

SCRIP

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Shkreli Arrested On Securities Fraud

When FBI agents arrested Martin Shkreli, who was fired from his CEO positions at Turing Pharmaceuticals AG and KaloBios Pharmaceuticals Inc., some had predicted it was a likely outcome after he spiked the price for a toxoplasmosis medicine, *Daraprim* (pyrimethamine), by more than 5,000% – catching the attention of antitrust investigators in New York and lawmakers on Capitol Hill.

But it was his activities at his previous drug firm, Retrophin Inc., that's got the 32-year-old former hedge fund manager arrested for securities fraud early on Dec. 17, where he was seen being escorted out of his midtown Manhattan apartment by law enforcement officials. Shares of KaloBios took an immediate hit – falling 53% in premarket trading, before the stock was halted.

The investigation into Shkreli's alleged fraud activities was first revealed in January after Retrophin disclosed a subpoena from New York prosecutors inquiring about the former CEO. Shkreli has been accused of diverting assets from Retrophin – a company he founded but was fired from last year – to pay

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his debts for his former hedge fund, MSMB Capital Management, which was closed in 2012. Retrophin has filed a lawsuit against Shkreli seeking \$65m.

The US Justice Department has charged Shkreli and his lawyer, Evan Greebel, who

served as an outside counsel to Retrophin – and was also arrested on Dec. 17 – with orchestrating three interrelated fraudulent schemes to defraud investors and potential investors in MSMB Capital and another

FRAUD CHARGES: Shkreli is accused of running a Ponzi-like scheme and scamming investors

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'Orphans' Hit Historic High; More 'Me-Too' Drugs Urged

John Jenkins, director of the FDA's Office of New Drugs, reported that 20 of the 42 new molecular entities or novel biologics approved so far in 2015 were medicines that had received orphan drug designation – an all-time high for those products since the enactment of the Orphan Drug Act in 1983.

"And the year's not over," he declared. But while "all of this focus on orphans is great,"

Jenkins pointed out "we still have diabetes, we still have hypertension, we still have cardiovascular disease" – considered common chronic diseases. So, he said, the FDA wants to see biopharmaceutical makers get back to developing what's been dubbed the "me-too" drugs for chronic diseases – medicines that have been criticized over the past decade for lacking innovation.

But Jenkins disputed the notion me-too drugs lack purpose and are simply a way for companies to make an easy buck, like what has been asserted by some critics – most notably Marcia Angell, the former editor of the *New England Journal of Medicine*, and the consumer watchdog Public Citizen. But, Jenkins argued, "me-too drugs can

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Eleanor Malone,
Editor,
Scrip Intelligence

Pharma isn't ready to wind down for the holidays just yet. We are witnessing a pre-Christmas flurry of deals, several of them significant in size.

Back in April 2014, when Novartis, GSK and Lilly announced an asset-swapping deal of impressive scale and ingenuity, we wondered whether this might become a template for a new kind of deal-making in pharma. It seemed such an elegant way for two or more companies to build critical mass in areas of strength while relieving themselves of non-core activities, with all parties standing to gain and none having to bow down under the domination of an acquiring entity. But could such an arrangement, with its attendant need for trustful and complex negotiation, ever be replicated?

Last week's announcement that Sanofi is in talks to hand over its animal health business in return for Boehringer Ingelheim's consumer healthcare activities and some cash (see p4) suggests that it could. It's not as complex as the GSK/Novartis/Lilly deal – which involved consumer health, animal health, vaccines and oncology assets – but it is an indication that asset swapping has captured big pharma's imagination. And, as Fitch Ratings points out, it offers a "balance sheet-efficient" way of carrying out a transaction. For behind the scenes insight into the "original" asset swap, read Sten Stovall's interview with GSK's chief strategy officer David Redfern on p8.

AstraZeneca was very busy last week, announcing the acquisition of a majority stake in oncology firm Acerta Pharma (p11), expanding its alliance with Chinese firm WuXi AppTec (p10), paying \$575m for a respiratory portfolio from Takeda (p9) and completing its acquisition of ZS Pharma. So many diverse deals in such a short space of time looked scattergun, but all of these agreements were strategic bolt-ons in core areas for the firm (oncology, respiratory, cardiovascular/metabolic and emerging markets).

Meanwhile, biopharma companies continue to reduce the number of eggs in their baskets as they double down on fewer therapeutic areas, as evidenced by Bristol-Myers Squibb selling HIV assets to ViiV Healthcare, the HIV joint venture in which GSK is the majority partner (p10).

Keep signing deals and we'll keep writing about them on www.scripintelligence.com over the holiday period. Our next issue comes out on 8 January.

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New PhRMA CEO: Drug Costs Must Be Viewed In Context

With the biopharmaceutical industry frequently coming under attack over the past year about the high prices of certain medicines – decades-old drugs with significantly hiked up prices and expensive new innovative medications for hepatitis C virus (HCV) and severely uncontrolled cholesterol – the new head of the Pharmaceutical Research and Manufacturers of America (PhRMA) urged policymakers and patients to consider the costs of those products in context.

In his first public speech as PhRMA's president and CEO, Stephen Ubl, who took the reins at the lobbying group this month, insisted on Dec. 15 at the FDA/CMS Summit in Washington that drug spending remains a "relatively small and stable portion of healthcare spending – somewhere between 10%-15%."

He acknowledged there was a spike in 2014 in prescription drug spending in the US – which he attributed, in part, to the new HCV medicines.

Indeed, US government actuaries reported in July that Gilead Sciences Inc.'s *Sovaldi* (sofosbuvir) and *Harvoni* (ledipasvir-sofosbuvir) and AbbVie Inc.'s *Viekira Pak* (ombitasvir/paritaprevir/ritonavir/dasabuvir), whose prices range from \$84,000-\$94,500 per treatment course, played a major role in the overall acceleration in dollars spent on Americans' healthcare for 2014.

But Ubl argued there were other factors that played into that 2014 leap in healthcare spending as well, such as lower patent expiries and the expansion of the Medicaid program, which provides coverage for the poor in the US, under the Affordable Care Act.

Unfortunately, said Ubl, whose appointment as the new president and CEO at PhRMA was revealed this past September, some of the ideas policymakers are advancing in Washington "are fit to that spike and they are not to the broader trajectory of prescription drug spending. Our challenge is to step back and look at these costs in context and to ensure we are promoting policies that fit the broader arc and not the spike," he declared.

Ubl, who previously served as the head of the medical devices lobbying group in Washington, AdvaMed, insisted the situation where Turing Pharmaceuticals AG raised the prices of its 62-year-old toxoplasmosis drug *Daraprim* (pyrimethamine) by more than 5,000% was anomalous. "Clearly there are policy ideas that we could work on to address that situation without fundamentally undermining the innovation model," he said.

Earlier this month Ubl penned an op-ed in the Washington newspaper *The Hill*, in which he accused Turing and another company that's been in the headlines for spiking the prices of older medicines, Valeant Pharmaceuticals International Inc., of essentially being "hedge funds masquerading as pharmaceutical companies" – borrowing a line delivered on Nov. 20 by Merck & Co. CEO Kenneth Frazier, who also serves as PhRMA's chair, at a forum focused on prescription drug costs hosted by Health and Human Services. "In stark contrast, the vast majority of innovative biopharmaceutical companies have research and development at their core," Ubl wrote in Dec. 11 his op-ed.

Nonetheless, he said the "firestorm around Turing and Valeant is causing some policymakers to advocate for sweeping change in public policies that risk slowing this progress and delaying the development of the next generation of treatments and cures for patients fighting Alzheimer's, Parkinson's and other rare and debilitating diseases."

Ubl pointed out that one proposal calls for federally determined price caps, which he said potentially could undermine the viability of important new medicines now in the pipeline. "These proposals ignore the reality of the highly competitive market for prescription drugs, where health insurance companies are able to negotiate deep discounts off the list prices of medicines, including more than 50% off the price of new hepatitis C treatments," he said.

At FDA/CMS Summit, Ubl explained he had been struck at the Nov. 20 HHS forum by the focus on value-based payment arrangements, "which I think is a very positive direction to move in." He also said he was "very sympathetic to payers' concerns that they don't have visibility into the pipeline. They don't know when these products are going to come to market. They don't know what the label is going to look like." Ubl said he believed there's a way to "modernize the way our companies communicate with payers to reduce that lack of visibility and uncertainty."

He argued that "powerful market forces are occurring, branded competition is happening faster than it's ever happened before," which Ubl contended has been bringing down the prices of medicines. And he noted that nearly 90% of prescriptions that are written today are for generic drugs – something Ubl said he didn't think "anyone could have foreseen" when the 1984 Hatch-Waxman Act was being developed.

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NICE Knockback For BMS's Opdivo

Bristol-Myers Squibb Co.'s immunotherapy *Opdivo* (nivolumab) is not cost-effective and should not be provided for NHS patients with lung cancer in England and Wales, according to draft guidance from the health technology assessment body NICE. BMS had offered a confidential discounting scheme to reduce the cost below its list price of £5,200 per month (for a patient weighing 73kg), but this failed to sway the National Institute for Health and Care Excellence.

"[This] draft decision is deeply disappointing for lung cancer patients and for us as we have worked extensively with the UK health authorities to enable prompt patient access to nivolumab," stated Johanna Mercier, general manager, Bristol-Myers Squibb UK & Ireland. The company intends to work with NICE to reach an agreement that will enable UK lung cancer patients to access the drug. BMS would not provide details of its proposed discount.

The draft guidance, which now goes out for consultation, is on the use of *Opdivo* specifically to treat adult patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) whose disease has progressed after prior chemotherapy. The PD-1 inhibitor has been lauded as a breakthrough for these patients, for whom innovative treatments are lacking and standard treatment is with older chemotherapy such as docetaxel. It has been designated as a promising innovative medicine by the UK regulator MHRA and made available through the country's Early Access to Medicines Scheme.

NICE's final guidance is expected in February 2016.

BMS noted that survival rates for these patients are significantly better on *Opdivo* than with docetaxel: the company's Checkmate-017 study in patients with advanced squamous cell NSCLC whose disease had progressed during or after one prior platinum-containing chemotherapy regimen showed 42% of *Opdivo*-treated patients still alive at one year compared with 24% of those treated with docetaxel. Global five-year survival rates for NSCLC patients with stage IV advanced or metastatic disease are only around 2-13%. Squamous NSCLC accounts for around 25-30% of all lung cancers.

Commenting on NICE's decision, Professor Dean Fennell, chair of thoracic medical oncology, University of Leicester, said: "Lung cancer continues to be the UK's biggest cancer killer and clinicians have

Bold Brandicourt Plots Mega Sanofi-BI Asset Swap

Sanofi and Boehringer Ingelheim are in exclusive negotiations to swap parts of their businesses. The deal would involve an exchange of Sanofi's animal health business Merial, which is worth €11.4bn, with Boehringer's consumer healthcare (CHC) business, worth €6.7bn. To make up the difference in value between the two businesses, Boehringer would make a cash payment to Sanofi of €4.7bn.

Privately held Boehringer's CHC business in China is excluded from the discussions.

The move follows similar transactions by other pharma companies recently, including the three-way mega asset swap of Novartis, GlaxoSmithKline and Eli Lilly which completed earlier this year.

"Strategically, Sanofi's scope of business narrows and becomes more focused – a current trend among global pharmaceutical companies – so in this sense the transaction is a modest positive, but the deal is not exactly transformative," said Bernstein analysts.

The latest news has proven that Sanofi's CEO – not even one year in the job – is not afraid of making big decisions in a small timeframe. At Sanofi's recent investor day, Brandicourt outlined a number of strategic priorities for the company. He highlighted CHC as one of the business areas in which Sanofi can "have or can acquire the assets to build competitive positions." He also said the animal health business and generics business in Europe would see Sanofi exploring divestment opportunities.

Sanofi believes the transaction with Boehringer would make it the number one ranked player in CHC with expected pro forma sales of approximately €5.1bn in 2015 and a global market share of around 4.6%. Sales of Boehringer Ingelheim CHC business (excluding China) are estimated at about €1.6bn for 2015.

The CHC businesses are "highly complementary," said Sanofi, "both in terms of products and geographies." Boehringer's CHC unit would boost Sanofi's presence in Germany and Japan where it is currently "limited."

Meanwhile, combining Merial and Boehringer's animal health business would create the second largest player in the global animal health market with pro forma sales of approximately €3.8bn in 2015. "In entering into exclusive negotiations with Boehringer Ingelheim, we have acted swiftly to meet one of the key strategic objectives of our roadmap 2020, namely to build competitive positions in areas where we can achieve leadership," commented Sanofi's CEO Brandicourt.

Germany would become a key center of Sanofi CHC business, while Lyon would be a key operational center of Boehringer's animal health business. The companies plan to finalize talks in the coming months and close the deal in 4Q 2016, subject to regulatory approvals.

Sanofi intends to use a portion of the proceeds of the transaction to repurchase shares. "As the transaction is dilutive to Sanofi's EBIT – Boehringer's CHC [is] smaller than Merial and also likely less profitable – the company will use the proceeds to buy back shares," noted Barclays analysts. This will make the overall transaction EPS neutral in 2017 and accretive in subsequent years, driven by synergies, they added.

The €11.4bn enterprise value for Merial is around 4.6 times estimated 2015 sales, and the €6.7bn enterprise value for Boehringer's CHC unit is 4.2 times 2015 estimated sales, according to Deutsche Bank analysts.

Boehringer's CHC activities

Boehringer CHC is the eighth largest CHC business in the world, with €1.4bn in sales in 2014, contributing 11% to Boehringer's net sales. The leading brands are the antispasmodic *Buscopan* (2014 sales of €219m; mainly sold in Europe and Latin America), the laxative *Dulcolax* (2014 sales of €204m; sold in more than 40 countries with a strong presence in the US), the multivitamins *Pharmaton* (2014 sales of €133m, with majority of sales in Latin America), the cough treatments *Mucosolvan* (2014 sales of €165m, mainly in China, Germany and Russia) and *Bisolvon* (2014 sales of €101m with a fragmented worldwide presence with largest countries being Spain and Italy) and the cold treatment *Mucoangin/Lysopaine* (2014 sales of €48m).

Sanofi's CHC activities

Sales of Sanofi CHC business were €3.3bn in 2014. The leading brands in Sanofi's CHC business are the allergy products *Allegra* (2014 sales of €350m) and *Nasacort* (2014 sales of €114m), the pain killers *Doliprane* (2014 sales of €310m), No-Spa (2014 sales of €109m) and *Dorflex* (2014 sales of €90m), the digestive products *Essentiale* (2014 sales of €235m), *Enterogermina* (2014 sales of €156m) and *Maalox* (2014 sales of €98m), the feminine care product *Lactacyd* (2014 sales of €104m) and the vitamins, minerals and supplements *Magné B6* (2014 sales of €88m). In 2014, 52.6% of CHC sales were generated in emerging markets, 21.2% in the US and 20.3% in Western Europe. sukaina.virji@informa.com

NICE Knockback For BMS's Opdivo

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long awaited a medicine that could extend survival for patients in the advanced stages of the disease. Nivolumab offers significant improvement both in survival and safety compared to chemotherapy and was licensed for use in these patients earlier this year, but must be recommended by NICE before patients can routinely be treated. If it is not reversed as soon as possible, the draft recommendation issued today could be a serious blow to lung cancer patients, many of whom can't afford to wait."

Opdivo became the first immunotherapy product to be approved in Europe for lung cancer in July 2015. Treatment is given until disease progression or toxicity, meaning that some patients may get it for just a month or two, whereas others could receive it for a year or longer.

