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Sanofi Starts 2018 As It Means To Go On: More Transactions Expected

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The end of last year was a challenging period for **Sanofi** but CEO Olivier Brandicourt believes the company is on track with its 2020 strategy, which focuses on reshaping the group's portfolio and sustaining R&D innovation.

Following this trend, divestment of its European generics business is next on the cards as Sanofi continues to cut historical chunks of the company to make space for new acquisitions in pharma and consumer health.

In 2017, Sanofi traded away its animal health business for **Boehringer Ingelheim GMBH**'s consumer health portfolio. Last year, the company also started preparing to divest its European generics business. The French big pharma expects to secure the sale of this unit by the third quarter of 2018.

Private equity firms and one pharma company are rumored to be on the list of potential buyers for Sanofi's European generics portfolio. Private equity bidders supposedly interested in the business include Advent International, BC Partners, Carlyle Group and a consortium of Blackstone Group and Nordic Capital, according to the *Financial Times*.

In the fourth quarter of 2017, Sanofi's earnings came in below analysts' expectations with an EPS of €1.06 compared with consensus of €1.15. The drug major also reported 2018 guidance that was lower than anticipated. Taking the biggest hit, sales of Sanofi's diabetes franchise declined by 15.6%, reflecting lower insulin glargine *(Lantus* and *Toujeo)* profits in the US.

Still, Brandicourt is optimistic about the company's prospects in 2018: "Q4 was challenging, but overall in 2017 Sanofi delivered stable business EPS in line with our guidance… Overall, we are pleased with the steps we have taken to strengthen the company," he said in a video interview posted on Sanofi's website in parallel with the company's annual results presentation on Feb. 7.

MORE M&A

Sanofi's chief noted on the company's Feb. 7 earnings conference call that the company had set aside around €20bn for acquisitions and bolt-on deals this year. Sanofi has already spent more than half of this pot, leaving it with around €7bn to spare.

As such, more M&A activity is expected this year for Sanofi – though not on the scale of its recent **Bioverativ Inc.** buyout.

Brandicourt cited a number of transactions the company carried out in 2017 and early 2018 as evidence of its growth, despite a weaker than expected 2017 performance.

In the previous 12 months, to highlight some of Sanofi's more exciting deals, the company acquired **Protein Sciences** for its novel flu vaccine, manufacturing capabilities and broader vaccine portfolio; and in January 2018 it spent €9.4bn to acquire Bioverativ for its hemophilia portfolio and €3.9bn to buy **Ablynx NV** for its Nanobody platform and rare disease pipeline.

"We are pleased with our progress and looking forward to accelerating our transformation in 2018," Brandicourt said, noting that the company is progressing with the business transformation strategy it laid out in 2015, which should be complete in

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Drug Spending Stalls
Growth declines as generics and biosmilars bite (p14-15)

Ready And Waiting
GSK says it's prepared for Advair generics in the US (p4)

from the editor

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Gilead Sciences is an interesting anomaly in the sector. It has booked revenues that have positioned it in the universe of big pharma for a few years now, while experiencing far greater swings between its highs and its lows than is usual among big pharma. Barely four years ago it was turbo-boosted by its astounding success in changing the paradigm for hepatitis C treatment (effectively ushering in the era of the rapid cure) with the launch of *Sovaldi* and follow-on products. Its subsequent decline once the bolus effect of the patient backlog had worn off and rival products launched was hard to avoid. What a rollercoaster the company is on.

Revenues fell 14% in 2017, having already dropped 7% in 2016. That contrasts with 2015, when they had risen 31%, following the massive 122% boost in 2014 with the onset of Gilead's HCV heyday. With the company's 2017 turnover of $25.7bn still well more than double the pre-Sovaldi $11.2bn it booked in 2013, it can hardly be called a failure.

But runaway success has a nasty habit of requiring heavy maintenance. Such a lot is now riding on newly launched and much vaunted HIV fixed-dose combo *Biktarvy* (see p7) and expensively acquired and yet to be commercially proven CAR-T therapy *Yescarta* to slow the descent. Even if late-stage pipeline products for rheumatoid arthritis and NASH make good, the company will continue to come down from its HCV high in 2015. Further serious M&A will be needed if Gilead's train is to match previous giddy heights again any time soon.

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Start-Up Quarterly Statistics: 2017 Fundraising Ends Better Than It Began
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But Q4 was the third sequential quarter with a decrease in financing totals. A review of biopharma start-up dealmaking and financing activity from October through December 2017, based on data from Strategic Transactions.

Deal Watch: Avid Transitions Into CDMO By Offloading Cancer Program To Oncologie
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Oncologie acquires PS-targeting candidate bavituximab, which may help other cancer therapies in attacking tumors. BridgeBio's newest spinout will develop former Novartis cancer candidate infigratinib.

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Walmsley: GSK Is 'Prepared' And 'Ready' For US Advair Generic Launch

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GlaxoSmithKline PLC is bracing for a challenging 2018 with the first interchangeable generic version of its blockbuster asthma drug *Advair Diskus* (fluticasone/salmeterol) likely to debut in the US, reducing revenues and impacting the bottom line.

During the company's fourth quarter and full year 2017 earnings call Feb. 7, CEO Emma Walmsley warned investors to anticipate a challenging year ahead, but she was also optimistic that growth from newer products will make up some of the loss.

2018 "will bring some challenges if the Advair generic comes, but we are very much prepared for it and ready for it, and what we are focused on is the new products," she said. Growth drivers include the respiratory drugs *Breo Ellipta* (fluticasone/vilanterol), *Anoro Ellipta* (umeclidinium/vilanterol), *Trelegy Ellipta* (fluticasone/umeclidinium/vilanterol),and *Nucala* (mepolizumab), along with the HIV drugs *Tivicay* (dolutegravir) and triple combo *Triumeq*, and the new shingles vaccine *Shingrix*.

Breo, a next-generation Advair of sorts, was slow to take off following the launch in 2014, but crossed the £1bn revenue mark for the first time in 2017. Tivicay (dolutegravir) and the combo regimen Triumeq, meanwhile, are expected to face new competition from **Gilead Sciences Inc.**'s *Biktarvy*, a combo regimen containing the integrase inhibitor bictegravir ,approved by the FDA Feb. 7. Together, Tivicay and Triumeq generated £3.86bn in worldwide revenues in 2018. As a sign of just how critical a franchise the dolutegravir brand has become to GSK, the company immediately filed a patent infringement suit against Gilead claiming bictegravir infringes its patents.

GSK has been readying for the eventual launch of an interchangeable generic Advair in the US for many years, since patent protection on the drug already expired. But a generic launch has been delayed by development and regulatory challenges given that the product is considered a complex generic, as Advair is an inhaled combination drug delivered through a device.

Two drug makers, including the apparent leader **Mylan NV**, received complete response letters from the FDA last year for their respective generics. Mylan has responded, however, and at the J.P. Morgan Healthcare conference in January management said it expects FDA action on the application later this year.

"It seems more likely now that the substitutable generic to Advair is launched in the US during 2018 given the filings that have been made," CFO Simon Dingemans said. Because the timeline, pricing and capacity for a generic all remain uncertain, GSK provided investors with 2018 forecasts both including and excluding a generic.

Even if a generic doesn't launch, sales of Advair in the US are expected to decline 20%-25% in 2018 due to ongoing pricing pressure and new competition, Dingemans said. If an interchangeable generic does launch in the US in July, the hit will be much deeper. US Advair sales would decline by more than half, to around £750m from £1.6bn in 2017, the company estimated. Last year, management presented investors with a similar forecast, but said a generic could reduce sales by £1bn.

"If exchange rates remain at the average January rates for the rest of the year, we'd expect a headwind of around 4% to sales and around 6% to EPS," Dingemans added. Nonetheless, he said GSK is increasingly confident that it will deliver on its longer-term financial outlook of mid- to high-single digit earnings per share growth over the five-year period through 2020.

TAX REFORM AND NEW GROWTH DRIVERS

The urgency has diminished somewhat, as GSK has reduced its reliance on Advair to drive growth. Advair generated £5.72bn worldwide in 2013, but only £3.13bn in 2017 as it has come under pressure from generics in Europe and price pressure and brand competition in the US.

Strong growth from new products and benefits from US corporate tax reform will help GSK reach its 2020 goal. GSK said it expects to benefit from US tax reform because its effective tax rate will drop by two to three percentage points to around 19% to 20%.

"The other important point is we think the tax rate is going to be stable where previously we expected it to be rising," Dingemans said. "That creates a bit more oxygen in the system we can use to drop to the bottom line or reinvest in in the business." He said some of the benefit will be directed toward meeting the 2020 EPS goal while some may be reinvested in R&D.

Growth from the company's newer respiratory brands was also notable this year. Breo sales grew 62% to £1bn, Anoro sales grew 70% to £342m, Nucala sales more than doubled to £344m. Nucala, an interleukin-5 inhibitor, was approved by the FDA in late 2015 for severe eosinophilic asthma.

"Nucala is expected to become one of the largest contributors to our respiratory portfolio by 2020," President-Global Pharmaceuticals Luke Miels said. In December, the FDA approved a new indication for treatment of adults with eosinophilic granulomatosis with polyangiitis (EGPA). EGPA is a rare disease of widespread inflammation in the walls of small blood vessels which can lead to tissue and organ damage. A supplemental application for treatment of chronic obstructive pulmonary disease is pending at the FDA.

GSK also has big expectations for Trelegy, but the triple combination (ICS/LAMA/LABA) was only approved by the FDA in September. Sales were negligible in 2017.

One uncertainty is whether or not GSK will make a move to increase its consumer health business. **Pfizer Inc.** is exploring strategic alternatives for its consumer health business, including a potential sale, and the company was taking final bids Feb. 1.

Walmsley has said GSK will take a look at Pfizer's business, but that her top priority will be pharmaceutical R&D.

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Three Strikes For Generic Advair With An FDA CRL For Sandoz: **http://bit.ly/2nVOMPI**

Bad News Teva Really Doesn't Need: A Potential Delay For Fremanezumab

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Investors in **Teva Pharmaceutical Industries Ltd.** don't have much reason for optimism, and now news that an important new drug, fremanezumab for migraine, could be delayed at the US FDA because of a manufacturing issue casts a dark cloud over one of the only bright spots.

Teva reported in its fourth quarter and full year 2017 earnings release Feb. 8 that fremanezumab could be delayed at the FDA because of a manufacturing issue at its third-party manufacturer **Celltrion Inc.** The South Korean biologics manufacturer is the sole source for active pharmaceutical ingredient (API) production for fremanezumab, which is one of three CGRP inhibitors pending at the FDA for migraine. A delay would be good news for rivals **Amgen Inc./Novartis AG** and **Eli Lilly & Co.**, which have their own CGRP drugs pending at the FDA.

Teva warned investors that remediation by Celltrion could delay the approval of fremanezumab, but said it is in active dialogue with the agency to see if it can maintain its priority review date. Teva used a priority review voucher with the submission in October in an attempt to close the gap between Amgen/Novartis, which were the first to file in the class with *Aimovig* (erenumab).

Amgen/Novartis have an FDA action date of May 17 for erenumab and the user fee date for fremanezumab is a month later on June 16. The agency should make a decision on Lilly's galcanezumab by Oct. 24. In a competitive market like the CGRP category is poised to be, being first to market or a close follower can make an important difference in near- and long-term commercial success.

Teva sees a way forward toward approval, because the FDA warning letter relates to the fill/finish part of the manufacturing facility, not the API portion. Nonetheless, it is a single manufacturing facility.

"We need to see how we can reach an agreement on this with FDA and hopefully ensure that the inspection of the API manufacturing will go ahead, of course, all with the aim of keeping the PDUFA date for the product," CEO Kare Schultz said.

It's not at all clear Teva will be successful in the attempt. The Jan. 26 warning letter to Celltrion cited an extensive number of GMP violations with many of the problems stemming from relaxed contamination controls. *(Also see "FDA Warning Letter Calls Attention to Celltrion's 'Poor' Aseptic Practices" - Pink Sheet, 7 Feb, 2018.)*

Celltrion is the sole source for API manufacturing for fremanezumab, but Teva said it is working to get a second supplier on board and build its own capacity longer-term.

