 1, 2017. Sibold succeeds ***David Meeker***, who will leave the company at the end of June, after 23 years of working at Genzyme and Sanofi. Sibold joined Sanofi in 2011 as head of the MS franchise and currently, he is head of Sanofi Genzyme's global multiple sclerosis, oncology and immunology organization.

In other news, ***Meeker*** will be joining **Rhythm**'s board of directors as chair. Rhythm is a biopharma company developing peptide therapeutics for rare genetic diseases and Meeker has been on its board since 2015. Prior to his role at Genzyme, he was director of the pulmonary critical care fellowship at the Cleveland Clinic and an assistant professor of medicine at Ohio State University.

Diplomat Pharmacy Inc. has appointed ***Atul Kavthekar*** chief financial officer and treasurer – effective May 1, 2017. Kavthekar has more than two decades of financial experience and before Diplomat, he was CFO of LivingSocial Inc., an e-commerce retailer. Previously, he has held executive roles at Walgreens and at Sears Holdings Corporation's health & wellness division, which includes the Kmart Pharmacy chain.

Vencerx Therapeutics, a company focused on neurodevelopmental disorders, has appointed ***Robert H. Ring*** CEO and Jeffrey Stevenson chair of the company's board of directors. Most recently, Ring was chief science officer of the science foundation Autism Speaks and before this, he headed the autism unit at Pfizer Global research and development. Prior to his role with Pfizer, he was at Wyeth Research in Princeton, heading mood disorders research and was program leader for various drug development programs.

Yaky Yanay has been appointed **Pluristem Therapeutics Inc.**'s co-chief executive officer and Erez Egozi has been named chief financial officer (CFO). Yanay will continue as the company's president but will no longer hold the position of chief operating officer and CFO. He joined the company in 2006 as CFO and secretary but before this, he was CFO at Elbit Vision Systems Ltd. Yanay is also co-chairman of Israel Advanced Technology Industries and is on its board of directors. Previously, Egozi was Pluristem's vice president of finance and secretary and before this, he held various senior financial positions at Verint Systems Inc.

Astellas Pharma Inc. has appointed ***John DeMay*** president, Astellas US Technologies Inc. (AUST), and he will act as the site manager for AUST based in Northbrook. DeMay will also continue in his role as head of the project and product management group. He joined Astellas in 2002 as an associate director of technical services and previously, he was executive director, pharmaceutical technology management for AUST.

Endomag, a cancer healthcare company, has appointed ***Peter Keen*** non-executive director – effectively immediately. Keen founded the technology investment firm Cambridge Innovation Capital and has been on the board of various private and public companies. He is director of both MRC Technology and the Biotechnology Growth Trust plc. and previously, he was senior independent director of Abcam PLC.

Recipharm AB has appointed ***Henrik Stenqvist*** executive vice president and chief financial officer (CFO) – April 24, 2017. With 24 years' finance and management experience, Stenqvist joins the company from Meda Group, where he was CFO.

Raymond Barlow has assumed his position as **e-Therapeutics Plc**'s CEO following the announcement on Jan. 9, 2017. Barlow was executive director of corporate development at Amgen Inc. and previously, he held various scientific, business and corporate roles with AstraZeneca PLC, Crucell NV and Johnson & Johnson.

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