This NICE guidance is the first provided by the organization for Opdivo, which is also under NICE assessment for use in melanoma, with a decision expected early in 2016. In September 2015, Merck & Co's competing PD-1 inhibitor *Keytruda* (pembrolizumab) received NICE approval for melanoma in a final draft guidance.

Further licensing approvals are expected in 2016 in Europe for Opdivo for indications including non-squamous lung cancer and renal cell carcinoma, as well as for a combination of Opdivo and BMS's *Yervoy* (ipilimumab) in melanoma, following green lights from the US FDA.

The funding situation for innovative cancer therapies in the UK is complicated by upheavals around the much-maligned Cancer Drugs Fund (which is being phased out in its current form by the end of March 2016) and the way NICE appraises new medicines.

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New Drugs Chief: Vouchers Put FDA In 'Distasteful' Situation

Just as the House Oversight and Government Reform Committee decided it was time to look into whether the FDA's priority review vouchers (PRV) are being exploited, lawmakers on Capitol Hill also felt it was necessary to keep the specific portion of the program going for another six months that awards the "golden tickets" to firms that win approval of rare pediatric disease medicines – even though high-ranking US regulators would like to see it end.

Tucked inside the mega \$1.1tn fiscal year 2016 "Omnibus" spending bill is a provision championed by Rep. GK Butterfield (D-NC) and Sen. Bob Casey (D-PA) that would extend the pediatric PRV program to Sept. 30, 2016.

When Congress created the pediatric PRV program in 2012 as part of the Food and Drug Administration Innovation and Safety Act, lawmakers set it up as a pilot – declaring the FDA could award as many of the vouchers as the agency saw fit to firms that qualified, but once the third one was given out, the program would expire one year later. That third voucher was awarded this past March.

A bill that passed the House in July, the 21st Century Cures Act, included a provision that would reauthorize the pediatric PRV program through Dec. 31, 2018.

A spokesperson for Casey said the senator is "still fighting" to get a similar measure into the Senate's companion to the Cures bill, which has yet to be revealed.

An earlier-created PRV program, which does not have an expiration date, awards the vouchers to makers of medicines aimed at treating neglected tropical diseases.

Holders of the PRVs can use them on a subsequent application that otherwise would not have qualified for a priority review or the companies can sell them.

PRVs are valuable because the bearers can shave off at least four months of the time it takes the FDA to examine a marketing application, which means a product can get to the US market much faster, banking cash for the drug maker.

But, as Oversight Committee Chair Jason Chaffetz (R-UT) and his colleagues pointed out in a letter to FDA acting Commissioner Stephen Ostroff, the resale prices of PRVs have climbed from \$67.5m to \$350m.

The lawmakers' probe actually started out examining the skyrocketing prices of older off-patent drugs – specifically looking at companies like Turing Pharmaceuticals AG, whose CEO Martin Shkreli decided to jack up the cost of the firm's toxoplasmosis medicine *Daraprim* (pyrimethamine) by more than 5,000%. But when Turing acquired KaloBios

Pharmaceuticals Inc. in November and that company went on to buy a Chagas disease drug benznidazole from Savant Neglected Diseases LLC, with Shkreli disclosing he planned to seek a neglected tropical disease PRV, that triggered concern by the House committee about companies that may be solely looking to capitalize on the resale of the vouchers.

Doctors Without Borders/Médecins Sans Frontières also raised concerns about the potential Shkreli could get his hands on a PRV.

"Companies can obtain this voucher without actually developing a new medicine and without having to ensure that medicines are affordably priced," the international medical humanitarian organization argued.

John Jenkins, director of the FDA's Office of New Drugs, told a small group of reporters at the FDA/CMS Summit on Dec. 14 that regulators are "not fans of priority review vouchers."

Jenkins emphasized, however, "we support the goal of trying to incentivize developing drugs for tropical disease and rare pediatric diseases." But, he said, "I think the whole program is built on faulty economic principles."

FDA Sold To Highest Bidder

Jenkins said the PRV program is flawed "because it places FDA's limited resources for sale to the highest bidder. It's very distasteful for FDA staff to see gloating about how someone has bought a voucher and now they are going to force the FDA to do a streamlined fast review on a product that doesn't qualify," he explained to reporters. "Everybody wants their project to be a number-one priority. If everything is a priority then nothing is a priority."

And, Jenkins pointed out, the FDA already has been criticized as being "in industry's pocket. So now you're going to sell our services on the open market to the highest bidder," he lamented.

While the voucher can change the timeline from a standard review to a priority review, "you can't magically change the benefit-risk profile of the drug, the amount of data that we have to review, the complex questions that have to be addressed, the need for advisory committee discussions," Jenkins said.

"We're not making pizza here. We are reviewing drugs and making very difficult decisions. And you don't want to rush unnecessarily making important benefit-risk decisions for new drugs," he declared.

Jenkins said he's shared his views with David Ridley, an associate professor of business and economics at Duke University, and his colleagues, whose 2006 proposal for

a PRV "prize" was the basis on which Congress created the neglected tropical disease voucher program in 2007.

In an email response, Ridley told *Scrip* he was aware that regulators were "understandably frustrated about some of the vouchers that have been awarded to date" and said "there's cause for concern" about the voucher being pursued by Shkreli.

The Duke economist said he agreed with Jenkins about the need to close some of the loopholes that allow drugs used abroad for many years to be eligible for a voucher.

But Ridley said he disagreed with Jenkins on the role of the markets. "As an economist, I see that the cost of priority review is in the millions of dollars, while the value of priority review is in the hundreds of millions of dollars, and I see an opportunity to make a change that increases efficiency while also creating an incentive to help people suffering from neglected diseases," Ridley said. "However, I can certainly understand why that view might not be shared. Analogously, many economists support tradable carbon permits as a means for reducing carbon emissions, while others see such a program as immoral."

Ridley pointed out that each company that redeems a voucher must pay the FDA an additional user fee of \$2.7m.

In 2015, the FDA budget included a forecast that three PRVs would be redeemed, so Congress provided the agency with an additional \$8m, he said. But only one voucher ended up being redeemed, so Ridley asked "where the \$8m went?"

"FDA received millions of additional dollars and in return reviewed one drug four months faster," he said, adding "that doesn't sound so onerous." While it may be difficult for the FDA to hire additional staff, "that's not a problem of the voucher program."

But in a Dec. 16 email reply to *Scrip*, Jenkins – who emphasized his views were his own and not those of the FDA – said Ridley was wrong about the \$8m. "Congress provided FDA with the authority to collect and spend up to \$8M in user fees, but the fees are only collected and available if a PRV is redeemed," Jenkins said. And, he said, "it is illogical to think that a one-time fee that is paid shortly before a voucher is redeemed will somehow provide FDA with the highly trained professional staff needed to conduct the priority review on the voucher application."

Highly trained reviewers, Jenkins said, "are not like day laborers" who are hired to meet surge work.

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Shkreli's Ponzi Scheme Trifecta: Lies, Deceit And Greed

With the answer to the big question about Martin Shkreli out of the way – The FBI confirmed it didn't seize his \$2m one-of-its-kind album of the American hip-hop group Wu-Tang Clan – what investors and patients likely are wondering is where do his now-former companies, Turing Pharmaceuticals AG and KaloBios Pharmaceuticals Inc., go from here?

After Shkreli was "perp-walked" out of his apartment in front of news cameras early on Dec. 17, investors panicked, driving shares of KaloBios down 53% in premarket trading, before the stock was halted.

Shkreli was released from jail on \$5m bond on Dec. 17 after being charged with defrauding investors of his former hedge funds, MSMB Capital Management and MSMB Healthcare, and misappropriating more than \$11m in assets from Retrophin Inc. – the publicly traded firm he founded and then ultimately was fired from – although his travel is restricted to the southern and eastern districts of New York.

Shkreli, who was ordered to appear in court on Jan. 20, faces a potential maximum of 20 years in prison if convicted for the seven counts against him.

Drug Price Probes Unaffected

It's unclear, for now, what will become of the two companies run by Shkreli, who has been called the "poster boy of price-gouging" and the "most hated man in America" for jacking up the price by more than 5,000% of a critical drug for toxoplasmosis, *Daraprim* (pyrimethamine).

Prosecutors emphasized the investigation that got Shkreli arrested had nothing to do with probes about Turing's drug pricing practices involving *Daraprim*.

Sens. Susan Collins (R-ME), chair of the Senate Aging Committee, and Claire McCaskill (D-MO), the ranking member, said Shkreli's arrest and indictment would not affect their bipartisan investigation into the sudden, aggressive price spikes of some decades-old drugs – insisting Turing is just one company among the four they are scrutinizing and the hearing they held earlier this month was just the first in a series.

While Jason Chaffetz (R-UT), chair of the House Oversight and Government Reform Committee, plans to hold a hearing early in 2016 focused on the prices of older drugs – as well as the FDA's priority review vouchers – he's not yet said whether he'll summon Shkreli to appear, which has brought condemnation from Rep. Elijah Cummings, the ranking member.

"Shkreli has lined his own pockets at the expense of patients who desperately need

their medications, and he should be ashamed of himself," said Cummings, who had already initiated his own investigation into drug pricing practices of Turing and others. Given the latest development involving the former Turing and KaloBios CEO, the Maryland lawmaker said it was "disgraceful" House Republicans have "refused our multiple requests" over the past year to send Shkreli even a single letter requesting a single document about his "outrageous abuses."

The Plot

Shkreli was charged on Dec. 17 with securities fraud, securities fraud conspiracy and wire fraud conspiracy for orchestrating three interrelated schemes to defraud investors in his two hedge funds and misappropriating Retrophin's assets.

One of Shkreli's alleged co-conspirators in the scheme, Evan Greebel, who was initially retained as an outside lawyer for Retrophin, also was released on a \$1m bond after being arrested earlier in the day and charged with wire fraud conspiracy.

Andrew Ceresney, director of enforcement at the Securities and Exchange Commission (SEC), told reporters that because Shkreli had repeatedly violated the law, "he should be barred from working in the securities industry or from being an officer or director of a public company."

Robert Capers, US attorney for the Eastern District of New York, said he hopes the arrests of Shkreli and Greebel sends a message loud and clear to other hedge fund managers, corporate executives and attorneys who may be committing similar crimes or thinking about doing so that the Justice Department, the FBI and the SEC will be "tireless" in their efforts to "uncover your schemes no matter how sophisticated, no matter how long it takes, we will bring you justice."

Shkreli essentially had engaged in a "trifecta of lies, deceit and greed," where he targeted investors and duped them into a scheme involving his hedge funds, which were "essentially worthless," said Michael Harpster, special agent-in-charge at the FBI.

Capers said the two defendants had constructed a Ponzi-like scheme, under which Shkreli used money from MSMB Healthcare to pay off debts from a series of bad trades he'd made under MSMB Capital. "He did that to conceal the lies he'd told to MSMB Capital investors that their investments were doing well and giving them handsome returns," Capers told reporters, noting the investigation into Shkreli started while he was still at Retrophin.

Shkreli also had dipped into MSMB

Healthcare cash to use for "seed" money to start Retrophin, the justice official said.

"He lied to investors about how both funds were doing," Capers said, adding that Shkreli also deceived the MSMB Healthcare investors about "what he was doing with the money – all along, promising their investor they would see exceptional returns."

When the hedge fund investors pressed Shkreli on the supposed exceptional performance he promised on their investments, he "found himself at a crossroads: either come clean and admit he lied and that he'd lost money or continue his lies and somehow pay the investors on the returns on his investments," Capers said. But, he said, "Shkreli did what he had done in the past. He made the wrong choice. He lied."

Capers accused the two defendants of using Retrophin as Shkreli's "personal piggybank."

Capers said Shkreli and Greebel "perpetrated their fraud" in a number of ways, including backdating documents, which was done in part to deceive the SEC in November 2012 that MSMB Capital was still in operation and had \$2.6m in assets under management.

Officials said that between February 2013 and August 2013, Shkreli and Greebel, along with other yet-to-be identified co-conspirators, used Retrophin resources to pay more than \$3.4m in cash and stock to settle claims by seven of the hedge funds' investors that they were misled on the performance of their investments.

After an external auditor for Retrophin questioned those settlements and determined the company was not responsible for the claims, Shkreli and Greebel executed indemnification agreements and issued promissory notes to Retrophin from the hedge funds, even though they knew those entities had no assets.

Shkreli and Greebel also devised an alternative approach to try to resolve things with the remaining defrauded hedge fund investors using "sham" consulting agreements, under which they paid out \$7.6m in Retrophin cash and stock to settle claims, which the auditors had previously determined were not the responsibility of the drug company.

"Shkreli was entrusted with protecting Retrophin and its shareholders' assets. Instead, he abused that power and used the company's assets to pay off his own personal debts," Capers declared, adding that "Greebel used his law license and training as a cover so Shkreli could perpetrate his fraudulent goals." But, he said, "At a certain point, when you continue to lie, it catches up with you."

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Shkreli Arrested On Securities Fraud (Continued from page 1)

hedge fund, MSMB Healthcare, by inducing them through material misrepresentations, and a scheme to defraud Retrophin by misappropriating its assets.

US Attorney for the Eastern District of New York Robert Capers said Shkreli ran his companies like a Ponzi scheme, where he used the assets of the new entity to pay off debts from the old entity.

According to the complaint from the Securities and Exchange Commission (SEC), the case involves widespread fraudulent conduct orchestrated by Shkreli from at least October 2009 through March 2014. Some of the fraudulent conduct was aided and abetted by Greebel, the SEC said.

From October 2009 through July 2011, Shkreli misappropriated about \$120,000 of investor funds from MSMB, and from July 2010 through September 2012, he made material misrepresentations to investors and those who may potentially invest in the hedge fund, the SEC said. In February 2011, Shkreli sold short over 32 million shares of an issuer in MSMB's account at a registered broker-dealer. In placing the short sales, Shkreli represented to the broker-dealer that MSMB had located sources from which to borrow the shares necessary to settle the trades through the his hedge fund's prime broker.

From January through March 2013, Shkreli misappropriated about \$900,000 of investor funds from MSMB Healthcare to fund the settlement of an arbitration proceeding brought by the broker-dealer in connection with MSMB's failure to settle its short sales – causing that broker-dealer to incur a loss of over \$7m, the SEC alleged.

The securities agency said Shkreli, aided and abetted by Greebel, fraudulently induced Retrophin to issue stock and make cash payments to certain disgruntled investors in the CEO's hedge fund by having them enter into agreements with the drug company that misleadingly stated the payments were or the release of potential claims against the drug firm chief. Shkreli misrepresented or failed to disclose to Retrophin's board the primary purpose of the agreements was to settle the potential claims against him, the SEC said.

In the end, said the FBI's assistant director-in-charge, Diego Rodriguez, Shkreli and Greebel used a series of settlement and sham consulting agreements that resulted in Retrophin and its investors suffering a loss in excess of \$11m.

Shkreli faces a potential of 20 years in prison.

The pharmaceutical industry has mostly distanced itself from Shkreli, who was

called "the most hated man in America" on social media after he jacked up the price of Daraprim.

At a Nov. 20 forum hosted by Health and Human Services, Merck & Co. CEO Kenneth Frazier, who also serves as the chair of the drug industry trade group the Pharmaceutical Research and Manufacturers of America, called Turing and Shkreli a "hedge-fund manager masquerading as a pharma company" and an "aberration."

"I don't like Turing being used as an exemplar of this industry," Frazier charged. "I don't consider them to be a part of the industry."

Shkreli has been at the heart of investigations on Capitol Hill. At a Dec. 9 hearing, Shkreli and Valeant Pharmaceuticals International Inc. CEO Michael Pearson were accused by senators of essentially holding Americans hostage to the ransom of their high drug prices for older medicines that have no alternatives.