"The second supplier is not ready right now, so we really have to resolve this together with the FDA and Celltrion," Schultz said. "We are optimistic that we can do that."

BAD TIMING FOR TEVA

A delay would be yet another big setback for Teva at a time when almost every part of its business is under pressure and the company is in the midst of a massive restructuring, laying off 25% of its workforce. *(Also see "Schultz Swings The Cleaver At Teva, Cutting 25% Of The Workforce" - Scrip, 14 Dec, 2017.)*

The generics business is facing serious challenges due to ongoing pricing pressure in the US and the specialty business is being crushed by the launch of the first generic version of Copaxone 40 mg. Rival **Mylan NV**'s generic was approved by the FDA in October and launched immediately after. *(Also see "Surprise! Mylan's Copaxone Generic Sets Teva Up For A Struggle" - Scrip, 4 Oct, 2017.)* Copaxone sales have taken a big hit as a result. US sales declined 25% to $622m in the fourth quarter and global sales declined 19% to $821m.

Generic medicines revenues declined 16% in the fourth quarter to $3.1bn, with US pricing pressure playing a big role. US generic medicines revenues decreased 15% to $1.2bn versus the prior-year quarter due to the persistent market dynamics. The company said the US generics environment further deteriorated in the fourth quarter, and the company said it would take a $17.1bn impairment charge related to US generics. Teva's new CEO has talked about raising the price of some generics in the US or discontinuing them altogether if they are unprofitable. *(Also see "J.P. Morgan Notebook Day 1: Tax Reform At Last, Allergan's Job Cuts, Teva Turnaround, Biogen's Cash, And Getting FDA-Friendly" - Scrip, 9 Jan, 2018.)*

Schultz updated investors on the restructuring program, noting that half of the 14,000-person workforce reductions will be completed by the end of the second quarter with the remaining to occur throughout 2018 and into 2019.

"We have had six announced closures of plants since we announced the restructuring plan, and we are expecting to announce another six plants by year end," Schultz said.

Teva reported revenues of $22.4bn in 2017, an increase of 2% over 2016, but the company reported a net loss of $16.3bn. Teva's stock has made some gains in the early days of Schultz's leadership, but the stock fell 10% on the New York Stock Exchange Feb. 8 to close the day at $18.64.

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Gilead's Yescarta Slowly Getting Off The Ground

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Gilead Sciences Inc.'s measured launch of the chimeric antigen receptor T-cell (CAR-T) therapy *Yescarta* is proceeding as expected, with 28 cancer centers in the US now ready to provide the treatment and $7m in sales for the fourth quarter.

Jefferies analyst Michael Yee said in a same-day note that Yescarta sales were higher than expected, considering they reflected only about one month on the market.

Yescarta (axicabtagene ciloleucel) was approved by the FDA in October for relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. European approval is expected in the first half of this year.

The product will one day need to earn its keep, as Gilead picked up the asset at high cost via its acquisition **Kite Pharma Inc.** for $11.9bn, or $180 per share, in August 2017.

In its Feb. 6 fourth quarter and full year 2017 earnings report, Gilead reported $7m in sales for Yescarta. Sales were included in the company's "other product" sales category, along with *Letairis* (ambrisentan), *Ranexa* (ranolazine) and *AmBisome* (amphotericin B for liposome injection). This category brought in $624m for the fourth quarter of 2017 compared to $621m for the same period in 2016.

As of the end of January, 28 cancer centers in the US were authorized to provide the treatment. By mid-2018, the company aims to reach institutions responsible for treating 80% of the 7,500 eligible patients.

Through the *Kite Konnect* program, the company is aiming to help patients and providers with enrollment, reimbursement and logistics.

Access and reimbursement are consistent with prelaunch expectations for new therapies in the in-patient hospital setting, the company reported.

As centers get better with handling patients and payment, it gets easier to bring in new patients in for treatment – momentum is slowly growing at each center as it gets up and going, CEO John Milligan told the call.

The first-mover advantage in this indication is very important, Milligan said. There is a lot of paperwork involved in getting set up as a center to administer the complex autologous treatment, including getting up to speed with the Risk Evaluation and Mitigation Strategy (REMS) program mandated by the US FDA as a condition for approval.

This has to be duplicated for each individual agent coming to the market. "It is more difficult to get the attention of the centers once they have something that works very, very well, which we believe they have with Yescarta. That is an important thing to consider," Milligan said.

Gilead has previously guided for a controlled launch to ensure that centers are comfortable administering the therapy, so that patients may safety receive it.

In its third quarter earnings report, Gilead had reported that 16 cancer centers were completing training for safe use of the drug and that the company was working toward an ultimate goal of 70 to 90 qualified US cancer centers. *(Also see "Gilead Says 16 Cancer Centers Getting Ready To Administer Yescarta" - Scrip, 26 Oct, 2017.)*

"We do see a slowly growing momentum at each center as they get up and going. So obviously, the second half of this year will be better for enrolling patients than the first half," Milligan said.

Meanwhile, the company is looking to expand labeling into earlier lines of therapy, exploring combinations with other immuno-oncology (IO) agents and considering new collaborations and acquisitions to access technologies, including gene editing, that will take CAR-T to the next level. In December, the company announced the acquisition of **Cell Design Labs Inc.**, with a $175m upfront payment. Cell Design Labs has developed proprietary technology platforms for engineering CAR-T therapies.

Gilead is looking to develop cellular therapies that can achieve greater responses, lessen side effects and increase the number and type of malignancies that can be treated. The company is interested in moving from autologous to allogenic, meaning off the shelf, approaches and to lower the incidence of cytokine-release syndrome, a life-threatening adverse event, and neurotoxicity.

"We are going to spread out our bets a little bit investing in various different technologies. Because it is hard to predict which will have the breadth to be important and also the specificity and depth of response that is going to be important," Milligan said.

HCV SALES STILL IN FREEFALL

Gilead needs new blood to rejuvenate sales. The Foster City, Calif. company reported $5.8bn in product sales for the fourth quarter of 2017, down from $7.2bn from the year-ago period, and $25.7bn for 2017, down from $30.6bn in 2016. The negative change was caused largely by declining sales of its hepatitis C virus (HCV) franchise, but the drop in its antiviral business was partially offset by rising sales for its new HIV combination products including the tenofovir alafenamide (TAF) backbone.

Gilead reported a net loss of $3.9bn in the fourth quarter, or $2.96 loss per share, compared to net income of $3.1bn, or $2.34 per diluted share for the same period in 2016. That includes an estimated $5.5bn charge related to the enactment of US tax reform.

The company reported $1.5bn in HCV sales for the fourth quarter, down from $3.2bn during the same period in 2016.

HIV and hepatitis B virus product sales rose to $3.7bn in the quarter, up from $3.4bn in 2016. Sales were driven by continued uptake of TAF-based products, including *Genvoya* (elvitegravir/cobicistat/emtricitabine/TAF).

Jefferies' Yee viewed the quarter as in line with expectations, with no major surprises.

The company is guiding for $20bn to $21bn in product sales for 2018, which is "slightly below sell-side consensus" of $21.5bn, Yee noted.

For its HCV franchise, the company is guiding for sales of $3.5bn to $4bn in 2018.

New products in the HCV markets have been disruptive, but going forward, the company doesn't see any further new entrants causing further disruptions.

The number of new HCV patient starts will continue to decline, but more slowly than in the past and HCV market share vs. competitors will stabilize by the middle of the year.

"Given these changes, Gilead's HCV revenue should be a more predictable, albeit smaller, piece of our financial story," Miligan said.

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Gilead's Biktarvy Approval Heightens ViiV Competition

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Gilead Sciences Inc. has been waiting for its new daily fixed-dose combination therapy for HIV, now known as *Biktarvy*, to provide new ammunition in its battle for HIV market share against **ViiV Healthcare**. But the competition wasted no time striking back with a patent infringement suit.

The US FDA's Feb. 7 approval of Biktarvy (BIC/F/TAF) – consisting of the novel integrase inhibitor bictegravir, the second-generation nucleotide reverse transcriptase inhibitor TAF (tenofovir alafenamide) and the older nucleoside reverse transcriptase inhibitor emtricitabine – gives Gilead a direct competitor against ViiV's *Triumeq*, which consists of the integrase inhibitor dolutegravir, the reverse transcriptase inhibitor abacavir and the nucleoside analogue reverse transcriptase inhibitor lamivudine. It could also enable Gilead to win market share in patients currently taking *Tivicay* (dolutegravir) as part of a non-proprietary combo including Gilead doublets such as *Truvada* (emtricitabine/tenofovir disoproxil fumarate (TDF) or *Descovy* (emtricitabine/TAF).

Within roughly two hours of the announcement of Biktarvy's US approval, ViiV issued a news release stating that it had filed patent infringement litigation in the US and Canada against Gilead asserting that bictegravir infringes ViiV's patents for dolutegravir "and many other compounds that include dolutegravir's unique chemical scaffold." The complaint asserts that similarities between bictegravir and dolutegravir suggest that Gilead simply copied the ViiV drug.

On Gilead's fourth quarter and full year 2017 earnings call Feb. 6, Chief Scientific Officer Norbert Bischofberger highlighted the imminent approval of Biktarvy, noting that the combo demonstrated non-inferiority against established HIV regimens in both treatment-naïve patients and those virally suppressed on other regimens.

"BIC/F/TAF met its primary objective of non-inferiority at 48 weeks across all four [Phase III] studies and no participants failed BIC/F/TAF for treatment-emergent virological resistance," the exec said. "Additional clinical trials of BIC/F/TAF are ongoing, including a dedicated study in women as well as a study in adolescents living with HIV."

Bischofberger said the combo should enjoy multiple advantages compared to its competition, including the fact that no treatment resistance was observed over the four pivotal studies and that it offers a favorable bone and renal safety profile compared to Tivicay-containing regimens. He pointed out that roughly half of US HIV-infected patients are now over the age of 50, making these safety factors increasingly important.

Biktarvy is approved specifically to treat HIV-1-infected patients with no prior treatment history with antiretroviral therapy or as replacement treatment for infected patients who are virologically suppressed on a stable regimen taken for at least three months with no history of treatment failure or of substitutions associated with resistance to any of the product's three components. The approval carries a requirement for three post-marketing studies – one in treatment-experienced HIV patients between the ages of 2 and 18, one in treatment-naïve patients at least four weeks old and weighing between 4 kg and 12 kg, and one to assess safety and pharmacokinetics in neonates either HIV-infected or exposed to and at high risk for the virus.

The combination also is under review by the European Medicines Agency, with Gilead anticipating approval during the third quarter of 2018.

On ViiV-parent **GlaxoSmithKline PLC**'s quarterly earnings call Feb. 7, the firm reported that the Tivicay/Triumeq franchise generated £3.86bn (more than $5.3bn) in revenue during 2017, making HIV a key growth driver for GSK.

Asked about the potential for patients to switch over to Biktarvy, ViiV Chief Strategy Officer David Redfern noted that the Gilead regimen only demonstrated non-inferiority to Tivicay-containing regimens in its Phase III program, and in some cases the Tivicay regimens were numerically if not statistically significantly superior.

"I think HIV is an increasingly chronic disease," Redfern said. "Patients who are well tolerated, well controlled, typically now visit their physicians probably only once every six months or so. So [treatment is] relatively conservative. … When you look at the clinical data, we don't see any good medical reason why patients well controlled and well treated on dolutegravir today should switch to something else."

During Gilead's Feb. 6 earnings call, CEO John Milligan was asked if he anticipated ViiV lowering prices of Tivicay and/or Triumeq as a strategy for maintaining market share. "That has never happened in the field of HIV, but I don't know what even GSK are planning," he said. "That's all I can tell you."

Bischofberger said one factor that might spur rapid adoption of Biktarvy is how quickly new Gilead HIV combos comprising TAF – such as *Genvoya* (elvitegravir/emtricitabine/TAF) – were incorporated into US HIV treatment guidelines. While cautioning that Biktarvy would require its own adoption process, he noted "it used to take a long time many years ago, but in the case of Genvoya it took exactly two weeks [after FDA approval]. So it's not true anymore that it takes a long time for [a new therapy] to get on the guidelines."

In a Feb. 7 note issued before the approval, BMO Capital Markets analyst Ian Somaiya said Biktarvy likely would play a key role in protecting Gilead's roughly $14bn HIV franchise and help the business grow to a projected $16.6bn in sales in 2021. Biktarvy approval and success are crucial for Gilead, he pointed out, because the company's Truvada and *Atripla* (efavirenz/emtricitabine/TDF) lose US patent protection in 2021, followed by Descovy in 2022, and *Odefsey* (emtricitabine/rilpivirine/TAF) and *Complera* (emtricitabine/rilpivirine/TDF) in 2023.

GAINING MARKET SHARE

In the near-term, Biktarvy seems best positioned to siphon market share from patients who take Tivicay with Truvada or Descovy due to the convenience of a single-tablet regimen and the renal safety benefit Gilead claims for bictegravir. Such patients comprise an estimated 8% of the US HIV treatment market, Somaiya wrote, while Triumeq patients make up 8%-9% of the US patient base. Shifting patients over to Biktarvy from Gilead's own Genvoya offers another 11%-12% of the market to target, he added.

"Collectively, between 25% and 30% of the HIV market (based on weekly IMS scripts) could be immediately accessible to BIC/F/TAF," the analyst said.

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CONTINUED FROM COVER

2020. "Our success with these projects has shown our ability to successfully manage complex business challenges and make immediate positive impact for the company," he added.

Through its Bioverativ purchase, Sanofi has brought in-house a "readymade franchise in the ten-billion-dollar hemophilia market," Brandicourt highlighted. However, he added that Sanofi would use this acquisition as a platform for expansion in rare blood disorders.

Still, some market spectators have raised concerns over the cost of Sanofi's recent deal making. Bernstein analysts, in a Feb. 7 note, listed over paying for acquisitions to make up for loss of revenue to generic competitors as one of the main risks associated with Sanofi.

But during the Feb. 7 broadcast Brandicourt remained firm that the company has maintained financial discipline while conducting recent deals and he noted that Bioverativ would be immediately accretive to earnings.

Sanofi has already stated it is committed to retaining Ablynx's facilities in Belgium,

Sanofi Started 2018 With A Bang But What's Next?

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but the same might not be true for Bioverativ's setup in Boston, US.

Forms Of Externalization At Work

- **FY 2017 group sales:** €35.06bn
- **Q4 2017 group sales:** €8.69bn
- **FY 2017 pharma sales:** €29.95bn
- **Q4 2017 pharma sales:** €7.31bn
- **FY 2017 business net income:** €6.96bn
- **FY 2017 EPS:** €5.54
- **2018 guidance:** Sanofi expects 2018 Business EPS to grow between 2% and 5% at CER

"We do obviously want to preserve the effect of these organizations... but integration topics will be taken up later in the year," Sanofi's president of global R&D Elias Zerhouni said during the company's conference call. He noted that the company already has over 900 employees in Belgium.

Zerhouni added that Sanofi was focused on closing its January acquisitions. However, he said the company had "good expertise" in integrating acquired businesses. He pointed to Sanofi's Genzyme unit that it acquired in 2011 for around €16.2bn.

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Theravance Banks $100m As J&J Bets Big On IBD Drug

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Before even going into Phase II trials, **Theravance Biopharma Inc.** has bagged the biggest player in inflammatory bowel disease – **Johnson & Johnson** – as a partner for its pan-Janus kinase (JAK) inhibitor which the firm is already talking about as a transformational treatment for ulcerative colitis and Crohn's disease.

It is a big deal too, with Theravance getting an upfront payment of $100m from J&J's Janssen unit for TD-1473, the firm's orally-administered and intestinally-restricted JAK inhibitor. The agreement could be worth up to $1bn but a lot has to be done in the clinic before the healthcare giant decides to really get behind the compound and part with more cash.

> The agreement could be worth up to $1bn but a lot has to be done in the clinic before the healthcare giant decides to really get behind the compound and part with more cash

In the second half of 2018, Theravance plans to initiate a large, Phase IIb/III adaptive design induction and maintenance study in ulcerative colitis with TD-1473, as well as a Phase II trial in Crohn's. Following completion of the latter and the Phase IIb induction portion of the ulcerative colitis study, Janssen can then elect to enter into an exclusive license arrangement by paying another $200m.

On a conference call, Theravance CEO Rick Winningham stressed that while his company will be running the trials, the input of Janssen to those studies will be key. He said that the latter's expertise and experience in both ulcerative colitis and Crohn's disease, across a range of mechanisms of action, will be vital in shaping the development, regulatory and commercial path for TD-1473.

Winningham added that when the company released preclinical data on TD-1473, a number of companies in the immunology field spoke to him about the possibility of collaborating on future development of the therapy. However, over the course of the last 18-24 months, it emerged that Janssen saw most clearly the advantages of a localised medicine, where the dose can be upped without the safety liabilities that systemic therapies have.

Brett Haumann, Theravance's chief medical officer, said on the conference call that Janssen has already provided lots of input in terms of optimizing trial design and its collaboration accelerates the process much more than if Theravance was going it alone. He pointed out that Janssen has been a leader in IBD for many years with flagship brands such as the huge-selling tumor necrosis factor (TNF) alpha drug *Remicade* (infliximab), *Stelara* (ustekinumab) and more recently *Simponi* (golimumab) and as well as trial design, it has expertise in recruiting patients, having developed "unparalleled biomarker datasets that can inform patient stratification to optimize clinical response to TD-1473."

TD-1473's activity is restricted to the site of inflammation in the intestinal wall, which prevents the risk of systemic exposure and serious side effects in contrast to other oral JAK inhibitors under development for IBD, according to Haumann. Among the latter, which are potentially much closer to the market, are **Gilead Sciences Inc.** and **Galapagos NV**'s filgotinib, which is in Phase III for Crohn's and ulcerative colitis, and **AbbVie Inc.**'s upadacitinib which is in Phase II for those two indications – both of those are being developed for rheumatoid arthritis. *(Also see "AbbVie's New Generation JAK inhibitor Looks Good But CV Specter Looms" - Scrip, 12 Sep, 2017.)(Also see "Galapagos Eyes Rare European Biotech Heavyweight Title, Launches $338m Offering" - Scrip, 18 Apr, 2017.)*

If all goes well after Phase II, Janssen will lead subsequent development of TD-1473 in Crohn's, with Theravance doing the same in ulcerative colitis through completion of the Phase IIb/III program. If TD-1473 is commercialized, Theravance, which has the option to co-commercialize in the US, would be eligible to receive up to an additional $700m, plus double-digit tiered royalties on sales elsewhere – the two companies will share profits in the US and expenses related to a potential Phase III program, split 67% to Janssen and 33%.

As for Janssen, its head of IBD R&D, Scott Plevy, said in a statement that adding TD-1473 to the company's immunology portfolio means it may offer a first-in-class oral, local acting pan-JAK inhibitor with broad use across GI-related inflammatory disease. Last year, Janssen signed another potential $1bn IBD pact with peptide drug developer **Protagonist Therapeutics Inc.** for its oral IL-23 inhibitor for Crohn's disease. *(Also see "Janssen Enriches Crohn's Portfolio In Deal For Protagonist's Oral IL-23 Inhibitor" - Scrip, 30 May, 2017.)*

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Boost For European Biotech As €345m Fund Opens

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While clearly lagging behind their US counterparts, European biotechnology companies and medtech firms across all stages of development can still attract significant venture capital if they are innovative enough.

That is what Olivier Litzka of Edmond De Rothschild Investment Partners (EdRIP) told *Scrip* as the Paris-based finance house unveiled its fifth fund, raising €345m ($430m). BioDiscovery 5 has surpassed its initial target of €250m, making it the largest life science and medical device venture fund to be raised in Europe.

Some two-thirds of the fund will be allocated for biotech investments with the other third going to medtech. Geographically, 30% is earmarked for the US, "where we will have no problem" finding suitable companies, Litzka said, but the other 70% is for European firms in the US.

He said the exit environment in Europe, particularly the via initial public offering (IPO) market, "is much better than it was 10 years ago," citing the growth of the Euronext bourse which has developed into a hub covering Paris, Amsterdam and Brussels. Those cities will soon be joined by Dublin as the Euronext has acquired the Irish Stock Exchange.

Litzka stressed that "it is not the Nasdaq," but Europe can now boast a "public market machinery that contributes to potentially lucrative exits" worth upwards of €100m. Times have changed since the €80m BioDiscovery 2 fund in 2004-5 because back then, "venture, Europe and life science sounded like a toxic mix, we had to help investors overcome the fear that it was a black hole where you don't see anything for ten years."

The experience of that first fund as well as BioDiscovery 3 (€150m) and 4 (nearly €200m) where backers saw returns through regular exits has meant that 80% of investors in BioDiscovery 4 have chosen to reinvest in the new fund. "They see money actually coming back which is a good thing," Litzka said, telling *Scrip* that EdRIP's investors comprise mainly insurance and health insurance companies, plus pension funds – and Biodiscovery 5 has also attracted backers based in Asia.

With the new 10-year fund, the plan is to make 15-17 investments. Up to 10% of the fund can be invested per company. Litzka spoke of the need to build a balanced portfolio, with some quite early firms and some more advanced, even late-stage, companies. "It is important for a fund to have a balance between risk and reward but which also offers investors liquidity."

EdRIP

The BioDiscovery team are looking to invest big in biotechs

BioDiscovery 1, 2, 3 and 4 saw EdRIP invest in 57 life science companies and Litzka pointed to its strong exit track record with 16 trade sales including Alzheimer's disease-focused **Chase Pharmaceuticals Corp.**, which was acquired by **Allergan PLC** in November 2016 for $125m upfront plus potential milestones of up to $875m to Chase's shareholders. That same month also saw Allergan complete the purchase of **Tobira Therapeutics Inc.**, another EdRIP-backed company which is focused on non-alcoholic steatohepatitis (NASH), in a deal that could bring in $1.7bn to its former shareholders.

EdRIP, which is rumored to be close to announcing a split from parent company La Compagnie Financière Edmond de Rothschild Banque, has also seen 18 IPOs from its portfolio companies, including the diabetes groups **Poxel SA** and **Cellnovo Group**, the CAR-T firm **Cellectis SA** and the Alzheimer's specialist **Probiodrug AG**.

As for BioDiscovery 5, three investments have already been made. One is in France's **Erytech Pharma SA**, which is hoping to get approval in the not-too-distant future for *Graspa* (eryaspase), its investigational treatment for acute myeloid leukemia, and the other two are US companies – the fibrosis specialist **Complexa Inc.** and **LogicBio Therapeutics Inc.**, which is working on gene therapy for the treatment of rare diseases in infants.

When asked by *Scrip* which therapeutic areas EdRIP is interested in, Litzka highlighted areas where the firm has expertise and there is medical need, listing neurology, immunology, cancer, diabetes and infectious diseases. "If we see a new area that we think is convincing, we will go for it and find the right experts to work with."

He spoke about opportunities in the Benelux countries, Switzerland, Germany and France and as for the UK, it is still an area of interest and a big investment is being looked at there by EdRIP. "Whether there is Brexit or not doesn't change the quality of research there," Litzka added, but pricewise, levels have to be reasonable to merit investment.

He concluded by noting that on average every year globally, there are 15 privately backed biotechs and the same number of medtechs that exit after raising around €100m or more. "It's not more than 15 but the good thing is it is never less than 15 - independent of any cycle, recession or other factors."

Every year, big pharma, big biotechs and medtechs buy companies to replenish their pipeline, "that's what they have to do and we aim to be part of one or two or three of those deals."

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Quality UK Biotechs Will Dodge Post-Brexit VC Drought

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European biotechs have a new source of capital with Edmond De Rothschild Investment Partners announcing the closure of its €345m ($430m) BioDiscovery 5 fund. Beyond March 29, 2019, when the UK exits the European Union, UK biotechs will find access to much of this money restricted.

As with many other European life science-focused venture funds, the European Investment Fund – bankrolled by the EU's European Investment Bank – is a prominent limited partner in BioDiscovery 5 and this could pose a future challenge for UK biotechs. The new fund will allocate approximately 70% of its capital to EU-domiciled businesses which will mean that, post-Brexit, UK biotechs will only be eligible for the smaller non-EU portion and will find themselves competing in a shallower more competitive pool with biotechs from the US and elsewhere.