Sen. Claire McCaskill (D-MO), ranking member on the Senate Special Committee on Aging, which convened the hearing, condemned Shkreli for spending \$2m to buy a one-of-a-kind record album from the hip hop group Wu-Tang Clan when patients, including babies, were having a hard time accessing Daraprim.

"I find it so disturbing and indeed, unconscionable that a company would buy a decades-old drug that it had no role in developing, didn't spend on a dime on the R&D for it and then would hike up the price to such egregious levels that it's having an impact on patient care. That is just plain wrong," declared Sen. Susan Collins (R-ME), chair of the committee.

Rep. Elijah Cummings (D-MD), ranking member on the House Oversight and Government Reform Committee, said Shkreli has refused to turn over documents the lawmaker requested. The hike in the prices of older drugs like Daraprim "can only get worse, because companies are seeing they can get away with it," Cummings declared at a hearing earlier this month.

In October, Eric Stock, chief of the Antitrust Bureau at the State of New York Office of the Attorney General, told Shkreli that his company "may be restraining competition unlawfully" by restricting the distribution of Daraprim. Imprimis Pharmaceuticals Inc. started compounding a form of Daraprim and making it available to patients for \$1 per pill – significantly lower than the \$750 per pill Turing charges.

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AZ Taps Swedish Roots For Novel Protein Research

AstraZeneca PLC is tapping its Swedish roots with a groundbreaking collaboration aimed at exploring the potential of an emerging class of proteins using the newly mapped Secretome for new drug development.

AstraZeneca – created in 1999 when Sweden-based Astra A/S merged with the spun-off Zeneca pharmaceuticals arm of now vanished UK conglomerate ICI PLC – has entered a three-year collaboration with Sweden's newly established Wallenberg Centre for Protein Research (WCPR) to develop new technologies for biologics production and to identify new targets for disease research in the area of the Secretome, which accounts for around a third of all human proteins and which plays a big part in most biological processes, including those involved in cardiac tissue regeneration, glucose balance and cancer growth.

This protein subset is therefore being targeted for use in identifying new biomarkers, drug targets and for developing novel biologics, the company said.

Under the alliance, announced Dec. 11 as part of a \$100m longer-term initiative, AstraZeneca's innovative medicines biotech unit, or iMED, will screen the Secretome library using the company's own assays to identify new protein-based targets for compound development across a range of diseases.

"Harnessing the power of the Secretome in this unprecedented way will help us to identify new biomarkers, drug targets and ultimately develop next-generation biological treatments," commented Pascal Soriot, AstraZeneca's CEO.

The collaboration promises to be cutting edge given that the Secretome was only fully mapped at the start of 2015 and thus remains largely unexplored by pharma.

"Currently the pharma industry relies on a specific set of cells called Chinese Hamster Ovary cells to make its biologic drugs in the great fermenter vats. Through the new agreement, MedImmune will be able to expand the source of cells it uses to biologics to other, more reliable and efficient cell lines for larger scale, better quality production," a spokesperson for AstraZeneca said.

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GSK Will 'Sit Out' Current Big M&A Frenzy

GlaxoSmithKline PLC says it will not join the current melee of big M&A sweeping the sector but will instead concentrate on 'bedding down' its constituent parts after its transformational asset swap with Swiss rival Novartis AG, completed last year.

GSK's complex, three-part transaction with Novartis, first announced in April 2014, leaves the British drug maker with a better balanced portfolio centred on vaccines, consumer health, respiratory and HIV medicines.

"We feel we've now got the pieces we need – it's taken awhile to get there and it's now about execution, so we don't see significant M&A being part of our plans going forward," David Redfern, GSK's chief strategy officer, told *Scrip*.

GSK's Focus Now Is 'Execution'

"The businesses we've now got in GSK represents about £24bn (\$36bn) of revenue, most of that being split between the consumer healthcare business representing around £6.5bn and a £4bn vaccine business – both of which are global leaders; an HIV business within pharmaceuticals that generates about £2bn; a respiratory business of about £5.5bn, and an emerging markets business representing most of the rest. So we're pretty focused on areas now where we've got real strength, real expertise. The Novartis deal was the final step to get us to this position so the real key for us now is execution," Redfern told *Scrip* in an interview.

A chartered accountant, Redfern has led GSK's new business development strategy since 2008. He is also chair of the HIV partnership, ViiV Healthcare Ltd, a role he has had since 2011. ViiV was set up in 2009 by combining the HIV management expertise of GSK and Pfizer Inc. The duo was joined three years later by Japanese pharma group Shionogi & Company Inc.

After much soul-searching GSK decided earlier this year to retain the full value of its ownership in ViiV Healthcare rather than floating a minority stake in the business on the stock exchange, as had been previously considered. The company reported 65% growth in sales of its HIV business in the third quarter of 2015 to £622m, driven by strong sales of the once-daily integrase inhibitor *Tivicay* (dolutegravir), which launched in 2013, and the combination pill *Triumeq*, which combines dolutegravir with the active ingredients in the nucleoside reverse transcriptase inhibitor *Epzicom* (abacavir/lamivudine).

Redfern says the company is keen to develop its HIV pipeline.

"In HIV, the business I'm responsible for, it's really about driving new product growth, such

Insights On Corporate Horse-Trading

In its transformative asset swap with Novartis, GSK gave its marketed oncology portfolio, related R&D activities, and rights to its AKT inhibitor to the Swiss firm, and also granted Novartis commercialization partner rights for future oncology products. GSK's main cancer portfolio at the time consisted of *Arzerra* (ofatumumab), *Revolade* (eltrombopag) which is marketed as *Promacta* in the US, *Tykerb* (lapatinib, marketed as *Tyverb* in the EU) and *Votrient* (pazopanib), as well as *Tafinlar* and *Mekinist*. Redfern said these were not easy decisions to take, and were part of a very difficult process.

"In these situations you need the top of the house – CEOs and boards – to decide what they're swapping; they can change their minds, and you need someone to give and someone to take – and in our case we had to agree to divest our marketed oncology products which was a big decision, and in Novartis' case they had to give up control of the consumer business and give up their vaccine business and you need people at the top to make those tough calls.

"CEOs are good at acquiring things and less good at giving things up. And [there is considerable] technicality [in] doing deals of that nature where the biggest issue is that the assets you're swapping, be it IP, people, manufacturing sites or technology are not always cleanly separable. So, if you take oncology clinical development at GSK, some are doing other things as well so you have to develop rules about who's in what camp; even IP – in this deal we sold the IP of ofatumumab (*Arzerra*) but we kept the multiple sclerosis indication. Because it's a biologic there's much debate about who owns the cell lines, who owns the manufacturing processes, so you have to carve that all out. So you get into enormous complexities quite quickly about the ability to separate it all, and the legal work snowballs.

"There were 400 lawyers working on that deal, pretty much full time, from five law firms, and the project management was huge. The deal was carried out fairly quickly. The first discussions took place in autumn 2013 and it was announced in Easter 2014 so it was very intensive between January and Easter of 2014," Redfern explained.

as dolutegravir and all its various combinations to gain as much market share as we can, and the follow on cabotegravir," a long-acting antiviral for HIV infection that has the potential for dosing every two to three months versus daily. Cabotegravir is in Phase II development, and GSK and partner J&J recently presented positive top-line data from the LATTE2 trial studying long-acting cabotegravir in combination with Janssen's long-acting non-nucleoside reverse transcriptase inhibitor rilpivirine in 309 treatment-naïve patients versus an oral regimen of three HIV medicines. GSK says the data supports moving cabotegravir into Phase III development.

'We missed the first wave with PD-1/L1s but we are very focused on the second wave'

Redfern is particularly excited about prospects for a once-monthly or once every two months injectable HIV therapy.

"That wouldn't be for all patients, but we do know compliance is very variable, and cabotegravir also has the potential for prevention as well as just treatment. Our Phase IIb data for HIV treatment with cabotegravir is very compelling. So next year we'll start a Phase III study – they tend typically to last 48 weeks – and we're interfacing with regulators as we go along."

He noted prevention of HIV is more complicated, "because no one is quite sure exactly what the target populations are. So you need to run larger, longer studies because you're really looking at that duration frame. We're going to probably work with the NIH to do some studies over the next few years, and that will take longer to come through."

He said GSK is using the integration with Novartis to reshape how the UK's biggest drug maker operates in the vaccine space, making that segment more global. In April, GSK said it would build a new global centre for vaccines R&D in Rockville, Maryland in the US. The site will become one of three global vaccines R&D centres for GSK, complementing existing global R&D centres in Rixensart, Belgium, and in Siena, Italy, a site which GSK acquired from Novartis in March 2015.

"We have some new product opportunities in the meningitis vaccines that we got from Novartis, and also our shingles vaccine *Shingrix* (zoster) which we now have great trial data on which we'll use to file with next year. So our priorities there are a combination of top-line revenue growth and restructuring in the vaccines business going forward," Redfern said.

GSK Hopes To Catch Next IO Wave

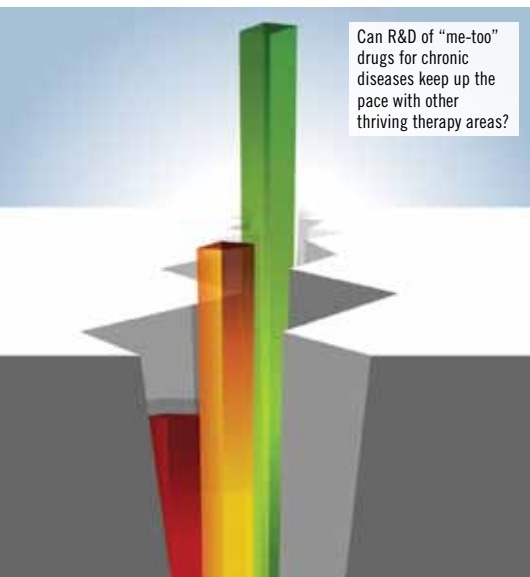
In its immuno-oncology R&D efforts, he said GSK is focusing on next-generation checkpoint modulators, including the OX40 agonist antibody GSK3174998 and first-in-class ICOS agonist antibody GSK3359609.

"We missed the first wave with PD-1/L1s but we are very focused on the second wave and have a number of interesting assets in the clinic," Redfern said. "We have invested heavily over the last six to seven years in epigenetics, the control system that helps regulate the DNA of cells and determines cell function, and we've got a number of lead programs on that, so we might be at the forefront of that," he said.

So overall, GSK's business strategy now is to hunker down and follow through with the activities it already has going on. "We might occasionally do a middle- or late-stage asset acquisition but it's largely an organic execution focus at this point," stated Redfern.

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'Orphans' Hit Historic High; More 'Me-Too' Drugs Urged (Continued from page 1)



Can R&D of "me-too" drugs for chronic diseases keep up the pace with other thriving therapy areas?

John T. Takeda/shutterstock.com

be me-better drugs." During the FDA/CMS Summit in Washington on Dec. 14, hosted by *Scrip's* parent company Informa, the new drugs chief insisted that "too much focus" has been placed on development of medicines to treat rare diseases and on gaining the FDA's breakthrough therapy designation – which is intended to expedite the regulatory processes for medicines to treat serious and life-threatening conditions – while other drugs that could be valuable to public health, specifically the me-too products, "are being left on the shelf."

Unfortunately, Jenkins said, many biopharmaceutical manufacturers have turned away from the me-too drugs and the diseases they are intended to treat, in favor of pursuing what companies and their investors are considering more innovative and lucrative products, like those that treat orphan diseases.

But, he warned, "that's not a good thing for public health." While there are available treatment options for diabetes, CV disease and hypertension, those products may not have the best risk-benefit profile, Jenkins explained. For instance, he said, what if drug makers had stopped at Merck & Co's *Mevacor* (lovastatin) and not pursued any other statins – leaving patients and doctors "stuck" with one medicine in that class. "I think we would agree the ones that came later were better," Jenkins said.

He acknowledged that a lot of me-too drugs are more challenging to develop – requiring larger datasets to demonstrate efficacy and greater safety information so regulators can decide whether the benefits of the product outweigh its risks. Nonetheless,

Jenkins argued the me-too drugs "are very important." He said the FDA has been working on ways it can help biopharmaceutical manufacturers get back to developing the chronic disease me-too drugs, and said the agency is aware it needs to provide better guidance and make its expectations for R&D programs "very clear."

Jenkins said the FDA also must meet with companies to come up with the most streamlined, efficient way to collect data, "so the costs of the development program won't be so large that people shy away from it."

In addition, he said the FDA needs to "carefully consider what we require preapproval and postapproval as far as what's the right bar to set the level for information."

Jenkins said the FDA now is at a place where it needs to reconsider the diabetes guidances – specifically, the requirements for CV outcomes trials (CVOTs) "to see if that's the right place for us to be in 2015 going into 2016." He noted the CVOT requirements and guidance were put in place in 2008 as a result of the debate over the CV risks observed with GlaxoSmithKline's type 2 diabetes drug *Avandia* (rosiglitazone).

"The agency has now essentially concluded we don't see an increased risk of heart attack with *Avandia*," Jenkins said.

Indeed, the FDA in November 2013 lifted the restrictions the agency imposed on the medicine three years earlier – reversing course on what it initially had concluded about a 2007 meta-analysis. Nonetheless, Jenkins said, "we still have the residual in guidance based on the *Avandia* incident." But he also noted that some CVOTs have "revealed some interesting findings."

Now, however, the FDA is "going to have to make some decisions about how to apply our standards in that area," he said, noting that it's been an "evolution in the understanding" of CVOTs since 2007. "I can't predict a timeline" for making any changes on the CVOT requirement, Jenkins told *Scrip* after the FDA/CMS Summit session. "We are initiating our discussions about it now. We've had some advisory committee meetings to discuss the diabetes CVOTs. We are expecting some soon to review. To date, I don't think any of them have raised questions of harm from the MACE standpoint, although one or two have had some unexpected findings from the study." He noted at least one CVOT has shown a possible CV benefit.

"We're going to have to weigh all of those factors as we're deciding where to go in the diabetes arena," Jenkins said.

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AZ Acquires Respiratory Assets From Takeda

AstraZeneca is to pay \$575m to acquire full rights to Takeda's *Daxas* (roflumilast), along with other respiratory assets. The move is the latest in a series of bolt-on acquisitions by the UK firm to bulk up its position in respiratory, one of its core therapeutic franchises.

Daxas is an oral PDE4 inhibitor used as an add-on to bronchodilation treatments to reduce exacerbations in patients with severe chronic obstructive pulmonary disease (COPD). It is by no means a blockbuster treatment, and concerns over the safety of the class look to have kept uptake quite low, according to analysts at Datamonitor Healthcare. However, the drug fulfils an unmet need in patients with severe disease.

AstraZeneca has already acquired North American rights to roflumilast from Actavis (now Allergan), which is known as *Daliresp* in the US. It reported sales of \$72m for the medicine in the first nine months of 2015. The deal with Takeda means it will no longer have to pay royalties on its US sales, and will have full global rights to the drug.

AstraZeneca has been building up its respiratory business, acquiring a portfolio of marketed and pipeline products from Almirall in July 2014, and then the rights to *Daliresp* and *Tudorza Pressair* (aclidinium bromide inhalation powder), also for COPD, from Actavis in February 2015. The latter transaction included additional pipeline assets and saw AstraZeneca pay \$600m up front. The Almirall deal cost it \$875m up front and up to \$1.22bn in milestones.

Respiratory products gave AstraZeneca around a fifth of its revenues in 2014, with around 39% generated in the US. The firm's second-best selling drug overall was *Symbicort* (budesonide + formoterol), its inhaled therapy for asthma and COPD, with sales of \$3.8bn. But *Symbicort* is feeling the heat in a competitive market place and the company is having to lower prices and provide additional patient assistance programs. The transaction is expected to close in the first quarter of 2016, and will be immediately accretive to earnings from 2016. Upon closing, about 200 staff will transfer from Takeda to AstraZeneca.