While no one likes to see a source of capital dry up, reduced access to EIF backed venture capital is not expected to be too much of a problem for the highest quality companies, according to Francesco de Rubertis, co-founder and partner at Medicxi.

"We don't see Brexit as being a problem for good companies. This is not a business of averages and so neither Brexit nor the EIF will have an impact on our investment strategy when it comes to UK companies. Fundraising is always competitive and so there may be some negative selection but high quality companies should not have a problem," he told *Scrip*. The European Investment Fund joined **Novartis** and Verily to create Medicxi's $300m Medicxi Growth 1 (MG1) fund that focuses on growth stage companies in European life sciences.

Similarly, Chris Hollowood, Chief Investment Officer and a Managing Partner of Syncona Investment Management Ltd, believes that while there may be a shake out, its impact will be fairly subdued. "We anticipate that there is likely to be some level of impact on classic 10 year style venture capital funds, who are the largest recipients of EIF activity. More broadly, however, we see the impact on the overall health of the life sciences and biotech ecosystem in the UK, which is healthy and growing, to be relatively limited," he told *Scrip*.

Syncona, which is structured as an evergreen, patient capital vehicle with a strong balance sheet, has been a major backer of UK biotech since its formation.

"The quality of the science base in this country is such that, for the best ideas, companies are already competing on a global stage for funding attention as they should be. Indeed, in our experience with our portfolio companies, over the past 5 years, we've seen a steady increase of US funders keen to invest in the space," noted Syncona's Hollowood. In that context, he doesn't see Brexit as a major consideration. "Investors, regardless of geography, will always be judging the quality of the company and the science as the primary consideration, and healthy competition will remain," he added.

Indeed, Steve Bates, chief executive of the UK BioIndustry Association and cheerleader-in-chief for the sector, is optimistic that UK biotechs will be able to weather the post-Brexit storm. "We don't believe that funds will dry up but we welcome the government's focus on strengthening the system. We have a good relationship with the treasury and British Business Bank and are working together to address potential challenges," he told *Scrip*.

In particular, BIA's Bates is reassured by changes announced in the UK government's Autumn budget which he believes will create new opportunities in the venture capital landscape in 2018. These include a doubling the annual allowance for people investing in knowledge-intensive companies through the Enterprise Investment Scheme (EIS) to £2m coupled with a doubling of the annual investment that knowledge-intensive companies can receive through the EIS and Venture Capital Trusts (VCT) to £10m. Both these changes will be effective as of April 2018 and already have State Aid clearance. "A key source of funding in 2018 will be the new funds available through the British Business Bank, whose funding was increased by £2.5bn, with much of this going towards a 'British Patient Capital' entity, launching in 2018. This entity will incubate an expanded VC Catalyst program that will invest on a commercial basis into UK venture and growth capital, alongside private investors. Importantly, fund managers operating in the UK can apply to the existing VC Catalyst program today," Bates added.

Indeed, the UK government's response to the Patient Capital Review reflected many of the calls that the BIA made in its submission, including opening up pension funds which could make a substantial difference to investment into the sector. "The Pensions Regulator will provide clarity around the ability of pension fund managers to invest in venture capital and innovative companies and the government will address barriers holding back Defined Contribution pension savers from investing in illiquid assets, such as private companies," he noted.

Hollowood also appreciates the efforts the UK government is making. "Clearly, ongoing support from government and a supportive regulatory and policy environment for the sector will always be important – and to this end we are observing and engaged in a very positive dialogue with the government. A priority in our view, which is already being considered, would be directing capital from the significant pension pool and deployment by the British Business Bank into the sector," he added.

For Hollowood, Brexit poses other challenges for UK biotech. "Of course there are wider issues which we consider in the context of Brexit – things like the attraction and retention of world class scientific talent to this country – but in terms of the day to day, our strategy of building globally competitive healthcare companies and supporting them deeply over the long term is unchanged."

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Small Study Offers Hope For PARP/PD-L1 Combos In Prostate Cancer

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SAN FRANCISCO – Phase II data for the combination of **AstraZeneca PLC**'s *Lynparza* (olaparib) with the company's PD-L1 inhibitor *Imfinzi* (durvalumab) in a small National Cancer Institute (NCI) study show potential for combinations of PARP and PD-1 or -L1 inhibitors in advanced prostate cancer.

Lynparza, which AstraZeneca has been developing in partnership with **Merck & Co. Inc.** since mid-2017, is approved for ovarian and breast cancer and Imfinzi is approved for bladder cancer. Data from the small NCI study of 17 patients treated with the combination of Lynparza with Imfinzi in metastatic castration resistant prostate cancer (mCRPC) were presented on Feb. 8 at the American Society of Clinical Oncology Genitourinary (ASCO GU) Cancers Symposium, held at the Moscone Convention Center in San Francisco.

Advances in prostate cancer were a big highlight of the meeting (*see article on page 13*), including Phase III data for newer androgen receptor inhibitors from **Pfizer Inc.**/**Astellas Pharma Inc.** and **Johnson & Johnson** in non-metastatic castration resistant disease – *Xtandi* (enzalutamide) and *Erleada* (apalutamide), respectively – but researchers also expressed optimism for new mechanisms, such as immunotherapy with checkpoint inhibitors.

Checkpoint inhibitors – including PD-1/PD-L1 and CTLA-4 – have proven effective in multiple tumor types, but have not been successful as monotherapies in prostate cancer, aside from tumors that have high microsatellite instability (MSI-high).

Bristol-Myers Squibb Co.'s CTLA-4 checkpoint inhibitor *Yervoy* (ipilimumab) has failed in two Phase III studies of metastatic CRPC – one in treatment-naïve patients and another in men who progressed after docetaxel chemotherapy.

Research suggests that 23% of advanced prostate cancer patients have DNA repair deficiencies, which has raised interest in PARP inhibitors for this tumor type, noted Fatima Karzai, director of the NCI's Prostate Cancer Clinic, when presenting results for Lynparza plus Imfinzi at the ASCO GU meeting. Her presentation focused on 17 patients in the study's prostate cancer cohort, but the ongoing trial also has enrolled individuals with triple negative breast, ovarian, colorectal and lung cancer.

The thinking is that increasing DNA damage through PARP inhibition will increase PD-L1 expression and complement the anti-tumor activity of immune checkpoint blockade – and logically, this is most effective in BRCA-mutated patients, explained Datamonitor analyst Zach McLellan.

Lynparza received breakthrough therapy status in January 2016 for treating advanced prostate cancer in patients with BRCA1/2 or ATM gene mutations who have received a prior taxane-based chemotherapy and at least one newer hormonal agent – J&J's *Zytiga* (abiraterone) or Astellas/Pfizer's Xtandi.

However, Karzai's Lynparza/Imfinzi presentation at the ASCO GU meeting covered the combination's efficacy in mCRPC regardless of DNA repair deficiencies. Of the 17 patients, 10 had at least a 40% decline in the level of prostate specific antigen (PSA), a marker of progression.

Seven of the patients for whom biopsy results were available had BRCA2 DNA damage repair mutations and these patients had more dramatic responses, ranging from a 50% to 99% decline in PSA.

The median progression-free survival in those with mutations was 16.1 months versus 4.8 months for those without mutations.

Activation of CD8-postiive and CD4-positive T-cells was associated with better response, Karzai reported.

"We are well aware that these results are very early on and are likely to change with time," the clinician acknowledged.

As for safety, Grade 2-4 side effects were generally expected; they included anemia, lymphopenia, diarrhea and nausea. However, several immune-related side effects also were reported, including two cases of sudden onset unilateral hearing loss, optic neuritis and arthritis.

The NCI is expanding the CRPC cohort to include up to 65 additional patients to obtain more data and to pursue additional correlative studies.

The Lynparza/Imfinzi study builds on previously reported data in unselected mCRPC patients. Given the novelty of the combination, these early outcomes are encouraging, but these are still preliminary results in a small subset of patients, Datamonitor's McLellan commented to *Scrip*.

"A larger trial will be needed to better determine the potential of PARP and PD-L1 combination. Further down the line, development outside patients with DNA repair deficiencies will be important for potential revenues," the analyst said.

Commenting on the single arm NCI data at the meeting, University of Washington specialist Bruce Montgomery said the response data were compelling, with limited toxicity, but that results from other studies are needed.

Phase III studies are ongoing for PARP inhibitors. The Phase III PROfound study tests Lynparza versus Zytiga or Xtandi. TRITON3 is testing **Clovis Oncology Inc.**'s *Rubraca* (rucaparib) versus Zytiga or Xtandi or docetaxel chemotherapy. The TALAPRO-2 trial tests Pfizer's investigational PARP inhibitor talazoparib with Zytiga or Xtandi.

Many trials are assessing checkpoint inhibitor/PARP combinations, including Bristol's PD-1 inhibitor *Opdivo* (nivolumab) with Rubraca and Pfizer/**Merck KGAA**'s PD-L1 inhibitor *Bavencio* (avelumab) with talazoparib.

Including new mechanisms – PARP and others – the CRPC market will become increasingly segmented, according to a Jan. 18 prostate cancer forecast report from Datamonitor.

Sales of key prostate cancer drugs totaled about $8.6bn across the US, Japan and five major EU markets (France, Germany, Italy, Spain and the UK) in 2017. The market is set to expand in value by 30% from 2017 to 2026, reaching a peak of $11.2bn, Datamonitor estimates. *(Also see "How The Prostate Cancer Market Will Look Over Next Decade" - Scrip, 30 Jan, 2018.)*

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J&J's Apalutamide, Astellas/Pfizer's Xtandi On Par For Non-Metastatic Prostate Cancer

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Astellas Pharma Inc./Pfizer Inc.'s *Xtandi* (enzalutamide) and **Johnson & Johnson**'s investigational apalutamide both demonstrated profound benefits over placebo in high-risk, non-metastatic castration resistant prostate cancer with similar results in Phase III trials, but both raised questions about safety.

Data from the PROSPER study of Xtandi and the SPARTAN study apalutamide, now dubbed *Erleada*, were presented on Feb. 8 at the American Society of Clinical Oncology Genitourinary Cancers (ASCO GU) symposium in San Francisco.

Both studies evaluated the drugs in non-metastatic castration resistant prostate cancer (nmCRPC) patients on hormonal therapy who have a rising level of prostate-specific antigen (PSA), but no other symptoms of progression.

ASCO said in a statement that the findings may be relevant to some 100,000 patients in the United States. Nothing is currently FDA approved for this nmCPRC.

The clinical community has expressed a lot of excitement about the prospect for having an effective treatment of these earlier-stage prostate cancer patients, Steven Benner, senior vice president and global therapeutic area head of oncology development at Astellas, told *Scrip* in an interview before the meeting.

"When the PSA is rising like this you know that the patients are on a path towards metastases and that has been a source of frustration, as there haven't been effective therapies that could be given in that setting. So we think these results are clinically very meaningful," Benner said.

Both studies measured metastasis-free survival (MFS), the time that passes until a cancer can be radiographically detected as having metastasized, or until death.

In addition to demonstrating a highly statistically significant improvement in time to development of metastases vs. placebo on top of background hormonal therapy, both drugs showed significant benefits on secondary endpoints, like median time to progression, as well as a trend for an overall survival benefit. Philip Kantoff, the discussant for both trials at the ASCO GU meeting, described the MFS efficacy data for both drugs as "very impressive" and a clear signal that the drugs "are very biologically active."

The studies haven't been compared directly, but the data presented at the meeting suggest that efficacy is similar and there is a "hint" of a difference in toxicity, said Kantoff, who chairs the department of medicine at Memorial-Sloan Kettering.

Flagging safety issues for each study, he questioned whether there was enough evidence of a clinical benefit for patients, particularly given that they are asymptomatic, so the safety bar is higher.

RASH, FALLS FRACTURES

J&J's SPARTAN study tested apalutamide against placebo on top of androgen deprivation therapy (ADT) in 1,207 men with non-metastatic CRPC at high risk of metastasis based on PSA tests.

Erleada is a new androgen receptor inhibitor that is being positioned as a successor to J&J's *Zytiga* (abiraterone), which had $2.5bn in sales for 2017. *(Also see "J&J Shows Grace Under Pressure From Biosimilars And Other Threats" - Scrip, 23 Jan, 2018.)*

The study was unblinded early based on a recommendation by the independent data monitoring committee in July 2017, and patients on placebo were permitted to cross over to treatment with apalutamide.

Apalutamide decreased the risk of metastasis and death by 72% compared with placebo and significantly prolonged median metastasis-free survival by two years (40.5 months for apalutamide vs. 16.2 months for placebo).

Data for overall survival – a secondary endpoint – were not mature but there was a trend toward a benefit, with a 30% reduction in risk of death for the apalutamide arm.

The treatment related dropout rate was 10.7% for apalutamide vs. 6.3% for placebo.

Kantoff expressed concern for data on three particular side effects – rash, falls and fractures. Overall and Grade 3/4 rates were as follows: Rash (23.8%/5.2% for apalutamide vs. 5.5%/0.3% for placebo; falls (15.6%/1.7% for apalutamide vs. 9%/0.8% for placebo) and fractures (11.7%/2.7% for apalutamide and 6.5%/0.8% for placebo).

Looking at Grade 3/4 rates and noting "twice as many falls" and "three times as many fractures," Kantoff said: "Yes, these are low frequency events but nonetheless they are important for patients."

There was a significant improvement on the secondary endpoint related to time to development of symptomatic progression in the SPARTAN study (a 55% reduced risk for the test drug arm), "which looks like a hint of some clinical benefit," but it's unclear what symptoms exactly are driving this result and whether in clinical practice the patients would have been treated with an alternative therapy before they occurred.

DEATHS POST-TREATMENT

Pfizer/Astellas' PROSPER study tested Xtandi vs placebo on top of ADT in 1,401 patients with nmCRPC. The ASCO GU presentation followed a positive topline release in September 2017. *(Also see "Pfizer Poised To PROSPER From Xtandi In Expanded Indication" - Scrip, 14 Sep, 2017.)*

Metastasis-free survival in the Xtandi/ADT arm was 36.6 months vs. 14.7 months for ADT/placebo, a highly significant result with a 0.29 hazard ratio, meaning a 71% reduction in the risk of progressing to metastases (p-value <0.0001).

The magnitude of the impact on MFS was really striking and exceeded the companies' expectations going into the study, Astellas' Benner said.

On the secondary endpoint of time to PSA progression, there was a 93% reduction in risk for the Xtandi arm vs. the control arm (37.2 months vs. 3.9 months, p-value of 0.0001).

Overall survival data are not mature yet but there was a trend toward an improvement for the Xtandi arm, with a 20% reduction in risk of death.

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Lilly's Basaglar, Crestor Generics Helped Hold Down Drug Spending Growth In 2017

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High-profile launches of generic and follow-on products helped stanch drug spending growth in several large categories in the past year, according to **Express Scripts Holding Co.**'s "2017 Drug Trend Report."

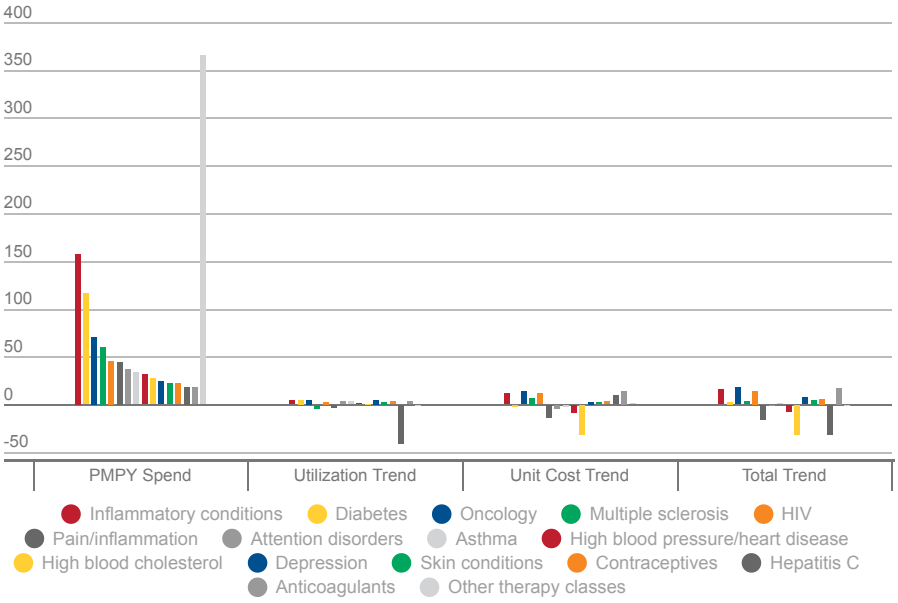
New insulin competition from the launch of **Eli Lilly & Co.'s** *Basaglar* (insulin glargine), a copy of **Sanofi**'s *Lantus*, helped keep commercial drug spending growth at 2.1% in the diabetes category, which is the second largest therapeutic class by drug spend, the pharmacy benefit manager (PBM) said.

Commercial plans' per member/per year spending in the cholesterol drug class – the tenth largest therapeutic category by drug spend – fell more than 30%, thanks to the entry of new generics, including copies of **AstraZeneca PLC**'s statin *Crestor* (rosuvastatin).

The generic launches, coupled with Express Scripts' utilization and management programs, helped hold the overall increase in per member spending at 1.5% for commercial plans, according to the PBM. This is less than half the 3.8% increase reported in 2016 and the lowest increase since Express Scripts began tracking drug spending data in 1993. *(Also see "Express Scripts Projects Higher Spending In Inflammation, Diabetes, Cancer" - Scrip, 6 Feb, 2017.)*

The report may be viewed as a ray of good news amid the rancorous debate in Washington over the cost of drugs and finger-pointing about which entity is most responsible for high prices – biopharma companies vs. insurers vs. PBMs. The findings also highlight the impact that first-time generics and follow-on biologic products potentially can have on market dynamics, even as the nascent US biosimilar market struggles to grab a foothold.

Express Scripts Drug Trend For 2017



Rank	Therapy Class	PMPY Spend	Utilization Trend	Unit Cost Trend	Total Trend
1	Inflammatory conditions	$157.49	3.9%	11.4%	15.3%
2	Diabetes	$116.23	4.2%	-2.0%	2.1%
3	Oncology	$70.66	4.3%	13.2%	17.4%
4	Multiple sclerosis	$60.20	-3.4%	6.4%	3.0%
5	HIV	$45.20	2.5%	11.1%	13.7%
6	Pain/inflammation	$44.06	-2.1%	-12.9%	-15.0%
7	Attention disorders	$36.12	2.9%	-3.2%	-0.3%
8	Asthma	$33.40	2.6%	-1.9%	0.7%
9	High blood pressure/heart disease	$31.41	0.6%	-7.6%	-7.1%
10	High blood cholesterol	$26.82	0.3%	-30.9%	-30.6%
11	Depression	$23.68	4.4%	2.4%	6.8%
12	Skin conditions	$21.80	2.2%	1.9%	4.2%
13	Contraceptives	$21.44	2.6%	2.9%	5.5%
14	Hepatitis C	$17.90	-40.4	9.2%	-31.2%
15	Anticoagulants	$17.67	3.0%	13.9%	16.9%
	Other therapy classes	$365.63	-0.9%	0.6%	-0.3%
	TOTAL	$1,089.75	0.7%	0.8%	1.5%

Express Scripts drug trend for 2017, ranked by 2017 per member/per year spend for commercial plans.

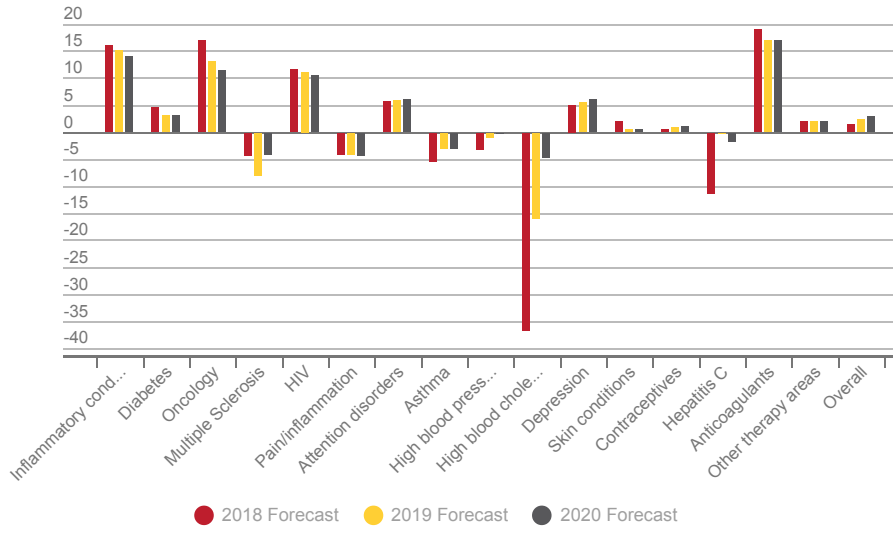
Source: Express Scripts 2017 Drug Trend Report

BASAGLAR COMPETITION

Drug spending trends for the top 15 therapy classes varied greatly in 2017: The cholesterol and hepatitis C categories declined by more than 30%, while inflammatory, oncology and anticoagulants increased more than 15%. Per member/per year spending in those categories still pales compared to "other," however. In several categories that saw either declines or relatively flat growth, Express Scripts credited the entry of new competition that helped drive down prices, as well as its own value and management solutions programs.

In the diabetes category, unit costs decreased by 2.0% due in part to pricing

Express Scripts Trend Forecast 2018-2020



Rank	Therapy Class	2018 Forecast	2019 Forecast	2020 Forecast
1	Inflammatory conditions	16.0%	15.0%	14.0%
2	Diabetes	4.5%	3.0%	3.0%
3	Oncology	17.0%	13.0%	11.3%
4	Multiple Sclerosis	-4.2%	-7.9%	-4.0%
5	HIV	11.5%	11.1%	10.4%
6	Pain/inflammation	-4.0%	-4.0%	-4.1%
7	Attention disorders	5.6%	5.9%	6.1%
8	Asthma	-5.3%	-2.8%	-2.8%
9	High blood pressure/heart disease	-3.1%	-0.9%	-0.1%
10	High blood cholesterol	-36.6%	-15.8%	-4.5%
11	Depression	5.0%	5.5%	6.0%
12	Skin conditions	2.0%	0.5%	0.4%
13	Contraceptives	0.4%	0.9%	1.0%
14	Hepatitis C	-11.1%	-0.1%	-1.6%
15	Anticoagulants	19.0%	17.0%	17.0%
	Other therapy areas	1.9%	2.0%	1.9%
	TOTAL	1.4%	2.4%	2.9%

Express Scripts trend forecast 2018-2020, ranked by 2017 per member/per year spend by commercial plans. Forecast numbers include impact of Express Scripts' utilization and management solutions programs.

Source: Express Scripts 2017 Drug Trend Report

pressure among insulins with the availability of Basaglar. The Lantus follow-on launched in late 2016 at a 15%-20% discount to the Sanofi product. Basaglar had a strong start, with Lilly reporting 2017 full-year revenues of $311.1m in the US. The company said the product is capturing about 25% of new patients in the basal insulin class. However, it's not clear how the market share gains are translating to the bottom line because Lilly has offered steep rebates to secure preferred formulary access over Lantus in some cases.

Express Scripts execs said the Basaglar launch provided leverage to reduce prices in the insulin category. Despite a 1.6% increase in insulin utilization, there was a 6% overall decline in insulin spending due to a 7.6% decrease in unit costs, the PBM told *Scrip*. Insulin accounts for 37.6% of all diabetes spending.

The diabetes category was "a much better story than in years past," said Glenn Stettin, senior vice president of clinical, research and new solutions at Express Scripts. For example, in 2016 diabetes drug spend rose 19.4%, with utilization and unit cost increases of 5.3% and 14.1%, respectively. Express Scripts expects the low growth rate trend in the diabetes category to continue and is forecasting drug spending growth in the low single digits for each of the next three years. (See chart.) The forecast trends take into account the expected impact of Express Scripts' management solutions programs on overall drug spend.

STEEP SPENDING DECLINE

The trends for the cholesterol category are also showing the effects of pricing competition.