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Business Bulletin

ViiV Buys New HIV Mechanisms From BMS

GlaxoSmithKline PLC's majority-owned ViiV Healthcare is buying a raft of novel late-stage and early stage HIV assets from Bristol-Myers Squibb Co which it hopes will offer new options for patients who have outlived the utility of other antiretrovirals, thereby expanding ViiV's pipeline and future product sales. As patients live longer and better with the HIV virus, many are outlasting the utility of various drugs and combination regimens that once suppressed the virus. ViiV hopes new treatments can come from the HIV candidates being bought from BMS which offer new mechanisms of action. Under the transaction, announced Dec. 18, ViiV will buy BMS's attachment inhibitor, BMS-663068, which began a Phase III trial in late February 2015 in heavily treatment-experienced HIV patients, who, because of drug resistance, past intolerabilities and/or drug contraindications, are not able to be treated with a viable three-drug regimen to suppress the virus. The drug, also known as fostemsavir, is designed to bind directly to the HIV gp120 protein, preventing viral attachment to the host CD4-positive T-cell and entry into the host immune cell. It has Breakthrough Therapy Designation from the FDA and is expected to be filed for regulatory approval in 2018, ViiV said. The second late stage asset being purchased from BMS is a maturation inhibitor (BMS-955176), currently in Phase IIb development for both treatment-naïve and treatment-experienced patients. A back-up maturation inhibitor candidate (BMS-986173) is also included in the deal.

Asian Firms Tweak Strategy Amid Biosims 'Stampede'

More biosimilar approvals for Asian firms in Western markets building on the success of players like Celltrion and Samsung and a shift away from local/regional development strategies were some of the key trends highlighted at a recent roundtable by Quintiles. Meanwhile, more firms join the biosimilars "stampede", with biologics worth about \$55bn in current sales set to go off patent by 2020. Dr Charu Manaktala, senior director and head of clinical strategy, strategic drug development, Quintiles Asia, said that there were more than 160 biosimilars in various stages of development for the six top-selling biologics such as *Humira* (adalimumab), *Enbrel* (etanercept) and *Rituxan/MabThera* (rituximab). "That's a huge number and attestation of the fact of how important these drugs are both from the healthcare and business perspective," Manaktala said. Manaktala referred to the rich pipelines of some Asian firms and also how they were now planning to develop products for global markets "right from the outset" rather than

the earlier approach of looking at local/regional markets followed by Western markets. "We are beginning to see a change in the development strategy for some of the Asian customers. This is supported by the availability of regulatory framework and guidelines as well as a better understanding of these requirements," she said. The Quintiles executive, though, declined to elaborate on the firms pursuing the global first approach.

AZ Strengthens China Hand

AstraZeneca, which unlike many of its multinational peers continues to show strong growth in China, is building on this with a large investment aimed at building capacity for the development and manufacture of pharmaceuticals in the region. The multinational has expanded an ongoing alliance with WuXi AppTec, a Chinese biologics manufacturer and contract research organization, to produce innovative biologics locally in China. AstraZeneca's MedImmune unit and WuXi set up a joint venture in 2012 to develop and commercialize MEDI5117, a fully humanized monoclonal antibody that targets interleukin-6, an inflammatory cytokine. The product is in clinical trials for the treatment of rheumatoid arthritis. Under their updated agreement, WuXi will remain AstraZeneca's exclusive partner for R&D manufacturing of innovative biologics in China, but AstraZeneca now has the option to acquire WuXi's biologics manufacturing capacity in Wuxi City in the next few years for around \$100m. AstraZeneca will also invest \$50m to build an additional facility alongside the existing manufacturing site in Wuxi City.

China Health Insurance Sector Entering Fast Track

What health issue is keeping company managers in China up at night? According to surveys conducted among middle management, the health issue of most concern is cancer. Employees want to know how to better protect themselves and their loved ones from getting the disease or being crushed by large treatment bills. While expanding national health insurance schemes are providing some protection against illness, it is in this environment that private healthcare insurance is burgeoning in China, although the sector still accounted for only around 3% of the country's total insurance market in 2014. Late last year, China's cabinet, the State Council, issued a policy to stimulate private insurance schemes to help meet increasing demand, with the coverage to include illness prevention, physical check-ups, and specialty drug, device and diagnostic services. The policy also encourages companies to provide health maintenance, chronic disease management and consulting services. Encouraged by such government policies and incentives, the market is expected to grow, and major global reinsurer Munich Re has now launched a program to help local insurance firms in China offer cancer insurance in the country. The program, started last year, is sold to individuals and groups and is offered as a standalone product or co-sold with other policies, says William Bossany, general manager of Munich

Re Health China. "We observe that the government is more actively promoting health insurance development, and the regulatory environment is now more mature for insurance companies to get into the health insurance business," he said.

Start-ups Stand Out

Venture capital and other private equity investment is booming with 13 recent drug developer financings totaling more than \$409m, including 10 startups with some large series A rounds, showing that the biotechnology industry remains attractive to investors even if the window is closing for initial public offerings in the US. The leader of the latest slate of biotech VC investments was Allena Pharmaceuticals Inc., which raised a \$53m series C round for its metabolic and orphan disease portfolio. However, other private equity sources also are funding drug developers, who may still provide an attractive return on investment via mergers and acquisitions despite the absence of a near-term IPO exit. For instance, the specialty vaccine maker PaxVax Inc. raised \$105m from a single investment fund and epigenetics-focused Constellation Pharmaceuticals Inc. closed a \$55m mezzanine financing backed by VC firms and other investors. It appears that the IPO window closed for biotech companies in November, since the last first-time offering by a therapeutics company was on Nov. 21 and there are no drug developers in the queue for a December IPO, but M&A still is very much an option for returning capital to biotech investors. The accounting and consulting firm Deloitte recently reported that life science and healthcare companies announced \$574bn worth of M&A deals during the first three quarters of 2015, exceeding the \$400bn in deal values disclosed for all four quarters of 2014, with biotech and pharma deal-making rising from about \$250bn in 2014 to roughly \$300bn for the first three quarters of 2015.

Valeant Stirkes Deal With Walgreens

In its latest effort to turn around its image and recoup its sales after its distribution network went bust, Valeant Pharmaceuticals is teaming up with Walgreens to offer its dermatology and ophthalmology products at discounted rates. Valeant announced Dec. 15 that it has inked a 20-year deal with the nation's largest retail pharmacy chain to distribute its products. Walgreens will sell Valeant's products at its 8,000+ locations. As part of the agreement, Valeant has said it will reduce the wholesale price of its dermatology and ophthalmology products by 10%. The pharma company will also offer this deal to independent pharmacies that have agreed to participate in distribution. Walgreens will begin offering the products in the first quarter of 2016 and the price reductions will go into effect over the next six to nine months. The deal includes the antifungal foot cream *Jublia* (efinaconazole), as well as the acne medication *Solodyne* (minocycline). Beyond that, Valeant will reduce the price of other products that have a generic equivalent – making its products available at the same cost as the generic alternatives. The price reductions will range from 5% to 95%, with an average discount of 50%. (Read more on p12.)

Amgen Reclaims Rights From GSK To Grow In Ex-US Markets

Amgen Inc. will reacquire ex-US rights to its cancer drug *Vectibix* (panitumumab) and bone drugs *Prolia* (denosumab) and *Xgeva* (denosumab) in 48 countries from GlaxoSmithKline PLC, which generated \$111m in combined revenue from the products in 2014.

The transaction will give Thousand Oaks, California-based Amgen an opportunity to expand its presence in emerging markets and grow its cancer and bone health infrastructure ahead of future product launches in those regions. The company will add its own resources in certain markets, but it will not take on any GSK employees who already are selling the products, Amgen spokesperson Kristen Davis said.

"Amgen originally partnered with GSK in these international expansion markets to capitalize on GSK's established presence in these markets. At the time, Amgen had little or no presence in many of the markets and decided to focus resources on other business activities and priorities," Davis told *Scip*. "Amgen now has a stated intention of growing the business internationally to ensure that we can serve an increasing number of patients around the globe. This transaction is part of this strategic goal and is an important part of our international expansion plans."

Financial terms of the new arrangement between Amgen and GSK were not disclosed, but GSK will earn milestone fees based on signing the agreement and successfully transitioning the biologics back to Amgen. The transaction will be accretive to Amgen earnings in 2017.

GSK originally licensed ex-US rights for *Prolia* and *Xgeva* in 2009 and for *Vectibix* in 2010 in markets that include Brazil, China, Colombia, Hong Kong, Israel, Singapore, South Korea, Taiwan and Thailand. In some countries, primarily in Asia, GSK only has commercial rights for *Prolia* and *Xgeva*, but the UK-based company holds the rights to both bone-strengthening drugs plus *Vectibix* in other markets.

"In some cases, Amgen will build a commercial presence to support the products. Commercialization decisions will be made on a country-by-country and product-by-product basis," Davis said.

Amgen chair and CEO Robert Bradway noted in a statement issued by the company after the stock market closed on Dec. 14 that the new agreement with GSK "allows Amgen to build additional commercial infrastructure in oncology and bone health, two strategically important therapeutic areas for Amgen with emerging late-stage pipeline assets."

The company's stock closed 1.9% higher at \$158.11 on Dec. 14 and gained another 1.3% to reach \$159.52 in after-hours trading.

Prolia and *Xgeva* are growth products for Amgen and *Vectibix* has the potential to become a growth product for the company when it regains GSK's ex-US rights. Third quarter 2015 sales grew 19% to \$378m for *Xgeva*, including \$105m outside of the US, and 25% to \$320m for *Prolia*, including \$115m outside of the US.

Ex-US markets generate a majority of sales for *Vectibix*, for which sales declined 4% year-over-year to \$132m in the third quarter, including \$78m outside the US, so regaining GSK's rights to *Vectibix* overseas could give Amgen a needed revenue boost for the biologic.

Vectibix is an epidermal growth factor receptor (EGFR) inhibitor approved in the US for first and subsequent lines of treatment for certain patients with metastatic colorectal cancer (mCRC).

Prolia, a RANK ligand inhibitor, is approved in the US to treat osteoporosis. The biologic may face competition in a year or so from the late-stage candidates abaloparatide from Radius Health and Amgen's own romosozumab.

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AstraZeneca Picks Up Majority Acerta Stake

In a move which AstraZeneca PLC says "completes its transformation in oncology," it is acquiring a 55% stake in privately held Dutch biotech Acerta Pharma BV for \$4bn, made up of \$2.5bn now and \$1.5bn later. The deal also includes an option to acquire the remainder of the company for a further \$3bn.

Acerta has a "potentially best-in-class Bruton's tyrosine kinase inhibitor (BTKi)" in Phase III trials for chronic lymphocytic leukemia (CLL). The oral product – acalabrutinib – is being positioned as a direct challenger to AbbVie's *Imbruvica* (ibrutinib). AstraZeneca believes it could have peak annual sales of \$5bn, and its first regulatory submission could come as early as the second half of 2016.

AstraZeneca confirmed its interest in Acerta last week following publication in the *New England Journal of Medicine* of Phase I/II data from acalabrutinib (ACP-196) earlier in December. The data were also presented at the recent American Society of Hematology (ASH) annual meeting in Florida.

Datamonitor Healthcare analyst Dr Joseph

Hedden is slightly less enthusiastic about acalabrutinib's prospects versus *Imbruvica* than AstraZeneca.

"I don't think we are talking about a successor here," he told *Scip*. "This is not a scenario where acalabrutinib is taking on an average drug, with average efficacy, safety etc. *Imbruvica* is really good, and it will be moving to first-line as a monotherapy soon. In the RESONATE-2 trial of *Imbruvica* there is a high progression free survival rate after two years of therapy in newly diagnosed patients (aged 65+), and I expect by the time acalabrutinib comes to market *Imbruvica* will be well established as a first-line drug."

He also noted that while the response in heavily pre-treated and 17p del patients do seem higher for acalabrutinib than *Imbruvica*, "I would want to see the Phase III direct comparison before making any conclusions."

At the ASH presentation, Hedden saw a lot on enhanced pharmacokinetics, "high affinity for BTK but not other targets and achieving maximal BTK inhibition with a lower, twice daily

dose," with the suggestion that this should not only improve efficacy, but lower off-target toxicity and be well-tolerated. However, "*Imbruvica* hasn't exactly been a problem drug in terms of toxicity – not like *Zydelig* for example. It has been stressed that no atrial fibrillation or bleeding events have been seen so far. While these have been documented with *Imbruvica* they have been manageable and not serious enough for a black box warning. I don't see acalabrutinib as having a huge safety advantage at present, not enough to force a change in prescribing practices anyway."

Hedden noted that AstraZeneca has been touting the BTK-PD1 potential combination has having major promise, but he believes this is just a characteristic of the current trend in immuno-oncology. "Pairing targeted therapies with the 'immunos.' We have seen early pairing of an anti-CD20 (*Rituxan*, *Gazyva*) with a small molecule (*Imbruvica*, *Zydelig*, venetoclax) but it is far too soon to say whether this is going to be an effective approach," he said.

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Valeant Talks Taxes, R&D, Walgreens And 2016

On the heels of a transformative deal, Valeant Pharmaceuticals International is taking a hit to its business, but CEO Michael Pearson is optimistic that the company is poised for a turnaround.

At an investors day with analysts on Dec. 16, Pearson admits, “we probably weren’t the easiest company to partner with,” about the deal announced Dec. 15 with Walgreens. Valeant is replacing the controversy-embroiled specialty pharmacy Philidor with a contract with Walgreens that will mean a 10% reduction in prices for its dermatology and ophthalmology products, but will mean growth in volume, hinted the executive.

Valeant intends to be “conservative” in the roll out of the price-reduced products through Walgreens, but expects to begin the first phase in January.

But the recent success of the Walgreens deal – which boosted the company’s ailing credibility with investors – wasn’t the only thing that Pearson discussed during the four hour meeting. He addressed the company’s advantageous tax structure, as well as R&D spend.

The Canadian company is an anomaly in the industry in both respects. Valeant has one of the lowest tax rates in the industry due to its inversion with Biovail several years ago. The move to Canada allowed it to drop its tax rate sharply and Pearson credits his team for keeping that rate low. “Our tax team works harder than any other team,” he told analysts.

As for R&D spend, Pearson admits that the companies only spent about 8% of revenues this year on drug development. “We invest in what makes sense,” he admitted, saying the company is constantly making capital allocation decisions about where to invest. The company touted its more than 200 R&D programs across 43 facilities. Unlike many of its pharma brethren – who typically invest 17% to 20% of their topline on R&D, Valeant and Pearson have not been quiet about thinking that strategy foolish. The company’s oft-criticized (and just as often touted) business model has it buying already-marketed or near-to-market products on the cheap and then using its large sales force, as well as pricing strategies to make a profit.

The recent deal with Walgreens, while an improvement from its scandal-laden former distribution system, is a detour from that strategy. Pearson has said in recent months that Valeant would spend more time paying down its \$30bn in debt next year, insinuating that it would be making fewer acquisitions and bringing in fewer new products. According to the company’s new guidance, the pharma plans to reduce its debt by



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\$2.25bn in 2016. “The fact that we have no money for deals won’t stop us from doing them,” Pearson said, admitting traditional dealmaking will resume in 2017. “We will continue to do creative things.”

One of its creative moves involves employee retention; about 700 Valeant employees were offered cash, stock or a mix of both. The incentive was not offered to executive management or Pearson. The company expects to spend about \$75m to keep people at their jobs.