Generic versions of rosuvastatin began launching in mid-2016 and helped contribute to a 7.4% decline in spending for traditional drugs used to treat high blood cholesterol during that year. However, therapeutic category declines were even more dramatic in 2017: with per member/per year spending falling 30.6% in the category, driven by an almost 31% drop in unit cost.

Express Scripts is predicting cholesterol category spend will drop 36.6% in 2018 and another 15.8% in 2019.

"With few new high blood cholesterol drugs in the pipeline, we expect downward unit cost trend to continue as market share shifts from brands to recently approved generics for Zetia (ezetimibe) and Vytorin (ezetimibe/simvastatin)," the report states. Express Scripts excluded both of **Merck & Co. Inc.** hypercholesterolemia drugs from its national preferred formulary in July.

MAKING A DIFFERENCE

Express Scripts credited its various utilization and management solutions programs, and value-based reimbursement arrangements, with helping to keep the lid on spending, particularly for specialty drugs, which accounted for 40.8% of total spending under the pharmacy benefit.

Spending on specialty drugs was up 11.3% in 2017, with increases in utilization and costs mitigated by plans participating in the Express Scripts' value program for inflammatory conditions.

In addition, "solutions such as Express Scripts SafeGuardRx help patients and payers obtain the full value of a medication and reduce the financial risk of treatment failures involving costly therapies," the company said.

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Eight Clinical Trial Read-Outs To Look Out For In Early 2018

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With input from Biomedtracker, *Scrip* highlights eight of the more interesting late-stage clinical trials due to read out in the next three months.

VTV'S AZELIRAGON

vTv Therapeutics Inc. is expected to announce data from the first part of the STEADFAST Phase III trial of its investigational Alzheimer's therapy azeliragon in patients with mild disease in late March. Azeliragon is an inhibitor of the receptor for advanced glycation end products (RAGE), which has been implicated in amyloid-β aggregation, tau fibril formation and chronic inflammation.

The study is being conducted under a Special Protocol Assessment (SPA) and was based on a post hoc subgroup analysis of a Phase IIb study conducted by former partner **Pfizer Inc.** Safety issues led to the study of a 20 mg/day dose being halted, but the analysis suggested that 18-month treatment with 5 mg/day of azeliragon added to an acetylcholinesterase inhibitor and/or memantine slowed the rate of cognitive decline in patients with mild AD.

Azeliragon has US FDA fast-track designation, but positive data from the initial Phase III read-out would be an "exceptional event given the long history of failed late-stage trials of AD drug candidates", said analysts from Biomedtracker.

Given the fact that Alzheimer's is a multifactorial disease, the company has previously said that it expected other candidates to be synergistic with azeliragon, if successful.

VBL'S OFRANERGENE

More gene therapy news is expected in the first quarter with top-line results due from GLOBE, a pivotal Phase III study of **Vascular Biogenics Ltd.**'s ofranergene obadenovec (VB-111) combined with bevacizumab in patients with recurrent glioblastoma multiforme (rGBM). VB-111 is a non-integrating, non-replicating, Adeno 5 vector engineered to express a pro-apoptotic Fas-chimera transgene in angiogenic blood vessels using VBL's proprietary angiogenesis-specific promoter.

In a non-randomized, open label Phase I/II study in patients with rGBM, the combination of VB-111 with bevacizumab following disease progression doubled median overall survival to 16 months compared with eight months for bevacizumab alone (p=0.05).

VB-111 has orphan drug designation for malignant glioma in the US and Europe and was granted fast-track designation by the FDA for rGBM based on the promising survival results. GLOBE is being conducted under an SPA and pending positive results, the company may be able to file for approval based on this single study given the high unmet medical need in rGBM, Biomedtracker believes. The product is also being developed in other solid tumors with a pivotal Phase III trial initiated in December 2017 evaluating VB-111 in combination with paclitaxel in ovarian cancer and an exploratory Phase I/II study in combination with a checkpoint inhibitor expected to initiate in non-small cell lung cancer in the first quarter of 2018.

Last November, **Vascular Biogenics Ltd.** licensed to **NanoCarrier Co. Ltd.** exclusive rights to develop and commercialize VB111 in Japan for all indications. The companies plan to explore future oncology partnerships with each other.

ESPERION'S BEMPEDOIC ACID

2018 will be a particularly important year for the development of **Esperion Therapeutics Inc.**'s bempedoic acid, with five different trials expected to report top-line data, Biomedtracker notes. The first Phase III data are expected in March from the 1002-048 trial, which is looking at a 180 mg/day dose as an add-on to ezetimibe therapy in patients with elevated LDL cholesterol (LDL-C). The 12-week data are expected to provide further clarity into bempedoic acid's ability to lower LDL-C, while also displaying its effectiveness as an add on to ezetimibe therapy in a larger dataset.

The oral small-molecule product is believed to work by inhibiting ATP citrate lyase (ACL), which is part of the cholesterol-synthesis pathway, a couple of steps upstream from the enzyme inhibited by statins. This leads to reduced cholesterol synthesis and upregulation of LDL receptor activity in the liver.

Bempedoic acid appeared to be safe and well-tolerated in Phase II. While there have been some liver function elevations, the company has said the rate is similar to what has been seen in studies of approved LDL-C lowering therapies, but the Phase III results will be important to confirm this.

In March 2017, Esperion said the FDA had said that the LDL-C lowering program was adequate to support approval of an LDL-C lowering indication for bempedoic acid, meaning that bempedoic acid could be approved without a cardiovascular outcome trial (CVOT). With top-line data from the CLEAR CVOT trial not expected until 2022, Esperion will wait to pursue an NDA for a cardiovascular disease risk reduction indication until the program is completed.

The company is also developing a fixed-dose combination of bempedoic acid and ezetimibe (generic *Zetia*).

Pending Phase III results, and the later CVOT data, Datamonitor Healthcare analysts forecast peak revenues of over $3.5bn for the drug, given the size of the dyslipidemia market.

ANTHERA SOLLPURA

Anthera Pharmaceuticals Inc. acquired *Sollpura* (liprotamase), a stable, porcine-free pancreatic enzyme replacement therapy (PERT) that consists of three pancreatic enzymes for the treatment of exocrine pancreatic insufficiency (EPI), from **Eli Lilly & Co.** in 2014 after the product was stalled by an FDA Complete Repsonse Letter in 2011 that requested an additional Phase III study.

EPI is characterized by low absorption of fat and other nutrients due to low levels of digestive enzymes produced by the pancreas. The condition is common in diseases such as cystic fibrosis, chronic pancreatitis and pancreatic cancer.

Anthera Pharmaceuticals has already conducted the Phase III SOLUTION non-inferiority study also comparing Sollpura to porcine PERT, but this narrowly missed its primary endpoint of non-inferiority to *Pancreaze* (a

porcine PERT) based on a co-efficient of fat absorption (CFA) measurement.

Its hopes now rest on positive data from the Phase III RESULT study to support a future marketing application. This is comparing Sollpura with *Pancreaze* in subjects with cystic fibrosis-related EPI. Top-line results are expected during the first quarter.

Anthera designed the study to address design flaws identified from SOLUTION. Notably, RESULT allows for more frequent and higher dose adjustments based upon clinical signs and symptoms and allows for dose titrations of Sollpura on an individualized basis to achieve maximum therapeutic benefit.

J&J'S ESKETAMINE

Excitement is building over new datasets from **Johnson & Johnson**'s Phase III program of intranasal esketamine for the treatment of treatment-resistant depression expected in early 2018. Esketamine is the S-enantiomer of ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist. Esketamine currently holds fast-track status as well as two breakthrough designations: for treatment-resistant depression and for major depressive disorder with imminent risk for suicide.

The product has already shown promising activity in the Phase II SYNAPSE study for treatment-resistant depression and the Phase II PeRSEVERe study for suicide-risk patients.

J&J is pursuing approval of treatment-resistant depression first, with depression for patients in imminent suicide risk afterwards. The Phase III program for the breakthrough designation for treatment-resistant depression consists of six trials: SUSTAIN-1, SUSTAIN-2, SUSTAIN-3, TRANSFORM-1, TRANSFORM-2, and TRANSFORM-3. The trials have enrolled over 2,000 patients and the first Phase III top-line results from these trials are due to start coming through shortly.

Assuming results are positive, in markets where the drug is expected to be approved, Datamonitor Healthcare forecasts 5% of major depressive disorder patients at second-line therapy or later, already receiving a SSRI or SNRI antidepressant, to augment with esketamine.

ARMO BIOSCIENCES' AM0010

The first signs of success for **Armo BioSciences Inc.**'s PD-1 booster product AM0010 are expected by the end of April. The company has just raised $50m in a Series C venture capital round as investors hope the company will be able to ride the second immuno-oncology wave with pegylated interleukins that are designed to augment the pioneering IO therapies such as the PD-1 inhibitors.

AM0010 is a PEGylated form of recombinant human interleukin-10 (IL-10) that elicits a cytotoxic T cell immune response towards tumor cells and has strong anti-inflammatory properties through the inhibition of TNF-alpha and IL-23.

AM0010 was licensed from Merck, and is being developed in numerous cancer indications, of which the lead is pancreatic cancer refractory to current immune therapies.

SEQUOIA is a pivotal Phase III study of AM0010 in combination with FOLFOX as second-line treatment in subjects with pancreatic cancer. The first interim analysis is due before the end of April 2018 and the second interim analysis, which could provide the basis for a US BLA submission, is expected to be conducted in 2020.

IMMUPHARMA'S LUPUZOR

ImmuPharma PLC hopes for top-line results from a pivotal 52-week Phase III trial of *Lupuzor* (rigerimod) in patients with SLE to be reported in the first quarter of 2018. The product, a polypeptide thought to act by modulating CD4+ signalling, has received US fast-track designation and its development is being conducted under an SPA.

As such, the number of patients (about 200) in the placebo-controlled Phase III trial of a 200 µg dose of rigerimod plus standard of care is lower than typical due to the Phase III pivotal trial having a similar design to the Phase IIb study, notes Biomedtracker, "so they believe they can again show relatively strong efficacy while also substantially lowering the cost of the study."

As Lupuzor is the company's only late-stage asset, positive trial results would mark an important milestone as well as positioning the drug for regulatory filing. "However, there were some issues with the Phase IIb trial and a number of drugs in SLE have failed despite promising Phase II data," the Biomedtracker analysts say.

Datamonitor Healthcare's forecast for Lupuzor is currently conservative, taking up to 7% patient share from **GlaxoSmithKline PLC**'s *Benlysta* (belimumab), **Roche /Biogen**'s *Rituxan* (rituximab); and **Bristol-Myers Squibb Co. /Ono Pharmaceutical Co. Ltd.**'s *Orencia* (abatacept) in moderate and severe patients without lupus nephritis, and up to 4% share from these drugs in moderate and severe patients with lupus nephritis.

ABBVIE/NEUROCRINE BIOSCIENCES' ELAGOLIX

Neurocrine Biosciences Inc. announced at the J.P. Morgan Healthcare Conference that data from two Phase III studies of elagolix in uterine fibroids are expected in the first quarter of 2018. Elagolix is being developed with **AbbVie Inc.** as an orally active, non-peptide gonadotropin-releasing hormone (GnRH) receptor inhibitor for the treatment of endometriosis and uterine fibroids and as an alternative to injected peptide GnRH receptor inhibitors such as AbbVie's *Lupron* (leuprolide) and **Allergan**'s *Trelstar* (triptorelin)

AbbVie is currently conducting two identical Phase III studies, M12-815 and M12-817, to evaluate elagolix in combination with estradiol/norethindrone acetate for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women, based on positive Phase IIb data form 567 patients. (The estradiol add-back is to prevent side effects such as hot flashes and bone mineral density loss.)

Elagolix has been granted priority review for the management of endometriosis with associated pain with a PDUFA date of May 4. AbbVie plans to submit a supplemental NDA for the treatment of uterine fibroids in 2019. *(Also see "10 First Approvals To Look Out For In 2018" - Scrip, 2 Feb, 2018.)*

AbbVie and Neurocrine are leading the competion with **Takeda Pharmaceutical Co. Ltd./Myovant Sciences Ltd.** to market the first oral gonadotropin-releasing hormone (GnRH) receptor antagonist.

Data from Myovant's two international pivotal clinical trials (LIBERTY 1 and LIBERTY 2) of relugolix in women with heavy menstrual bleeding associated with uterine fibroids are not due until 2019.

There are no FDA-approved drugs for long-term treatment of uterine fibroids, but Lupron was approved in 1990 for temporary (up to three months) preoperative use to reduce uterine fibroid-related blood loss and to correct the ensuing iron-deficiency anemia. Allergan's ulipristal acetate (*Ella*), an oral progesterone receptor modulator approved in Europe for the treatment of uterine fibroids, is currently in the NDA phase with an FDA approval decision expected in late March or May of 2018. *Published online 7 February 2018*

Workforce Roundtable Part 1: Recruiting Biopharma Leaders As The Talent Pool Shrinks And Diversifies

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The biopharmaceutical industry has been so good at forming new companies that it's created a looming leadership challenge: as today's CEOs and board members near retirement age, there aren't enough experienced executives behind them to fill all of the soon-to-be empty seats.

Baby boomers will be between the ages of 60 to 78 in 2024, according to the Bureau of Labor Statistics, but as they flood into retirement, Generation X and millennials will only trickle into the workforce, because growth in the labor force is slowing. Companies will have to wade into a smaller, more diverse labor pool and figure out how to recruit, train and retain the next generation of biopharma talent, which will include more women and people of color than ever before.

Scrip spoke with Sabrina Johnson, CEO of Daré Bioscience Inc.; Mike Grey, executive chairman of the Amplyx Pharmaceuticals Inc. board of directors and a venture partner at Pappas Ventures; Robin Toft, president and CEO of the life science executive recruiting Toft Group; and Rowan Chapman, head of the Johnson & Johnson Innovation Center in California, in a roundtable interview about the challenges and opportunities ahead in recruiting new talent now and in the future. It took place in January during the J.P. Morgan Healthcare Conference in San Francisco

SCRIP: *What are the biggest challenges that you see right now in terms of recruiting and nurturing and bringing up new leadership as we get to the point where some folks might like to retire and hand over the reins?*

SABRINA JOHNSON: We're a women's health-focused company, and we purposely decided that we wanted to make sure we had a lot of women on our team, so [we have] diversity from that perspective. And on our board, we're publicly traded and wanted a majority female board.

We've seen it's not so much a challenge in finding really talented women – we've been able to very easily find very talented women, and I'm very committed to mentoring talented women. But it's more [about] being flexible around how we think about work hours and time and how we structure it.

We've ended up leveraging, for some women who want the ability to be with their families and young children, real flexibility in terms of their hours and schedules and whether we dictate that they need to be full-time employee versus a consultant.

We've got some millennials on our team, and I know it's kind of a cliché, but they like to work out, go surf when they want to go surf, and come to work when they want to work, and we've allowed them the flexibility so that we can attract that talent.

MIKE GREY: *Will you hire me? I want to go surfing.*

JOHNSON: One of the people we really were attracted to was a woman at a great company, and we really wanted to attract her to our start-up. Part of that was to say, "Hey, you don't have to be here at 8 a.m. You can go do the morning surf and get here at 10, as long as you get the work done."

I think it's [about] finding a way to make it an attractive workplace. The talent is out there.

GREY: I think it's hard to find. I primarily work in start-ups, and you think about three components of a start-up: technology or the science, the money and the people. The money is the easiest, technology is the next easiest, and the people is the hardest. You could have the most thorough recruitment process and in my opinion it's about a 50-50 success rate in really getting the people that fit. And the tragedy is, you can spend hours and hours doing it, and you know in the first week whether you made the right decision or not.

I think finding those people is really hard and the only way we've been able to do it successfully is working with people we know. And the challenge of that is, it potentially confines the gene pool, as it were, but we've had success in putting great teams together.

And picking up on some of Sabrina's points as well, Lumena, which we sold three years ago to Shire, had 17 people; 12 women, five men. It wasn't by design. All the other companies have been pretty

Roundtable Panel

Sabrina Johnson is CEO of **Dare Bioscience Inc.**, a biotechnology firm dedicated to women's reproductive health that became a public company in a 2017 reverse merger with Cerulean Pharma Inc. Johnson, a first-time CEO, previously was president of **WomanCare Global Trading**, a specialty pharmaceutical company, and before that was chief operating officer and chief financial officer at Cypress Bioscience Inc.

Mike Grey, executive chairman of **Amplyx Pharmaceuticals Inc.**, is a member of several other biopharma boards of directors and a venture partner at Pappas Ventures. He is an advocate and mentor for young CEOs. Grey previously was president and CEO of **Lumena Pharmaceuticals Inc.** until its acquisition by **Shire PLC** in 2014. Before that, he was president and CEO at **Auspex Pharmaceuticals Inc.**, **SGX Pharmaceuticals Inc.** and **Trega Biosciences Inc.** He also spent 20 years with **Glaxo Inc.** and **Glaxo Holdings PLC**.

Robin Toft is president and CEO of **Toft Group**, an executive recruiter for the life science industry with a reputation for recruiting women and minorities into key roles, and helping hiring executives overcome unconscious bias. Toft previously was managing director at the life science executive recruiting firm Sanford Rose Associates.

Rowan Chapman, head of the **Johnson & Johnson** Innovation Center in California, leads the team that manages and builds the big pharma's portfolio of co-investments with biopharma, medical device and consumer health firms across the state. Chapman also spearheads the division's diversity efforts. She previously was head of health care investing at GE Ventures, head of precision diagnostics at GE Healthcare, and a partner at Mohr Davidow Ventures.

much 50-50, I suppose, and not just 50% as the lower level employees. It's across the board.

The biggest thing was that flexibility, because the world isn't fair and typically women have more responsibilities outside the workplace than men, and [you have to be] flexible to accommodate those. Surfing was not the problem, but picking up the kids from school or dropping them off at school, and being flexible around that. So people go home at 3:30 and then get back online at 8:30 or nine or whatever.

That flexibility was really good, and having that environment, it was by far and away the most efficient company I've ever been associated with. It achieved incredible things, and it was so successful, because it was so collaborative and rather competitive, and people did what needed to be done, and that was important to make it a success.

JOHNSON: I think that culture kind of fosters that. When you have that flexibility, I honestly feel like people feel more committed and more dedicated.

ROBIN TOFT: They will walk across water for you if you just give them flexibility in their day, right? It's the number one thing I talk to CEOs about as a search professional, and nobody wants to give it to them.

GREY: It's probably because it establishes trust. We're not going to say you have to be here from nine to five or eight to five or whatever, but here's your task. I trust you to go and do your job, however you think best to do it.

TOFT: Yes, performance-based goals. I think a lot of managers don't know how to lead with performance-based goals. You hit your goals; that's all I care about. I don't want to watch where you are. I'm not going to count cars in the parking lot. I don't care – just get it done, and let me know if you're having trouble. I think that sort of leadership is rare, actually.

GREY: So, that's a lot easier in a 17-person company than it is in 117,000-person company or whatever J&J is. [*Chapman noted J&J is about 130,000.*]

ROWAN CHAPMAN: When I think about this, I think about it in three different aspects, which connect to what you're saying. I think the workplace of the future is around being diverse, being porous, and [defining your] culture. Everything you were just talking about is culture – are you setting the right culture? It's different for different companies. I'm not going to argue one culture is the right thing for one company or another, they're just different, as long as there is a culture and people connect to that culture.

> 'You want them to hire people from big companies to calm them down a bit. And in a big company, you actually want some of those crazy entrepreneurs, or you can become very complacent'

J&J, for example, has a very strong culture. It's a creative-based culture and whoever you meet, you can connect in that way, even if they're a completely different person. A start-up might have a different culture. I personally have been in academia, I've been in start-ups, I've been in venture capital, I've been in a bigger company than J&J. And within different companies, different pockets of the company have different cultures.

But the two areas which I am becoming fascinated by are these concepts of diversity and porosity. So diversity, maybe you think about it as a women's thing. I don't really think about it as a women's thing. I just want to make sure that there's a different set of perspectives at the table, whoever those perspectives come from.

We can certainly talk about diversity at great length, but porosity is something that's new. And by porosity, I mean people working in big companies or small companies, because when I was growing up in my career you were either a start-up person or a big company person. And on the venture capital side, there'd be almost an arrogant, "Oh, these big company people, they don't know how to be in a start-up, because they're so in their box, they can't do it." And you talk to the big company people, "Oh, those start-up people. You know, we're just not a cultural mix."

I think the most interesting is when you get people who have different experiences in their careers [together]. And when we're trying to, at J&J, partner with start-ups, you want that drive [that start-ups have], but you also want to make sure that they're actually doing the right thing from the development standpoint in a way that, if they get acquired by a large company, the whole thing doesn't have to be repeated. You want them to hire people from big companies to calm them down a bit. And in a big company, you actually want some of those crazy entrepreneurs, or you can become very complacent. I think that part is opening up.

JOHNSON: That is true. It is really helpful to have [both perspectives]. I think of our team – built at Cypress Bioscience for about 13 years, and at Daré building that team – in both circumstances they very much looked for people that had both sets of experiences, had been on both sides of the table.

I had a great mentor, Jay Kranzler at Cypress, who helped and championed me, pulled me up, but also had very strong views about certain things that I carried with me. One was about diversity of perspective and he wanted everyone to be smarter than him.

GREY: Well, it's tough to be smarter than Jay, actually.

JOHNSON: Yeah, I know, but [smarter] in their own functional areas. It definitely helps to have the perspective of people who have been at the big companies and the smaller companies, particularly if you're in a mode where you have to partner, and know what the big pharma is going to want or appreciate in your program.

SCRIP: *Since you tried to hire from both of those perspectives, do you find it is really hard to pull the big pharma person in? It seems like right now there's an interest in pharma people moving over to biotech and start-ups.*

JOHNSON: There is. I think people get to a kind of point in their career where they want something different or sometimes those cultures in the large organizations aren't as flexible. They struggle sometimes with the flexibility. So sometimes it's not like I don't want to be in a

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big company, it's just that, "Gosh, I need a job where I can do X, Y and Z, and I can't do it there." Or it's, "I'm ready to do something different, or have a bigger role." Someone might say, "I'm in a very siloed role in a big organization, and I want a little more breadth."

GREY: I think the biggest challenges is – I spent 20 years in Glaxo and then 20-plus in small organizations – and I think that diversity of experience is right. In important key positions, then we do want people who have had that big company experience, because you don't really need to do it quickly, you need to do it right. But the advantage that small companies have is speed of decision-making. They don't need three committees to decide to change protocol or whatever happens in the regulation of larger companies. We can make that decision the same day. But it still has to be the right decision, and it still has to be executed correctly. The challenge is that you want to hire senior people, and senior people in big companies don't usually do things. They tell other people to do things. And that's the biggest challenge, because you need to have doers. In a small company, in a 10, 15, 20, 25-person one, everybody "does." They don't just "tell."

TOFT: It is my experience that most large pharma company people would jump at the chance to work for a start-up, but most of them are unproven in start-ups, so they have a very hard time even interviewing. Everyone wants big company/small company people. And if you're a big company-only person, they say, "They're unproven in a start-up." And we say, "That is true, but we believe they're going to fit in." So, for instance, they're a Rowan person that we think, maybe they can do this. They're very frustrated; they're not getting to be able to do what they need to do. So, it's a lot of convincing someone to entertain someone for the first time in a start-up. Someone has got to test pilot them. But usually there are some people that can do both, go back and forth.

CHAPMAN: I've hired people from start-ups and from big companies into both different environments. In big companies, I've hired people from start-ups, and at start-ups I've hired people from big companies. And I think there's a big difference in the way people are compensated and measured in big companies and small companies. And I know that's one of the big challenges in trying to do that crossover.

TOFT: It's very differential. So when you want to make that move from a big company to a start-up, you have to be okay with risk, because they're going to ask you to trade cash for equity. One, they have to be able to wear all the hats and work hands-on and be willing to do so. Then, two, they have to be risk-tolerant. That's important, because now we're going to trade the way that you get paid – and all this money left on the table, you're going to have to trade that for something else, the upside in this company.

Published online 8 February 2018

Workforce Roundtable Part 2: Creating A 'Sticky' Workplace, Boardroom Roles For Women, Millennials **http://bit.ly/2svnuo2**

How Buffett And Friends Can Succeed, And How Pharma Would Be Affected

VIREN MEHTA

"Prices Will Come Down Substantially. Watch." This is the president of the US talking about drug prices during his State of the Union Message to the US Congress!