Lower Prices Mean Falling Sales

The company revised its guidance for the fourth quarter and the coming year, giving analysts a rather bleak outlook. Valeant now expects to have earnings per share in the range of \$2.55 - \$2.65 for the fourth quarter, down from a previous range of \$4.00 - \$4.20. Revenues will also take a major hit; the company now expects to bring in \$2.7bn - \$2.8bn for the quarter, down from \$3.25bn - \$3.45bn. The 18% revenue drop accounts for much more than the missing sales from Philidor, which only accounted for about 7% of Valeant’s total sales. Valeant admitted that the end of the Philidor relationship will cost the company \$250m in the final quarter of this year. It’s likely that the pricing controversy and scandal with Philidor has doctors changing their prescribing habits.

The company provided guidance for 2016 as well, expecting to bring in earnings per share of \$13.25 - \$13.75 apiece, missing analysts’ consensus estimates of \$14.20 per share. Revenues are expected to be in the range of \$12.5bn - \$12.7bn, in-line with

expectations. Valeant now expects to have cash flow from operations of about \$600m, down from its previous estimates of over \$1bn.

“Today’s announcement indicates that the specialty pharmacy impact is not only immediate, but somewhat worse than expected,” wrote BMO Capital Markets analyst Alex Arfaei in a Dec. 16 note. “While 2016 revenue guidance is in line with consensus, lower-than-expected EPS guidance indicates to us that the increase in expected volume from the Walgreens agreement is not enough to offset the loss of more profitable products from the specialty pharmacy business at higher prices, at least in the near term.”

Arfaei estimates that only \$1.4bn of 2016 revenues will come from the company’s dermatology business, which would mean a decline of almost 20% from this year.

Valeant was all doom and gloom during its meeting with analysts. The company expects its recently approved female libido drug, which is acquired through Sprout Pharmaceuticals for \$1bn, will have sales of \$100m - \$150m next year. The company hopes to rebrand it a bit and steer the focus away from it being “a female Viagra.” The company believes that patient expectations have been too high for the drug and that the sales force will have to focus on further physician education.

More Controversy

Valeant is still mired in controversy despite the steps it has taken to move forward and turn around its image. The company continued to defend itself on Dec. 16 when QLT accused the company of being delinquent on milestone payments that it owed.

Valeant contends that it doesn’t owe QLT anything until all approvals required to sell the product have been obtained and accused QLT of bringing up a two-year old claim at an advantageous time.

“In November 2015, after no attempt to pursue its contractual remedies and at a time that Valeant was in the news and experiencing substantial negative publicity, QLT sent a letter threatening to go public with its claims,” said Valeant in a statement.

Valeant called the actions “deeply disappointing” and “frivolous,” noting that going public with the claim would be “viewed as a bad faith, opportunistic attempt to damage Valeant in breach of your obligations under Section 10.7 of the Asset Purchase Agreement.”

Valeant has said it will continue to defend its position and believes that it does not owe anything to QLT, nor would it pay \$2m to keep QLT from going public with its claims.

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R&D Bites

Lantus Follow-On Basaglar OK'd

Eli Lilly & Co. and its partner Boehringer Ingelheim GmbH won the first-ever US approval of a follow-on version of Sanofi SA's *Lantus* (insulin glargine) – a clearance for marketing that was permitted under the FDA's 505(b)(2) abbreviated pathway, which permits an application to rely, in part, on safety and efficacy data from an innovator's product. Like *Lantus*, Lilly's and BI's drug, *Basaglar* (insulin glargine injection), is indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes and in adults with type 2 disease. US regulators said Lilly had demonstrated that *Basaglar*, a long-acting human insulin analogue, was "sufficiently similar" to *Lantus* to "scientifically justify reliance." But given the declining US sales of Sanofi's drug, it's unclear how successful *Basaglar* will be on the American market. Indeed, Sanofi reported in October that US sales of *Lantus* – the firm's top-selling drug – had plummeted 20%, causing the French company's overall diabetes franchise sales to drop 6.6% in the third quarter.

AZ Scores CHMP Hat Trick

AstraZeneca PLC won three positive opinions in the latest pronouncements from the European Medicines Agency's top drug advisory panel, giving fresh support to the British pure pharma's expanding pipeline. Most notable of the three recommendations by EMA's Committee for Medicinal Products for Human Use (CHMP), announced Dec. 18, was for *Tagrisso* (osimertinib), a daily tablet for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a mutation in the EGFR gene. Mutations of the EGFR gene may develop in tumors and reduce the effect of EGFR-blocking medicines. *Tagrisso* is intended for use in tumors with one such mutation, T790M. The CHMP reviewed *Tagrisso* under EMA's accelerated assessment program and recommended conditional approval for the medicine. These are two of the European agency's main mechanisms to facilitate earlier access by patients to medicines that fulfill unmet medical needs. At its latest meeting the CHMP also backed AstraZeneca's heart drug *Briqique* (ticagrelor) at 60mg dosing for treating patients with a history of heart attack and at high risk of having a further atherothrombotic event; and *Zurampic* (lesinurad) in combination with a xanthine oxidase inhibitor (XOI), was also recommended for the adjunctive treatment of hyperuricaemia in adult gout patients who have not achieved target serum uric acid levels with an adequate dose of a XOI alone.

AZ's PD-L1 Data Not Enough For Lung Cancer Filing

AstraZeneca PLC's chief medical officer has warned once again that a trial of the company's PD-L1 inhibitor durvalumab will not provide strong

enough data to support a regulatory submission for the drug as a standalone treatment for advanced lung cancer. However, preliminary findings from the company's lead monotherapy trial, ATLANTIC, show that it does work. Durvalumab demonstrated clinical activity and durable responses in third-line or later stage patients with programmed death ligand-1 (PD-L1)-positive non-small cell lung cancer (NSCLC) that lacks epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) alterations, according to an initial analysis of the Phase II single-arm study. The company said it would fully evaluate the data and present the results at a scientific congress in 2016. As previously reported in *Scrip*, however, advances by competitors in the lung cancer space means AstraZeneca no longer expects to be able to file for approval of durvalumab as a monotherapy based on the ATLANTIC data – although CMO Sean Bohan said the final decision would be made after a full analysis of the data.

Merck's Bridion Wins FDA Approval, Finally

After previously being rejected three times by the FDA, Merck & Co.'s *Bridion* (sugammadex), an injectable drug intended to reverse neuromuscular blockade induced by rocuronium or vecuronium – agents used during certain types of surgical procedures – finally made it across the US regulatory agency's finish line on Dec. 15. *Bridion*, a modified gamma-cyclodextrin agent, currently is marketed in about 60 foreign countries, but Merck had struggled in convincing the FDA to approve the product. The product initially was developed by Dutch drug maker Organon, which was acquired in 2007 by New Jersey pharma Schering-Plough Corp. – a company Merck bought in 2009. Organon had submitted the original new drug application (NDA) for *Bridion* in October 2007, with the medicine winning a unanimously recommendation for approval in March 2008 by a panel of FDA advisers. But the FDA in July 2008 rejected the NDA, telling Merck it needed to characterize the safety of the drug on repeat exposure, specifically the nature and frequency of anaphylaxis and other hypersensitivity reactions, and to define the frequency and time course of events related to the agent's administration and other characteristics of the adverse reactions. After conducting further trials, which also faced controversy due to concerns that investigators may have been unblinded to treatment assignment, Merck has finally secured an FDA nod. Regulators said clinicians should be aware of the possibility of a hypersensitivity reaction or anaphylaxis and should intervene as appropriate. The FDA also warned in a statement that cases of marked bradycardia – abnormally slow heart action – some of which have resulted in cardiac arrest, have been observed within minutes after the administration of *Bridion*.

EMA Accepts Neulasta Biosimilar Filings

Amgen's *Neulasta* (pegfilgrastim) is coming under increasing competitive pressure after the European Medicines Agency revealed that its scientific committee, the CHMP, has two biosimilar versions

of the neutropenia drug under review. Gedeon Richter plc announced on Dec. 8 that it had filed for EU approval of its biosimilar pegfilgrastim, seeking the same indications as *Neulasta*. Earlier this year the Hungarian company signed a licensing and distribution agreement with Germany's Stada, and the biosimilar is expected to be launched by the two firms in geographical Europe (excluding Russia) once the originator's patent expires, Richter said. The Richter drug is presumably one of the two products listed by the EMA, but the identity of the other remains unclear, as the EMA does not divulge any other details of filings beyond the substance name. Two likely candidates are Sandoz and Apotex, which have both submitted biosimilar pegfilgrastim products to the US Food and Drug Administration. Sandoz declined to comment on whether it had also filed pegfilgrastim with the EMA, saying only that it had "the declared goal of filing 10 biosimilar submissions between 2015 and 2017", of which three were etanercept (Amgen/Pfizer's *Enbrel*) and pegfilgrastim in the US, and etanercept in the EU. Apotex's pegfilgrastim product has been developed with India's Intas Pharmaceuticals, whose offshore marketing arm, Accord Healthcare, gained EU approval of a version of filgrastim (Amgen's *Neupogen*) last year. At the time of publication, Apotex had not responded to an enquiry from *Scrip* as to whether it had filed pegfilgrastim in the EU. Apotex already has approval for a biosimilar filgrastim product in the EU, as does Sandoz.

Kitov Plans 2016 NDA For Arthritis Combo Drug

Kitov Pharmaceuticals, which went public in the US in November, ended Dec. 15 with a 25.2% stock price gain at \$4.47 per share based on positive Phase III results for lead drug candidate KIT-302 and the Israeli company's plans to seek US FDA approval for the treatment of osteoarthritis. KIT-302 combines Pfizer Inc's former blockbuster and now generic non-steroidal anti-inflammatory drug (NSAID) *Celebrex* (celecoxib) with the calcium channel blocker amlodipine besylate, a longtime generic hypertension therapy sold by Pfizer as *Norvasc*. Kitov's two-drug combination pill exceeded the 152-patient Phase III clinical trial's primary endpoint, which was a reduction in daytime systolic blood pressure that is at least 50% of the decrease achieved with amlodipine besylate alone. Tel Aviv-based Kitov will submit a new drug application (NDA) to the FDA in the second half of 2016 based on the Phase III data, which show that the mean blood pressure reduction of 10.6mm/Hg for patients treated with KIT-302 for two weeks exceeded the mean decrease of 8.8mm/Hg in the amlodipine besylate-only group (p=0.001). Results for celecoxib-only and double placebo groups were not reported, and Kitov did not disclose any effects of KIT-302 on inflammation and pain – two factors that are important to osteoarthritis patients. Neither inflammation nor pain were endpoints in the study. Kitov expects KIT-302 to be the first NSAID indicated for the treatment of both osteoarthritis pain and hypertension with the potential to lower healthcare costs by treating two conditions with one drug.

Baxalta Races Full Steam Ahead Into 2016 With Hematology At The Fore

Baxalta Inc. is “energized and optimistic” for the New Year and expects to continue building up a strong portfolio and research pipeline on the back of a successful first 6 months as an independent new business.

Dr. John Orloff, chief scientific officer and head of R&D at Baxalta – which was spun out from Baxter International in 2014 as a biopharma-focus unit – told *Scrip*, following a number of clinical updates presented by the company at the America Society for Hematology (ASH) annual meeting held earlier this month, that his company has “a lot of momentum coming into 2016.”

“We had a successful 2015 and Baxalta is a very active organization that has been transformed over the last year and a half. We are very energized and optimistic for the value creation we will continue to develop moving forward into the New Year,” he said.

In recent weeks Baxalta has received US FDA approvals for two new blood disorder treatments: in early December, Vonvendi (BAX 111) was approved to treat rare inherited bleeding disorder, von Willebrand disease; and *Adynovate* (BAX 855), an anti-hemophilic factor (recombinant) PEGylated product, was approved for use in hemophilia A patients in late November.

BAX111, for von Willebrand disease, joins a market of around four approved therapies for the condition but Baxalta’s offering is the first recombinant option. “Our product can be produced to meet patient needs, for example, if the patient’s Factor VIII levels are low, Vonvendi can be combined with Factor VIII but if their levels are okay it can be given without. It will help personalized treatment to patients,” Orloff said.

Von Willebrand disease affects up to 1 in 100 people, making it the most common inherited bleeding disorder worldwide but the condition varies in severity. Type 3 disease, the most severe form, affects only 1 in a million people worldwide. Vonvendi is a synthetic version of von Willebrand factor, a protein key to the coagulation process. Orloff said the therapy is expected to be filed for approval in Europe in 2017, following a pediatric study that is due to start in the second half of 2016.

Meanwhile, Baxalta’s CSO said newly approved hemophilia A treatment *Adynovate*, a product that has a longer half-life compared to standard by one and half fold, “gives patients another option,” for their treatment. Launch is under way for this product in the US and Baxalta will file for approval in Europe in the first

quarter of 2016. As required by the European regulators, the company is conducting pediatric trials for *Adynovate* in both previously treated and treatment naive children.

Baxalta is also developing a gene therapy product for the treatment of hemophilia B. However, in early dose-ranging trials for the product, the company was met with concerns around T-Cell immune responses in patients. Orloff said these responses were seen in patients given the high dose of the treatment. “We wanted to push the dose up to that ceiling but we have since come down and a patient has seen 20-25% expression on this second dose cohort,” he said.

So far eight patients have been treated with the gene therapy product and Orloff said the company expects to dose up to 16 patients in the current clinical trial before moving into Phase III. “We are starting to solidify the correct dose for a Phase III trial,” he said.

Hemophilia is becoming a better served patient population with a number of key players involved in drug development for this disease. However, Orloff said Baxalta is “committed to continuing and maintaining our leadership in this space. It has been our legacy to be leaders in hemophilia.”

He said moving forward Baxalta will approach “alternative treatments” for the disease beyond factor replacement. “Both hemophilia A and hemophilia B are factor deficiencies and our whole approach has been to replace the factor that is missing. Successfully, we keep pushing the envelope with longer half-life products to give patients more options for treatment,” Orloff said. “However, as we look at the competition there are alternative mechanisms emerging that are not based on factor replacement. I think there may be a role for these products in the treatment of patients with inhibitors – here there is some unmet need as there are patients who continue to bleed on factor replacement products.”

Elsewhere in its hematology pipeline Baxalta has a program in thrombocytopenia, a rare disease that Orloff said has current treatment options which “have been in the dark ages for some time.”

Baxalta’s product uses a recombinant enzyme opposed to plasma (standard of care) for the treatment of thrombocytopenia. The therapy is currently being tested in a Phase I trial, but Baxalta expects to “ramp up manufacturing in 2016,” and it aims to launch a late-stage study the following year.

M&A Frenzy Outside; Cool Focus On Growth Within

Baxalta has been at the center of a number of M&A rumors since it went public in July this year; including one official takeover bid from Ireland-based specialty pharma, Shire, in August – which continues to rumble in the background. However, Baxalta’s management has not been keen on the idea of a buyout so soon after the company’s founding as an independent firm.

Shire initially went directly to Baxalta’s board with a bid after the new company became a public entity, offering a stock-swap in which it would issue 0.1687 shares in Shire for every full share in Baxalta, valuing its target at roughly \$30bn. But Baxalta quickly turned down that offer, which would have given it a 37% interest in the combined company. However, as recently as the third-quarter earnings season, Shire continued to tout the benefits of a merger with Baxalta.

Orloff said of a possible takeover in the future, that while it wasn’t his area to comment on specifically, “The company feels strongly about its pipeline, the value we create and the products we are developing for patients.”

He added: “We have our nose to grindstone developing a strong pipeline and the organization is really committed to this effort. Since the spinout from Baxter you can see that we at Baxalta are really committed to our portfolio development, as is evident by all of our submission ongoing and the recent approvals we have received. I think this shows the commitment people at Baxalta have despite the potential distractions of takeover talks and rumors.”