The New Year is already full of intrigue, and we're only a few weeks into 2018. The last week of January in particular threw a 1-2-3 punch at the industry:

- The new US Secretary for Health and Human Services (HHS) Alex Azar was sworn in. On the surface it may sound like good news to have one of industry's own to guard the hen-house. But his confirmation hearings repeatedly pushed him to confirm that lowering unreasonable drug prices will be his top priority, echoing the language the FDA Commissioner Scott Gottlieb has now practiced consistently. More noteworthy are the comments by President Trump at Azar's swearing-in that the HHS secretary will get the US drug prices "way down…because it is very unfair to our country."
- Trump doubled down at his State of the Union speech that "the drug prices will come down substantially. Watch."
- As if on cue, JPMorgan Chase & Co, Amazon, and Berkshire Hathaway announced that they are going to do something to disrupt healthcare, (let us call this consortium 'JAB', as our healthcare systems around the world really do need a jab in the jaw if a new path is to be paved.)

Many pundits rushed to pronounce JAB the patent treatment to cure all that ails the healthcare systems. "Disruption is finally here" has been the common refrain.

Could new partnership finally signal a gear shift in US healthcare machinery?

Shutterstock: BigTunaOnline

RESHAPING HEALTHCARE?

As the dust settled, however, experienced experts pushed back on this notion, listing more than a handful of initiatives by major corporations over the past couple of decades, all to break the cycle of healthcare cost spiral, but with little or no success.

The commentary around the JAB announcement centered on how Amazon may have found the creative path to begin to reshape the healthcare system. Bringing the likes of Warren Buffett of Berkshire Hathaway and entrenched financiers of JPMorgan along should only bolster its resources to tackle a challenge that others have failed at.

The incumbent leaders of the current healthcare establishment (which includes the comparatively well-resourced biopharma sector) are concerned of course, but seem inured to this relentless restlessness among practically all of their stakeholders.

And the fact is that any effective control of drug costs has remained elusive, and the options for the very vocal government leaders seem limited – so far. Yes, the FDA can speed up generic approvals, and somehow improve its maze of regulations that enable the biopharma companies to game the competitive landscape, and thereby pricing. Secretary Azar has more levers at his disposal, but the present Washington climate precludes many of the most potent initiatives, including granting CMS powers to negotiate drug prices. Perhaps this government has a secret plan that can revamp the system, but for now it remains mostly talk, and hence unexciting.

The excitement around the JAB consortium announcement is anchored around its ability to bypass various regulatory constraints that limit government officials' capacity to act. The JAB should be able go after the way PBMs seem able to skim at both ends of the value chain, and circumvent insurance companies' profit motives that put them in cahoots with PBMs and others trying to take advantage of the regulatory veil.

The combined employee size of the three JAB companies is small at around one million, but not so small that their technological prowess and global scale could not become an impactful test case. They are sure to have studied their predecessors' lack of material success, and must be planning to deploy better tools and incentives for their employees, harnessing the increasingly powerful IT bandwidth of today to lead to much more rational healthcare choices.

Yet this is likely to take longer and yield meager results, unless the JAB initiative finds a way to break away from the present healthcare system, which can be best described as a mound of Band-aids.

The idea is simple, though obviously it calls for radical steps. Put the patient truly in the center, with a holistic online tool that enables her to invite all who care for her, from providers on the one hand, to a personal network of family, friends, and other patients on the other; and enable this small team to see the patient data, and communicate real time. This tool enables the right member of this team to respond to patient needs and should provide motivation, education and better outcomes. The patient has a team/network of providers who can practice medicine as good doctors were trained to do.

I am talking about the creation of a parallel health care offering. Start with self-insurance by employers, to remove the self-

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Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.

Click here for the entire pipeline with added commentary: http://bit.ly/2mx4jY3

Selected clinical trial developments for the week 2–8 February 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
H. Lundbeck AS/Otsuka Holdings Co. Ltd.	*Rexulti* (brexpiprazole)	schizophrenia	ZENITH; *International Journal of Neuropsychopharmacology*, Feb. 3, 2018.
Phase III Interim/Top-line Results			
Astellas Pharma Inc.	peficitinib, oral JAK inhibitor	rheumatoid arthritis	RAJ3, RAJ4; met primary endpoints.
Allergan PLC	ubrogepant, oral CGRP inhibitor	acute migraine	ACHIEVE I; met co-primary endpoints.
Johnson & Johnson	apalutamide	prostate cancer, non-metastatic	SPARTAN; improved metastasis-free survival.
Bavarian Nordic AS	Imvamune vaccine	smallpox	Achieved both primary endpoints.
Shield Therapeutics PLC	*Feraccru* (ferric maltol)	iron-deficiency anemia in chronic kidney disease	AEGIS-CKD; missed primary endpoint.
AstraZeneca PLC	*Farxiga* (dapagliflozin)	diabetes, type 2 and renal impairment	DERIVE; improved glycemic control.
Celgene Corp.	*Pomalyst* (pomalidomide) plus bortezomib, low-dose dexamethasone	multiple myeloma, relapsed/refractory	OPTIMISMM; improved PFS primary endpoint.
JCR Pharmaceuticals Co. Ltd.	agalsidase beta, biosimilar (JR-051)	Fabry's disease	Pharmacodynamics similar to original.
Bristol-Myers Squibb Co.	*Opdivo* (nivolumab) with ipilimumab	non-small cell lung cancer, first-line	CheckMate 227; met PFS primary endpoint in high tumor burden.
Spectrum Pharmaceuticals Inc./ Hanmi Pharmaceutical Co. Ltd.	*Rolontis* (eflapegrastim)	chemotherapy-induced neutropenia	ADVANCE; met primary endpoint, non-inferior to pegfilgrastim.
YL Biologics (Lupin Ltd. and Yoshindo)	etanercept, biosimilar (YLB113)	rheumatoid arthritis	Efficacy and safety similar to *Enbrel*.
Updated Phase III Results			
Astellas Pharma Inc./Pfizer Inc.	*Xtandi* (enzalutamide) plus androgen deprivation therapy	prostate cancer, non-metastatic	PROSPER; improved survival.
Roche	*Tecentriq* (atezolizumab) plus bevacizumab	advanced renal cell cancer, first-line	IMmotion151; improved PFS versus sunitinib.
Array BioPharma Inc./ Pierre Fabre Group	encorafenib plus binimetinib	melanoma, BRAF-mutant	COLUMBUS; overall survival improved versus vemurafenib.
pSivida Corp.	*Durasert* (fluocinolone acetonide) three-year insert	posterior segment uveitis	Prevented recurrence at 12 months.
Phase III Initiated			
ViiV Healthcare	*Tivicay* (dolutegravir) and *Epivir* (lamivudine)	HIV-1	TANGO; switch to two-drug regimen.
Endo International PLC	*Xiaflex* (collagenase clostridium histolyticum)	cellulite	RELEASE; by local injection.
Pharma Two B Ltd.	P2B001 (low-dose pramipexole plus rasagiline)	Parkinson's disease	Early-stage disease.
Phase III Announced			
Idorsia Pharmaceuticals Ltd.	ACT-541468	insomnia	Three studies.
Idorsia Pharmaceuticals Ltd.	aprocitentan	hypertension	In resistant disease.

Source: Biomedtracker

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interest or profit motive introduced to the system by the insurance providers. Then a post-acute and outpatient care platform for example provides positive reinforcement when the patient is well controlled, and thus can be well managed remotely, with much greater contribution by the patient's personal network. This would save substantial time and cost. And this remote care delivery can continue when active intervention is needed, now with greater engagement of the medical provider team. Only during acute episodes do these patients need hands-on care, for which a fresh, new initiative can bypass the currently sclerosed approach. This calls for the setting up of a group of well-trained, like-minded and closely monitored providers who can practice best standard of care. This practice structure would enable normal diagnostics and basic malpractice insurance, with little need for defensive medicine, nor for irrational malpractice insurance.

Is the JAB consortium thinking this boldly? Only time will tell. Are they capable? Of course, as are most other such initiatives, provided they can be peeled away from the current system.

IMPACT ON PHARMA

How would any such initiative change the biopharma incentives? The piecemeal approaches by various governments and other participants continue to bloody the industry's nose, but leave their profit focus more or less in place. A JAB consortium willing to be venturesome would change the industry practice fundamentally.

The biopharma company would get paid for the value it creates. In other words, we all know how Apple, Samsung or any other IT product vendor must survive. The customer will pay for the value. True, healthcare choices are not so simple, but on this patient centered platform anchored on value and fully integrating standard of care, each prescription will be more readily chosen objectively and rationally.

Genuinely needed biopharma products prepared to be evaluated along this value framework have nothing to fear. But a significant majority of products may be doomed, as is the case with so many electronic products.

The JAB consortium has a great opportunity to pierce the regulatory veil, the veil that distorts the healthcare system at every level. More importantly, such an initiative can demonstrate how a parallel, effective option can be created well and impactfully. Only one such success will usher in a rationally functioning healthcare system. A healthy society cannot be far behind.

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APPOINTMENTS

A management shake-up at ***Axovant Sciences*** as its chief executive officer ***David Hung*** has resigned from his position and the company's board. President and chief operating officer ***Marion McCourt*** has also resigned, while directors ***Kate Falberg***, ***Tony Vernon*** and ***Patrick Machado*** have resigned as members of the board. ***Pavan Cheruvu***, who was appointed to the Roivant executive leadership team in 2017, has replaced Hung as chief executive officer. ***Roger Jeffs***, former president and co-CEO of United Therapeutics, and ***George Bickerstaff***, former CFO of Novartis Pharma, have joined the Axovant board. Hung will continue to serve as a scientific advisor to the Roivant family of companies.

Eliot Forster has stepped down as chief executive officer of **Immunocore**, and will be replaced, in an interim capacity, by chief commercial officer ***Andrew Hotchkiss***. Forster will continue to work with Hotchkiss and the Immunocore leadership team to assist the transition and a search for his successor is underway. Hotchkiss joined Immunocore as chief commercial officer in 2017. In his new role as CEO, he will also sit on the Immunocore board.

Sangamo Therapeutics Inc. has appointed ***Heather D. Turner*** as senior vice president and general counsel, effective immediately. Turner will oversee all legal matters for the company and will report to Sangamo's chief executive officer. She has over 18 years of experience advising public and private life science companies and joins Sangamo from Atara Biotherapeutics, Inc., which she joined in 2015 and where she served as executive vice president, general counsel and secretary, and most recently as head of portfolio strategy. From 2007 to 2015, Turner served as general counsel and secretary at Orexigen Therapeutics, Inc.

Circassia has announced changes to its board: ***Jo Le Couilliard***, ***Sharon Curran*** and ***Heribert Staudinger*** have each been appointed as a non-executive director with immediate effect. Le Couilliard was most recently senior vice president, local commercial transformation at GlaxoSmithKline, while Curran was most recently vice president, global specialty franchise and customer excellence at AbbVie Inc, having previously held a number of senior roles at AbbVie, Abbott and Eli Lilly. Heribert is currently immunology clinical lead at Sanofi Genzyme and has held a number of leadership roles at Boehringer Ingelheim, Chiesi, Merck and Schering Plough. Meanwhile, ***Jean-Jacques Garaud*** and ***Marvin S Samson*** will retire from the board at the company's 2018 annual general meeting, and will not seek re-election as non-executive directors.

MaxCyte, the global cell-based medicines and technology company, has appointed ***Richard Douglas*** to its board as an independent non-executive director. Douglas was formerly senior vice president of corporate development and corporate officer at Genzyme from 1989 until Genzyme was acquired by Sanofi in 2011. He currently serves as an advisor to RedSky Partners, a biotechnology-focused advisory firm.

CANbridge Life Sciences, a biopharmaceutical company focused on developing Western drug candidates in China and North Asia, has recruited ***Michael Glynn*** to its advisory team, where he will provide leadership, direction and input on the CANbridge commercial strategy and planning as the company prepares for its first commercial launch. Glynn has more than 40 years of general management and commercialization experience in Asia Pacific, Japan, the Middle East, Latin America and the US. Most recently, he was senior vice president, global commercial operations, for Synageva BioPharma.

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