While Baxalta may be playing small fish to bigger M&A predators, it is not at the bottom of the food chain itself. The company has a model based on external innovation, Orloff said, noting that of its current six oncology products, only one is derived from its own labs.

“We have a research group in Vienna supporting the development of our hematology gene therapy pipeline and we also have a small group in Munich, Germany, working on autoimmune diseases. Outside of these groups we have no plans to build our own specific research units, so any new assets we would want to bring into the pipeline will come from external environments,” Orloff said. He said the company is seeking assets that will fit with its key areas of hematology, immunology and oncology – preferably clinical stage programs.

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GSK, J&J Plan Filings For Third-To-Market IL-6 Inhibitor Sirukumab

GlaxoSmithKline PLC and Janssen Biologics, a Johnson & Johnson subsidiary, will seek regulatory approvals for sirukumab in 2016 based on positive Phase III results in rheumatoid arthritis, setting the biologic up to compete with two other interleukin-6 (IL-6) inhibitors when it hits the market in 2017.

GSK said on Dec. 16 that there were no unexpected safety findings during the companies' three Phase III trials in moderately to severely active RA, but detailed data will be reserved for future conference presentations and journal publications. If approved following 2016 regulatory submissions, sirukumab will launch years behind Roche's IL-6 inhibitor *Actemra* (tocilizumab) and probably months after the forthcoming competitor sarilumab from Regeneron Pharmaceuticals Inc. and Sanofi.

Competition may be fierce among the first three IL-6 inhibitors for RA, since Roche has a \$1bn-plus interest in maintaining its blockbuster market share

Actemra was approved in the US as an intravenous treatment in 2010 and as a subcutaneous injection in 2013. The biologic generated \$1.1bn globally in the first nine months of 2015, which was up 22% from the same period in 2014.

Meanwhile, Regeneron said in its third quarter earnings report on Nov. 4 that it recently submitted a biologic license application (BLA) for sarilumab to the US FDA, which means the IL-6 inhibitor could be approved and on the market before the end of 2016. Positive top-line Phase III results for sarilumab were reported in May.

Competition may very well be fierce among the first three IL-6 inhibitors for RA, since Roche has a \$1bn-plus interest in maintaining its first-mover status and blockbuster market share.

Also, Sanofi and new CEO Olivier Brandicourt include sarilumab in the French big pharma's basket of six key products that will drive revenue growth with a combined peak sales total of €12bn to €14bn.

And then there's sirukumab, which could be a significant new product for GSK and J&J as well. Approval of the IL-6 inhibitor for RA will help GSK maintain a diverse immunology and inflammation portfolio that currently is heavy in respiratory therapies and allergy treatments,

although the company also intends to develop sirukumab as a treatment for asthma.

For J&J, sirukumab could help the company make up for sales lost to *Remicade* (infliximab) biosimilars that launched outside the US in 2015 and which could hit the US market in 2017, UBS analyst Matt Miksic noted in a Nov. 23 report.

However, like *Actemra*, sarilumab and sirukumab are likely to struggle for major RA market share given the propensity of rheumatologists to prescribe tumor necrosis factor (TNF) inhibitors like *Remicade*, Amgen Inc.'s *Enbrel* (etanercept) and AbbVie Inc.'s *Humira* (adalimumab) before any other biologic. Biosimilar *Remicade* and future *Humira* and *Enbrel* biosimilars also could make it more difficult for brand-name alternatives to TNF inhibitors to gain market share.

Datamonitor Healthcare expects sarilumab and sirukumab to perform in the commercial market like *Actemra*, which means the new therapies will compete only with non-anti-TNF therapies.

A recent study in Slovenia suggested that a second anti-TNF may not be the best option for patients who fail first-line treatment with a TNF inhibitor, and larger studies along the same lines are under way, but it remains to be seen how the outcomes of those inquiries will impact *Actemra* or IL-6 uptake in the future.

For sirukumab, a Phase III extension study is ongoing to assess longer-term safety and efficacy in patients with moderate to severe RA, but the Phase III studies that GSK highlighted on Dec. 16 include: SIRROUND-D, a placebo-controlled study with 1,670 individuals who did not respond to disease-modifying anti-rheumatic drugs (DMARDs); SIRROUND-H, a study that compared sirukumab with *Humira* in 559 biologic-naïve patients who could not tolerate or were unresponsive to methotrexate, or who were not good candidates for the oral drug; and SIRROUND-T, an 878-patient placebo-controlled study in people who did not respond to or couldn't tolerate anti-TNF biologics.

SIRROUND-LTE, the extension study, enrolled patients from SIRROUND-T and SIRROUND-D. A fifth Phase III clinical trial, SIRROUND-M, is a placebo-controlled trial in Japanese patients who are unresponsive to methotrexate or sulfasalazine.

Outside of RA, GSK initiated a Phase III clinical trial for sirukumab in November for the treatment of giant cell arteritis (GCA), an inflammation of the lining of the arteries that occurs most frequently in the temples. *Actemra* also is being evaluated in a Phase III trial for GCA.

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Apotex Seeks To Dance Quick Step In Biosims Appeal

Apotex Inc. revealed in court documents late on Dec. 14 that it anticipates the FDA to make a decision on the company's 351(k) application for its pegfilgrastim biosimilar "within the next several months" – providing some insight into the status of the product, whose verdict was due nearly two months ago and for which the firm has kept a tight lip.

Apotex made the disclosure as part of its motion to the US Court of Appeals for the Federal Circuit, in which the company is seeking an expedited appeal of a Florida court's decision to impose a preliminary injunction (PI) that prevents the firm from marketing its pegfilgrastim biosimilar for 180 days after FDA approval.

The biosimilar is referenced on Amgen Inc.'s long-acting human granulocyte colony-stimulating factor (G-CSF) *Neulasta*.

Amgen has accused Apotex of violating the disclosure and negotiation procedures of the Biologics Price Competition and Innovations Act (BPCIA) – the law that gave the FDA the authority to approve biosimilars. But with the FDA's action on the pegfilgrastim biosimilar on its way – albeit still under a vague timeline – Apotex is arguing the PI, issued on Dec. 9, is causing "immediate harm" to the company because it would be prevented from putting the product on the market right away once the firm got regulators decision in hand.

In its motion, Apotex actually noted there's plural "product(s)" awaiting approval at the FDA. Indeed, along with its pegfilgrastim biosimilar, Apotex's 351(k) application for its filgrastim biosimilar, which is referenced on Amgen's human granulocyte colony-stimulating factor *Neupogen*, was accepted by the FDA in February.

Apotex noted that even under an expedited schedule, the FDA may approve the company's "product(s)" before the Federal Circuit issues an opinion.

The company also said there was "good cause" to expedite the appeal and oral arguments because it is "narrowly focused" on a single legal issue: whether the notice of commercial marketing provision of the BPCIA is mandatory when a biosimilar applicant has complied with the law's notice and disclosure requirements – the so-called patent dance.

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How England Might Just Solve The Cancer Drugs Problem



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A sustainable way for oncology drug manufacturers to get their treatments to patients in England could finally be a reality soon. NHS England and HTA body the National Institute for Health and Care Excellence (NICE) have put forward their provisional plans for conditional reimbursement, which could help promising but “data lite” drugs that would have come unstuck under the old system.

A better system for reviewing whether cancer drugs should be funded on the National Health Service is overdue. A 2010 report by the then National cancer director for the Department of Health, Sir Mike Richards, found that the UK came tenth out of 14 high-income countries in terms of overall cancer drug uptake and 12th when comparing uptake of cancer drugs older than five years. The Conservative Party's short-term solution, when it won a majority in the new coalition government in 2010, was a new Cancer Drugs Fund (CDF). This would run from 2011 to 2014 with a £200m a year budget (plus £50m for October 2010 to March 2011) and would provide access to drugs that were rejected by NICE, or awaiting or undergoing an assessment. A new value-based pricing system for innovative new drugs, to be ready for 2014, was supposed to make the fund redundant. But VBP never materialized and the fund will stagger on until 1 April 2016. Its total budget, set initially at £650m, will reach £1.27bn by the end of the fund's life span.

The fund did improve access, says the National Audit Office's (NAO) Investigation into the Cancer Drugs Fund. “The Fund has become part of mainstream cancer services – in 2014-15, it supported almost one in five of the patients starting a new chemotherapy treatment ... Between 2009 and 2013, use of new cancer drugs (those launched in the previous 5 years) increased in the UK relative to the average in other comparable countries,”

said the report. But it did nothing to address the failings in the system, and the overspend prompted NHS England to slash numerous drugs from the list of funded treatments. Critics claim the CDF was a colossal waste of time and money. “It was never sensible and did what everyone thought it would do; be shambolic and overspend. England has wasted five years not putting in place a sensible and sustainable policy,” said Eric Lowe, chief executive of Myeloma UK.

One of the big failings of the current NICE system is that it has difficulty recommending drugs for rare or end-of life cancers. Certainly, NICE has been less disposed to say yes to oncology drugs. According to the NAO's investigation, NICE recommended or partially recommended 47 of the 102 cancer drugs it appraised. “This positive recommendation rate, 46%, was lower than the rate for other drugs, 81%,” it says. However, drugs rejected by NICE are routinely available elsewhere in Europe and without the help of a dedicated fund. For example NICE said no to Roche's Avastin (bevacizumab) for several types of cancer, but Roche says it is widely reimbursed in Europe. It is funded in 26 out of 28 European countries for metastatic colorectal cancer and in 20 countries for metastatic breast cancer.

One issue that has lead NICE to say no is uncertainty as drugs for rare diseases and end-of-life conditions seldom come with the full data packages that HTA bodies would like to see. NICE decides whether a drug is cost-effective based a drug's cost per QALY (quality adjusted life year) and treatments costing more than £20,000-£30,000 per QALY are not generally considered cost-effective, although NICE can use limited flexibility for end-of-life drugs to boost this up to £50,000 per QALY. The system works well to secure value for money for chronic disease treatments but uncertainty drives up the cost per QALY for

drugs for end-of life or rare diseases so that they do not appear cost-effective.

The details for the new scheme are still out for consultation as Scrip 100 goes to press and as yet are sketchy, but they do give NICE the opportunity to deal with uncertainty. It will be able to publish one of three initial recommendations around the time of marketing authorization: “recommended for routine use”; “not recommended for routine use”; and crucially “recommended for use within the Cancer Drugs Fund.”

The latter means that NICE will not have to reject outright promising drugs backed by data that is too weak to secure a positive recommendation. Instead, the company has up to 24 months to collect a pre-determined data set (which the company has to finance), during which time the drug is to be financed by an interim “managed access fund.” When the evidence is in, NICE will review the product again and consider the impact of the new data on cost-effectiveness. It will then decide whether to recommend it for routine funding. Cost-effectiveness thresholds look set to stay the same as the cost per QALY for these drugs financed by the interim fund “must have the potential to lie within the current thresholds specified by NICE.”

More flexibility to deal with uncertainty has improved access to the same medicines in other countries where authorities ask companies to gather more evidence, perhaps in the form of a new trial, observational data, or a registry. For example, NICE rejected Celgene Corp's Imnovid (pomalidomide) for multiple myeloma, citing substantial uncertainty regarding its relative effectiveness. But according to Celgene, other countries found a way to deal with this uncertainty. The firm highlights a pilot “pay for benefit scheme” in the Netherlands that gathers evidence involving a “value-based price.”

These types of agreements appear across Europe. Italy agrees to fund expensive cancer drugs on the condition that a registry is set up to accumulate more data, says Mondher Toumi, director of the European Market Access University Diploma at the University of Lyon, France. And in Germany, the G-BA, the body in charge of HTA assessments, can issue a “time limited resolution,” which means the decision is valid for a set period until more data is generated. In France a company and a payer agree a price and when there is uncertainty they set another higher price with the difference held in a bank account. If the company comes back with enough additional evidence to justify the better price, that extra money account goes to ➤

the firm. If not, it goes back to the health service. Toumi believes that something like this could complement a new conditional reimbursement system in England.

A lack of flexibility in dealing with uncertainty in England has been disappointing for firms and companies will likely be pleased at the chance to remedy this. The patient access schemes approved by the department of health to help companies improve cost-effectiveness for NICE could in theory include evidence generation to support a higher price later on. But by November 2015, 43 out of the 61 patient access schemes accompanying NICE recommended drugs involved simple discounts with other types of scheme seemingly being phased out. Wim Souverijns, general manager of Celgene UK and Ireland, says that the company would welcome the chance to commit to outcomes in relationship to prices and revenue generated by the products in question. "But feedback from the department of health [has been] 'don't come back with any complex schemes, stick with the rebates and we are happy'. It's sad because we could do so many things together to measure impact and outcomes and to educate the system." Souverijns believes a fantastic opportunity has so far been missed.

Another issue impacting the availability of

cancer drugs is price. Industry's critics claim it has been slow to adapt to a changing market that can no longer afford to pay whatever companies ask. Myeloma UK's Lowe is unimpressed with the prices companies charge for end-of-life drugs. "They don't listen to the market or to their customers. Up until now we've just accepted that we pay premiums for drugs that bring side-effects, marginal benefit and poor data... In no other industry does this happen." But whether reasonable or exorbitant, UK prices are similar, if not lower than elsewhere in Europe. Roche's UK prices have come under heavy fire. Nevertheless, they are not much different from what the firm charges in other countries, says Tina Bachelor the firm's head of communications. "The difference is that other European markets don't demand a big discount... only in England because of financial pressures." Roche had to give two discounts to make sure Kadcyra (trastuzumab emtansine), rejected by NICE and reimbursed in 15 other European countries, stayed on the Cancer Drug Fund's list.

Other countries have other ways of reigning in spending if treatment could be costly. Common in Italy and France are volume caps, which see companies repay the health service if they sell beyond fixed quotas. In France, which Toumi describes as a low-price

high-volume market, the more a company exceeds the quota, the bigger the rebate it gives, which can equate to a 50-60% discount on the drug. Another interesting idea, says Toumi, is that companies operate within a fixed budget based on assumptions about the money available and how many patients need treatment. The price is then set according to those assumptions and companies must repay any money if they exceed that budget.

Under England's new system, companies will have to come up with a "managed access agreement" based on what the drug will cost the NHS and the data collection agreement. But this is only for drugs entering the interim fund, and the impact on pricing strategies for drugs entering routine funding is unclear.

Meanwhile, big prices may be less palatable for England because it spends less overall on medicines than other comparable markets. The UK spends around \$400 per capita on pharmaceuticals, which is lower than spending in Spain, Italy, France and Germany, says Toumi. Germany and France spend around \$600 per capita, he adds. In 2011 the UK spent less on medicines as a percentage of GDP than Japan, the US, France, Spain, Italy and Germany, says the Office of Health Economics. The new system is unlikely to have any effect on the UK's drug budget.

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Galapagos Soothed By Gilead's \$725M Up Front For Filgotinib

Galapagos NV, which suffered a major shock in September when AbbVie decided not to exercise its option on their JAK1 inhibitor filgotinib, has secured \$725m up front from Gilead Sciences Inc. for the promising rheumatoid arthritis treatment.

The September decision by AbbVie sent Galapagos' share price plummeting: it lost 27% of its value in a matter of hours to close at \$44.60 (Sept. 25).

The latest news did not prove to be a total salve for Galapagos. Its stock price climbed by just over 11% and shares were trading at \$58.54 around midday GMT (Dec. 17).

Under the latest agreement, Galapagos and Gilead will collaborate on the global development of filgotinib starting with the initiation of Phase III trials in rheumatoid arthritis. Galapagos will co-fund 20% of global development activities and Gilead will be responsible for manufacturing and worldwide marketing and sales activities.

Galapagos has the option to co-promote filgotinib in the UK, Germany, France, Italy, Spain, Belgium, the Netherlands and

Luxembourg, in which case the companies will share profits equally. If Galapagos exercises its option to co-promote in Belgium, the Netherlands or Luxembourg, it will also book sales in these countries.

Galapagos will receive an upfront license fee of \$300m and Gilead will make a \$425m equity investment in Galapagos at €58 per share, which represents a 20% premium to the average share price over the last 30 days. After this, Gilead will own around a 15% stake in Galapagos.

Galapagos is eligible for further development, regulatory and commercial milestone payments up to \$1.35bn, plus tiered royalties on global sales starting at 20%, with the exception of the co-promotion territories where profits will be shared equally.

AbbVie Rejection

AbbVie, which apparently failed to give Galapagos a heads up about the decision ahead of issuing a press release, said it would be pursuing its internally-developed candidate ABT-494 instead of filgotinib.

The choice was a total shock to investors who had assumed AbbVie's opt-in was merely a formality after the stellar Phase II data that Galapagos announced in mid-August. At that time, Galapagos and analysts were calling data from filgotinib potentially best-in-class. Analysts were particularly impressed with the safety data for the drug, which they believed could be a major differentiating factor.

The rationale behind AbbVie's decision was speculated to come down to finances.

When AbbVie and Galapagos inked their initial partnership in 2012, AbbVie (then Abbott Labs) paid \$150m upfront and \$250m in milestones up until the delivery of Phase II data in rheumatoid arthritis. Galapagos was also eligible for another \$1bn in development, regulatory and sales milestones, as well as double digit royalties on the drug.

While AbbVie's decision prompted concerns about the integrity of the Galapagos drug, it is more likely AbbVie was trying to avoid paying \$1bn in further milestones or splitting potential revenues with its own product.

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Policy & Regulation Briefs

All Eyes Are On New Patent Court

The final step in creating a unitary patent system in Europe has been taken with the completion of a legal framework containing the implementing and financial rules for the new patent as well as the rules governing the level of renewal fees and the distribution of the fees among the European Patent Office and the participating member states. Describing the move as a “hugely significant occasion for the European patent system,” EPO president Benoît Battistelli said that preparations for the unitary patent were now complete. “We are now legally, technically and operationally ready to deliver the unitary patent. The only remaining step is the opening of the Unified Patent Court and the finalization of the ratification process at national level. We hope this will happen in 2016 and we are convinced that it will boost innovation in Europe and will be beneficial for the European economy, especially for European SMEs.” In future, the EPO will be able to issue patents with unitary effect across the participating countries (ie, practically all of the EU member states), and they can be challenged or enforced in the new Unified Patent Court. At least 13 countries (including France, Germany and the UK) must ratify the UPC agreement before it can start operations – so far eight countries, including France, have done so, “with several more expected to ratify shortly,” the EPO said. Agreement on the distribution of income generated by the payment of renewal fees was reached last month by the Select Committee, which consists of representatives of countries taking part in the new system. The EPO will be entitled to 50% of each renewal fee, while the other 50% is to be distributed among the member states participating in the unitary patent scheme.

BioMarin’s Vimizim Gets NICE Final Nod

BioMarin Pharmaceuticals’ enzyme replacement therapy, *Vimizim* (elosulfase alfa), has been given the thumbs up by NICE, the UK’s health technology appraisal body, for use on the National Health System to treat mucopolysaccharidosis patients. On Dec. 16 NICE issued final guidance under its Highly Specialized Technologies Program recommending Vimizim for use on the NHS to treat mucopolysaccharidosis type IVa (also known as MPS IVa and Morquio A syndrome). The HTA’s decision followed the development of a managed access scheme by BioMarin and NHS England. The five-year, fixed fee agreement – the first of its kind in UK – includes a mechanism to monitor how well the medicine has worked in practice before future funding decisions are taken. Affecting around



88 people in England and approximately 3,000 people worldwide, mucopolysaccharidosis type IVa is an extremely rare, inherited lysosomal storage disease. People born with the disease lack the N-acetylgalactosamine-6-sulfatase enzyme, which is responsible for breaking down large sugar molecules (glycosaminoglycans) in the body that cells can’t use. NICE’s evaluations put the cost of the drug at around £394,680 per patient annually. Based on the estimate that 77 people may want the treatment, the cost of Vimizim could amount to £30m per year. The discount offered to the NHS was not disclosed but Meindert Boysen, technology appraisals program director at NICE, said: “The committee concluded that the combined funding arrangements specified in the managed access agreement offered acceptable value for money in the context of the uncertainty of the clinical benefits and will be used to inform a future review of this guidance.” Vimizim was approved in Europe in April 2014 and is also available in the US, Canada, Australia and Brazil.

Frustrated Roche Hopes NICE Will Eventually Back Kadcykla

Roche Holding AG hopes the UK’s National Institute for Health and Care Excellence will continue seeking possible ways to provide the Swiss drug maker’s breast cancer therapy *Kadcykla* (ado-trastuzumab emtansine) on the publicly-funded National Health Service despite rejecting it in final guidance on cost grounds. NICE on Dec. 16 confirmed its earlier stance to reject the therapy despite the Swiss company’s offer of a price discount. The cost-effectiveness agency issued similar guidance in 2014. Still, Kadcykla will remain available in England through the British government-funded Cancer Drugs Fund (CDF). Roche voiced disappointment over NICE’s latest decision. “We have written to NICE to say that we are prepared to offer the same discount that was required to retain Kadcykla on the CDF,” a spokesperson for the Basel-based group said, without disclosing what that was. But a spokesperson for the HTA in a statement replied that “although Roche recently agreed a price discount with NHS England to allow Kadcykla to be retained on the Cancer Drugs Fund, they made no changes to the patient access scheme available for the NICE appraisal, which means it is still above the top of our specially extended range of cost effectiveness

for cancer drugs.” Kadcykla is licensed to treat HER2-positive breast cancer which has spread to other parts of the body, cannot be surgically removed and has stopped responding to initial treatment. It costs about £90,000 per patient at its full list price.

NICE Rejection Of Celgene’s Otezla Finalized

NICE, the health technology appraisal body for England and Wales, has issued final guidance not recommending Celgene’s psoriatic arthritis drug *Otezla* (apremilast) for use on the National Health Service; but the committee has given the nod to four products for the treatment of juvenile idiopathic arthritis. In final guidance issued on Dec. 16 NICE continued, as in previous draft guidance, to reject the use of Celgene’s drug, an oral small-molecule inhibitor of phosphodiesterase 4, for use on the NHS to treat adults with active psoriatic arthritis that have either not responded to disease-modifying antirheumatic drug (DMARD) therapy, or where such therapy is not tolerated. Psoriatic arthritis patients in the UK are usually treated initially with non-steroidal anti-inflammatory drugs (NSAIDs) and DMARDs such as methotrexate. Most people whose disease doesn’t respond to these drugs will be treated with a tumor necrosis factor alpha inhibitor (TNF-alpha inhibitor) starting with the lowest-cost drugs as recommended by NICE, these include: etanercept, infliximab, adalimumab and golimumab. While there is a need for new drugs for second-line treatment in psoriatic arthritis – as currently around 10% of patients stop TNF-alpha inhibitor treatment each year, either because it is contraindicated, or because of loss of effectiveness or adverse effects – NICE said there was not enough robust evidence demonstrating that Otezla slows progression of the disease compared to TNF-alpha inhibitors. NICE highlighted that this negative guidance does not mean that people currently taking Otezla will stop receiving it; patients have the option to continue treatment until they and their clinicians consider it appropriate to stop. NICE’s final decision continues to conflict with recommendations for the drug elsewhere in the UK, as the Scottish Medicines Consortium (SMC) approved Otezla for use on NHS Scotland to treat psoriasis and psoriatic arthritis earlier this year.



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The Rehabilitation Of AstraZeneca

Last Friday was triple witching. This last hour of the US stock market on the third Friday of December (also March, June and September) is associated with significant volatility as the index futures and options and stock options all expire at the same time and are settled.

In a week when AstraZeneca Plc announced two significant developments, I was struck by how it epitomized an analogous – if longer drawn-out – triple witching of the pharmaceutical sector. The most obvious, and first leg of the sector's witching is the widespread expiry of the patents protecting the industry's blockbuster products. Some companies like Roche Holding AG have been much less affected by this patent cliff than others because of their biologics bent. Others, like Novartis International AG, have endured the genericization of their small molecule drugs, such as Novartis's blood pressure-lowering agent Diovan (valsartan). Many companies reached the bottom of their patent cliffs in 2015 and the acceptance of this by investors has led to a renaissance of the pharmaceutical sector as measured by its average price to earnings (PE) ratio. Over the last year or so, the pharmaceutical PE ratio has been rising to regain its rightful place above that of the S&P 500 index.

Because of their high margins and expected earnings growth, it is logical that the pharmaceutical companies' earnings should trade at a premium to the broader market. However, within that average, there are some companies whose blockbuster patent expiries will continue to result in sales declines. AstraZeneca is one of those companies. While its sales are expected to decline for some years yet, investors have gotten used to the idea so this decline is said to be 'in the price' of AstraZeneca. Indeed, knowing this declining sales trajectory did not stop the bigger predator Pfizer, Inc. from attempting the acquisition of AstraZeneca last year.

The second leg of pharmaceutical witching started last year with the political furore surrounding the pricing of Gilead Sciences, Inc.'s HCV antiviral drug Sovaldi (sofosbuvir). The drug pricing debate ballooned further in 2015, brought about by the backlash by more than one presidential candidate against egregious price increases by specialty pharmaceutical companies such as Turing Pharmaceuticals AG and Valeant Pharmaceuticals International, Inc. On the one hand, the inability of companies like Valeant to grow mainly by price increases is now largely in the price of the sector, if not completely in Valeant's recent financial guidance reduction. On the other, bigger



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branded pharmaceutical companies like AstraZeneca and Pfizer have largely taken more sedate and sensible price increases for their drugs. Indeed, at a recent London breakfast hosted by the pharmaceutical analyst from Cowen & Co., the statement "what other industry can continue to justify mid- to high single digit price increases" was met with nods of comfort by investors (including me, I might add).

The third pharmaceutical witching is that of corporate development transactions, which have dogged not just AstraZeneca in the sector's attempt to address the patent cliff. The past few years have been littered with the strategic missteps of big pharmaceutical companies buying the wrong company or licensing the wrong drug. Who can forget the acquisitions of NeuTec Pharma Plc and Inhibitex, Inc. by Novartis and Bristol-Myers Squibb, Co. (BMS), respectively? AstraZeneca has also had transactions that it would like to forget, such as the acquisition of Arrow Therapeutics Ltd. and its collaborations with Targacept, Inc. and Rigel Pharmaceuticals, Inc.

Lately, however, something eminently sensible has been happening at AstraZeneca – in contrast with the hit and miss approach of old. The acquisition of Almirall SA's respiratory division was a very sensible bolt-on to AstraZeneca's existing respiratory franchise and was not accompanied by the public relations hullabaloo of GlaxoSmithKline Plc's (GSK) and Novartis' recent asset swap – a transaction whose benefits seemed to have already waned in the third-quarter results of both companies. The subsequent respiratory-focused acquisitions of Pearl Therapeutics, Inc. and Actavis Plc's North American respiratory business built on the recent prowess of AstraZeneca's US commercial team in influencing managed care organizations to relegate GSK's respiratory products, which resulted in a recent GSK profits warning. And

then, the icing on this respiratory cake was last week's deal with Takeda Pharmaceutical Company Ltd. to acquire respiratory assets including Daxas (roflumilast). It is good to know that at least someone is looking at the smog that envelops Beijing and the large number of young smokers in southern European and emerging markets and thinking commercially about the future.

But at the end of the week AstraZeneca announced that its anti-PD-L1 monoclonal antibody durvalumab (MEDI4736) had not provided strong enough clinical data to support a regulatory submission. For me, the banquet of strategic and commercial respiratory thinking that I had increasingly come to appreciate was soured by the taste of the oncology therapeutic area and senior management team. The latter is particularly poignant since while the CEO's bonuses and pay rises will benefit from the creation of AstraZeneca as a global respiratory behemoth, after promising the moon for durvalumab amongst other products, its relegation will not affect his remuneration one iota. Investor rapprochement was so close.

The Magna Biopharma Income fund holdings include Roche, Novartis, Gilead Sciences, Pfizer and BMS.

Andy Smith

Andy Smith is chief investment officer of Mann Bioinvest. Mann Bioinvest is the investment adviser for the Magna BioPharma Income fund which has no position in the stocks mentioned, unless stated above. Dr Smith gives an investment fund manager's view on public life science companies. He has been lead fund manager for four life science-specific funds, including International Biotechnology Trust and the AXA Framlington Biotech Fund, and was awarded the Technology Fund Manager of the year for 2007.

Biomedical Enterprise Ambitions: A Galaxy Not So Far, Far Away

If the proper resources are provided to the National Institutes of Health (NIH) over the next five years and intensive efforts are made, extraordinary accomplishments in the biomedical research and development enterprise may be achieved, said Francis Collins, the agency's director.

Certainly, without the belief the NIH and its funded scientists, along with the advances from industry that followed, could achieve great things, medicines like statins for cardiovascular disease, drugs to treat and control HIV infection and immunotherapies for cancer would not be where they are today.

And like the Jedi master Yoda in the epic movie series Star Wars, Collins and his top team members who put together a list of aspirational objectives for potential advances, or "stretching goals," as part of a new five-year plan think those ambitions may very well be reached – that is, with the "force" of funding and the belief from the biomedical community they can do it, not just simply try.

Or, as Yoda said, "Do or do not. There is no try."

In developing the NIH-Wide Strategic Plan, Fiscal Years 2016–2020: Turning Discovery Into Health – a blueprint ordered last year by Congress as part of its NIH appropriations for fiscal year 2015 – Collins told *Scip* he and his team wanted to do more than lay out objectives with priorities and measures for accountability, but sought to give something for those involved in the biomedical research and development enterprise to aspire to, with the hopes of also inspiring others to want to join in on the efforts.

And Collins now has the money in hand – at least for the first year of the five-year plan – thanks to the enactment of the Consolidated Appropriations Act (HR 2029), commonly called the Omnibus bill, which President Barack Obama signed on Dec. 18, funding the US government through Sept. 30, 2016.

Indeed, the NIH got a sweet bump of \$2bn, or 6.6% boost, over last year's levels – the largest increase for the agency since FY 2003 – which Collins called "a gratifying event, in contrast with the last 12 years or so where we've been in pretty rough shape and losing purchasing power steadily."

"We were obviously greatly relieved," he said in an interview. "And believe me, we will figure out how to use the money."

Collins said he wanted to include the list of 14 "bold predictions" on the last page of the five-year plan – the first attempt at an NIH-wide strategy since about 1992 – so that

people reading the report don't get to the end of it and wonder "what could actually happen" if the agency actually follows the path it has laid out.

While some may be skeptical the list of advances may be overzealous and too audacious, Collins said he "wouldn't be surprised if we actually reached all of them" – hoping other scientists would think "that's a goal that really would be fun to work on."

He acknowledged "there are people a little worried that we will now be held 100% accountable for this and if one of these bullets isn't achieved by 2020 that that will be bad."

Collins believes 'many thousands' of cancer patients will experience enhanced survival from the application of precision medicine by 2020

But, said Collins, who said he was responsible, or "to blame," for many of the ideas on the predictions list, "I don't feel that way at all."

"I think it's good for us to stretch out and say, 'Here's what we might be able to do, now watch and see whether we can get there.'"

Among the potential advances Collins and his team said could be achieved by 2020 is the ability for NIH-supported clinical trials to demonstrate that at least a half-dozen interventions thought to be clinically beneficial actually have no value – a goal the NIH chief said he personally had placed on the list, calling it an "important aspect for the public."

Collins noted that while much of what the NIH and its dollars are invested in is trying to find out what works, he pointed out that part of the agency's job is also to delve into what may in the end be useless – the things everybody thought were meaningful treatments or diagnostic tests, but actually haven't been helping anyone.

He said a lot of that "un-ringing of the bell" of discovery work will be concentrated on health maintenance and disease prevention, like screening tests.

For instance, Collins said, the NIH could take a look at some of the interventions for which the US Preventive Service Task Force – an independent volunteer panel of 16 experts convened by the US Agency for Healthcare Research and Quality – struggles with in

making recommendations about benefit when there's a lack of data to know for certain.

But he also said the NIH would examine drugs routinely given to patients that "maybe we have not really looked at carefully enough."

Collins and his team also believe "many thousands" of cancer patients will experience enhanced survival from the application of precision medicine by 2020 – a goal he declared now has a chance to be reached thanks to the Omnibus funding, which will now allow Obama's initiative, unveiled this past January, to move forward.

Among the other ambitious goals the NIH officials said could be reached by 2020 if funding continues and the effort is made are improved outcomes of several drugs through the application of pharmacogenomics in real-world clinical settings.

They also predicted that NIH-supported research would directly contribute to FDA-approved therapies for at least a dozen rare diseases.

In addition, the authors of the NIH strategic plan envisaged that a candidate vaccine that induces a broad antibody-binding response to multiple strains of the influenza virus would be in trials within the next five years – critical to getting to a universal flu vaccine – and that vaccines against respiratory syncytial virus would be in efficacy field tests.

They also said a pivotal efficacy trial of a novel HIV vaccine, which is expected to begin in the Republic of South Africa in 2016, would confer at least 50% protection against acquiring the infection.

But Collins noted the other 44 pages of the report were aimed at fulfilling the mandate from Congress in providing lawmakers and Americans with a framework for carrying out the agency's mission and focusing its funding to ensure the public is getting a return on its investment.

The report details how the NIH plans to advance opportunities in biomedical research, foster innovation by setting priorities, enhance scientific stewardship and excel as a federal science agency by managing for results.

Congress to use it to hold the agency accountable going forward in its appropriations cycles and at other times when authorizing committees want to know the status of something.

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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.

Late-stage clinical developments for the week 11-17 December 2015					
Lead Company	Partner Company	Drug	Indication	Market	Comments
REGULATORY APPROVAL					
Merck & Co. Inc.	—	Bridion (sugammadex) injection	anesthesia	US	To reverse the effects of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide, which are used during certain types of surgery in adults.
Otonomy, Inc.	—	Otiprio (ciprofloxacin otic suspension)	ear infections	US	For the treatment of pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement. Otiprio is a single-dose, physician-administered antibacterial. Otonomy anticipates launching in the first quarter of 2016.
SUPPLEMENTAL REGULATORY APPROVAL					
Helsinn Healthcare SA	Pharmacosmos	Monofer (iron isomaltoside 1000)	anemia	EU	Pharmacosmos has announced that the indication for Monofer, a high dose IV iron therapy, has been widened. It can now be prescribed to adult patients with iron deficiency when either oral iron preparations are ineffective or cannot be used or where there is a clinical need to deliver iron over a short duration. Formerly it was indicated for the treatment of iron deficiency anaemia only.
Merck & Co. Inc.	—	Gardasil 9 (Human Papillomavirus 9-valent Vaccine, Recombinant)	human papillomavirus (HPV) prevention	US	The FDA approved an expanded age indication for Gardasil 9, Merck's 9-valent HPV vaccine, to now include use in males 16 through 26 years of age, for the prevention of anal cancer caused by HPV types 16, 18, 31, 33, 45, 52 and 58, precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, and genital warts caused by HPV types 6 and 11.
BTG plc	Wellstat Therapeutics	Vistogard (uridine triacetate)	drug toxicity	US	For the emergency treatment of adults and children who receive an overdose of the cancer treatment fluorouracil or capecitabine, or who develop certain severe or life-threatening toxicities within four days of receiving these cancer treatments. Wellstat Therapeutics developed Vistogard and BTG will market, sell and distribute the drug for this indication in the US.
Teligent Inc.	—	Cefotan (cefotetan) for Injection	bone and joint infections / intra-abdominal infections / respiratory tract infections / skin and skin structure infections / urinary tract and reproductive tract infections	US	Teligent has received approval of its sNDA from the FDA for Cefotan. This is its first product approved from the portfolio of discontinued and withdrawn NDAs and ANDAs, which it purchased from AstraZeneca on Sept. 25, 2014. Teligent is working with their manufacturing partner to launch the product in early 2016.
ACCELERATED/CONDITIONAL APPROVAL					
Roche Holding AG	Chugai	Alecensa (alectinib)	non-small cell lung cancer (NSCLC)	US	The FDA granted accelerated approval to Alecensa for the treatment of people with anaplastic lymphoma kinase (ALK)-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib.
REGULATORY FILING ACCEPTED					
Merck & Co. Inc.	Bristol-Myers Squibb	MK-6072 bezlotoxumab	Clostridium difficile-associated diarrhea/infection	EU	The EMA currently lists bezlotoxumab as being under evaluation by the Committee for Medicinal Products for Human Use for European approval as a anti-diarrheals, intestinal anti-inflammatory/anti-infective medicine as of Dec. 7, 2015.
Valeant Pharmaceuticals International Inc.	AstraZeneca (AZN)	brodalumab	psoriasis	EU	The EMA currently lists brodalumab as being under evaluation by the Committee for Medicinal Products for Human Use for European approval as a immunosuppressant as of Dec. 7, 2015.
ORPHAN DRUG DESIGNATION					
Aduro Biotech	—	CRS-207	pancreatic cancer	EU	Aduro Biotech announced that the EMA granted Orphan Drug Designation to CRS-207 and GVAX for the treatment of pancreatic cancer.
Aduro Biotech	ANI Pharmaceuticals	GVAX Pancreatic Vaccine	pancreatic cancer	EU	Aduro Biotech announced that the EMA granted Orphan Drug Designation to CRS-207 and GVAX for the treatment of pancreatic cancer.
Advaxis Inc.	—	axalimogene filolisbac	anal cancer	EU	Advaxis announced that the EMA has granted Orphan Drug Designation to axalimogene filolisbac for the treatment of anal cancer. Axalimogene filolisbac was previously granted Orphan Drug Designation in the US for the treatment of anal cancer.
FAST-TRACK STATUS					
MedicNova Inc.	—	MN-166 (ibudilast)	amyotrophic lateral sclerosis	US	For the treatment of patients with amyotrophic lateral sclerosis.
REGULATORY FILING					
Egalet Corporation	—	Arymo ER (morphine sulfate) extended-release tablets	moderate to severe pain	US	For the management of pain severe enough to require daily, around-the-clock opioid treatment and for which alternative treatments are inadequate

KemPharm Inc.	–	KP201 / acetaminophen	acute pain	US	KemPharm has submitted a US NDA under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for KP201/APAP and has requested priority review. KP201/APAP is an immediate release (IR) combination of KemPharm's prodrug of hydrocodone, KP201, and acetaminophen and is being developed for the treatment of acute pain.
SUPPLEMENTAL REGULATORY FILING					
Bristol-Myers Squibb Company	Ono	Opdivo 20mg, 100mg Inj. 20mg, 100mg Inj. (nivolumab)	renal cell cancer	Japan	ONO Pharmaceutical announced that it has submitted a manufacturing and marketing approval partial amendment application for Opdivo for the treatment of patients with unresectable or metastatic renal cell carcinoma in Japan.
PRIORITY REVIEW					
PaxVax Corporation	–	Vaxchora	vaccines	US	PaxVax announced that the FDA has accepted for filing and review the BLA for its affiliate PaxVax Bermuda single-dose oral cholera vaccine Vaxchora. PaxVax also announced that the FDA has granted Vaxchora priority review status. The FDA's action date for the Vaxchora BLA is June 15, 2016.
REGULATORY REVIEW EXTENSION					
Clovis Oncology Inc.	Celgene	rociletinib	non-small cell lung cancer (NSCLC)	US	The FDA has extended the PDUFA date for Clovis' NDA for rociletinib by the standard extension period of three months with the new goal date of June 28, 2016. Rociletinib is an investigational therapy for the treatment of patients with mutant epidermal growth factor receptor (EGFR) NSCLC who have been previously treated with an EGFR-targeted therapy and have the EGFR T790M mutation.
SPECIAL PROTOCOL ASSESSMENT AGREEMENT					
Spectrum Pharmaceuticals Inc.	Hanmi Pharmaceutical	SPI-2012 (eflapegrastim)	neutropenia / leukopenia	US	Spectrum has reached agreement with the FDA on the SPA for the Phase III clinical trial of SPI-2012. This trial will evaluate the safety and efficacy of SPI-2012 as a treatment for chemotherapy-induced neutropenia in patients with breast cancer, and will serve as the basis for the BLA filing. Spectrum expects to start the pivotal trial soon and plans to complete enrollment in 2017.
PHASE III TRIAL INITIATION					
Apple Tree Partners	Camurus	CAM2038	drug addiction	–	Braeburn Pharmaceuticals and Camurus announced that the first patient has been enrolled in a Phase III clinical trial of CAM2038 for treatment of opioid dependence. The Phase III trial is designed to demonstrate the long-term safety and clinical efficacy of CAM2038 weekly and monthly injections in patients with opioid dependence. The study is a part of the pivotal registration program for CAM2038 for which Braeburn and Camurus have received guidance from both US FDA and the EMA.
CorMedix Inc.	–	Neutrolin	catheter complications	–	CorMedix announced that the first patient has been enrolled and dosed in the LOCK-IT-100 (Catheter Lock Solution Investigational Trial) Phase III clinical study. The LOCK-IT-100 study will assess the efficacy and safety of Neutrolin in preventing catheter-related bloodstream infections in subjects receiving hemodialysis therapy as treatment for end stage renal disease to support marketing approval in the US.
Soligenix Inc.	–	SGX301 (synthetic hypericin)	cutaneous T-cell lymphoma (CTCL)	–	Soligenix announced that patient enrollment has been opened for its Phase III, multicenter, randomized, double-blind, placebo-controlled study evaluating SGX301 as a treatment for CTCL referred to as the FLASH study (Fluorescent Light Activated Synthetic Hypericin). The study is anticipated to complete enrollment with primary data available in the second half of 2016.
PRODUCT LAUNCH					
Allergan plc	–	Viberzi (eluxadoline)	irritable bowel syndrome	US	Allergan announced that Viberzi for irritable bowel syndrome with diarrhea is now available by prescription in the US.
Takeda Pharmaceutical Company Ltd (4502:JP)	–	Ninlaro (ixazomib) capsules	multiple myeloma	US	Ninlaro is now available in the US for use in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.
AbbVie Inc.	Takeda	Leuplin PRO for Injection Kit 22.5 mg (24-week depot formulation leuprorelin acetate), Lupron	breast cancer / prostate cancer	Japan	Takeda announced that Leuplin PRO is now available in Japan for the treatment of prostate cancer and premenopausal breast cancer. Leuplin is currently available in the US, Europe, and Asia.
Merck & Co. Inc.	Kyorin	KIPRES OD Tablets 10mg (montelukast sodium), Singulair	allergic rhinitis / asthma	Japan	Kyorin has launched Kipres for the treatment of bronchial asthma and allergic rhinitis. The product received marketing authorization from the Ministry of Health, Labour and Welfare in August.
TaiGen Biotechnology Co. Ltd.	R-Pharm	Taigexyn (nemonoxacin) capsules	community-acquired pneumonia	Taiwan	TaiGen has launched Taigexyn capsules in Taiwan. In December 2014, the Taiwan Food and Drug Administration approved the NDA and granted the new drug license for the oral formulation of Taigexyn to TaiGen.

Source: BioMedTracker

ARIAD Pharmaceuticals, Inc. has appointed **Paris Panayiotopoulos** president, CEO and to its board of directors – effective Jan. 1, 2016. Panayiotopoulos most recently was president of EMD Serono, Inc. and will succeed ARIAD's founder, chair and CEO **Harvey J. Berger**. Previously, Panayiotopoulos was at Eli Lilly & Co.

Dimerix Ltd. has appointed **Liz Jazwinska** to its board as non-executive director. Currently, Jazwinska is the strategic alliances director at Institute of Medical Biology, A*STAR, Singapore. She brings over 25 years of R&D management experience to the company and has previously held senior positions in industry, academia and government bodies in the UK, Singapore, Australia and New Zealand. Previously, Jazwinska founded and led Asia Pacific Partnering Group at Johnson & Johnson Research Pty Ltd. in Sydney.

Aclaris Therapeutics, Inc. has appointed **Brett Fair** senior vice president of commercial operations. Fair has over 18 years' experience in pharmaceutical commercialization and business development and joins the company from Aqua Pharmaceuticals. Before this he held roles in global commercial and business development at GlaxoSmithKline (GSK) and started his career at Allergan.

RNAi therapeutics company, **Alnylam Pharmaceuticals Inc.**, has appointed **Michael Bonney**, current board member and former CEO of Cubist Pharmaceuticals, chair of its board of

directors – effective Jan. 1, 2016. **John Clarke**, founding investor and current chair, will remain on the board as a director. Former chair and CEO of Allergan, **David Pyott**, has also been appointed to Alnylam's board – effective immediately. In addition to serving as Cubist's CEO and a member of its board, Bonney was also previously its president and chief operating officer. He has also held various positions at Biogen, Inc. and prior to this he was at Zeneca Pharmaceuticals. Bonney has been a director of Alnylam since 2014 and is currently a director of the Celgene Corporation, the Whitehead Institute for Biomedical Research and the Gulf of Maine Research Institute. Pyott was CEO of Allergan from 1998 to 2015 and prior to this he was the head of Novartis nutrition division and a member of the executive committee of Switzerland-based Novartis AG. He is a lead director and member of the board of Avery Dennison Corporation and the supervisory board of Royal Philips in the Netherlands.

Immunocore Ltd., a company focused on treating cancer, viral infections and autoimmune diseases, has appointed **James Sandy** chief development officer and **Julian Hirst** director of corporate finance. Most recently, Sandy was chief development officer at Creabilis Ltd. Prior to this, he held numerous positions at Pfizer Inc., including head of EU and Asian development operations, development team leader within the gastrointestinal therapeutic area and oncology therapeutic area head, EU. Hirst was previously

vice chair and head of corporate finance at Panmure Gordon, head of EU technology and a managing director at UBS and head of EU media at Morgan Stanley.

Entasis Therapeutics, a company focused on bacterial infections, has appointed **Paul G. Ambrose**, **Karen Bush**, **Stanley A. Nasraway**, **Mark Noe** and **Brad Spellberg** to its scientific and clinical advisory board. Ambrose is currently president of the Institute for Clinical Pharmacodynamics, honorary research fellow in infectious diseases at the University of Oxford and adjunct associate research professor at the University at Buffalo. Bush is a fellow of the American Academy of Microbiology, adjunct professor of biology and professor of practice in a biotech program at Indiana University. Nasraway is a professor of surgery, medicine and anesthesia at Tufts University School of Medicine and director of the surgical intensive care units at the Tufts Medical Center in Boston. Noe is vice president of the Groton Centre of Chemistry Innovation and leads various supporting teams in Pfizer research and development including academic and industry relations for the chemistry area. He is also on a number of external scientific advisory panels for the biotech and academic industry. Spellberg is chief medical officer at the Los Angeles County University of Southern California Medical Centre and professor of clinical medicine and associate dean for clinical affairs at the Keck School of Medicine at USC.



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