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Why Is Drug Pricing Higher In US? Study Takes Aim At R&D Argument

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Amgen, Biogen, Pfizer and Teva generated more than twice their global R&D budgets with higher pricing in the US compared to Western Europe and Canada, researchers at Memorial Sloan Kettering found.

The premium prices that biopharma manufacturers charge in the US compared to Europe and Canada often generate more "excess revenue" than companies spend on research and development, according to a study by Memorial Sloan Kettering Health Policy and Outcomes Center Director Peter Bach and researchers Nancy Yu and Zachary Helms.

The study, which was published in the Health Affairs blog on March 7, challenges the argument that pricing is set higher in the US than in other countries to help fund innovation. The researchers compared the amount earned in the US with higher prices against worldwide R&D spending to evaluate the claim.

The analysis comes as drug pricing continues to be a major political issue in the US. The Donald Trump Administration expects pricing will be addressed in legislative and regulatory efforts to repeal and replace the Affordable Care Act. The Administration has not released specifics on the policies it supports. However, the president discussed legislation that would allow the Department of Health and Human Services (HHS) to negotiate drug prices and set mandated drug rebates in the Medicare Part D program in a meeting with Rep. Elijah Cummings, D-Md., March 8, according to a release from Cummings's office. Those measures have long been supported by Democrats in Congress and staunchly opposed by Republicans, so it would be a heavy lift to get them passed.

Drug pricing critics in the US have also pointed to geographic pricing disparities as justification for congressional proposals that would allow importation of cheaper drugs from Canada. Payers, and even some drug company executives, are questioning whether the US market should continue to "carry the water" for the rest of the world by shouldering higher prices.

The Memorial Sloan Kettering analysis found "the premiums pharmaceutical companies earn from charging substantially higher prices for their medications in the US compared to other Western countries generates substantially more than the companies spend globally on their research and development."

This finding "counters the claim that the higher prices paid by US patients and taxpayers are necessary to fund research and development. Rather, there are billions of dollars left over even after worldwide research budgets are covered." The researchers looked at the 15 drug companies that manufactured the 20 top-selling drugs globally in 2015.

Lowering the "magnitude of the US premium" to a level where it matches global

CONTINUED ON PAGE 7

from the editor

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President Trump's campaign to bring down medicine prices "for the American people" (see p3) has ridden on the subtext that US patients pay high prices to fund medical advances enjoyed by those abroad at lower cost. However, a new study indicates that even once R&D is covered, US patients may be paying over the odds. PhRMA disagrees and has laid out its counter-arguments to Cathy Kelly – see our cover story for full analysis.

If Trump re-mounting his drug pricing soapbox and Memorial Sloan Kettering taking aim at the R&D cost defense weren't bother enough, the Brexit vote could leave companies with a large financial hole as knock-on currency fluctuations are reflected in international reference pricing (see p4).

Elsewhere in the issue, don't miss our centrefold infographic on the outlook for the 16 top pharma companies out to 2025; part two of Mandy Jackson's immuno-oncology round table (p10), or the leadership lessons of candid biotech CEO Øystein Soug (p16).

Also, remember – if you like *Scrip*'s weekly issue, there's lots more content online: make sure you're set up to receive our daily email alerts.

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How To Make A Global First-In-Class Drug In China
The story so far of how an aspiring Western returnee researcher became a fully charged pharma entrepreneur in China's wild world of drug innovation
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Top Asia Execs To Watch: WuXi NextCode, Fosun Kite, Novartis Japan
The coming of spring has brought a flurry of senior executive moves at companies across Asia including WuXi, Fosun-Kite, Novartis, BGI and Chi-Med.
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Trump's Tweets On Drug Prices; Industry Says 'Huh?'

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US President targeted drug prices again on Twitter, and later in the day House Democratic Rep. Elijah Cummings announced a meeting with Trump March 8 to discuss lowering drug prices.

President Trump isn't walking back on his promise to lower drug prices in the US – and that may be the one thing industry is clear about after his latest tweet on the issue on March 7.

"I am working on a new system where there will be competition in the drug industry. Pricing for the American people will come way down," Trump said in the tweet capped with an exclamation point. The tweet came the morning after House Republicans unveiled their plan to repeal and replace the Affordable Care Act. The new Republican legislation, called the American Healthcare Act, relies heavily on tax credits to help people buy health insurance, but it doesn't include any policy related to drugs.

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Pharmaceutical stocks dipped in the immediate reaction to Trump's tweet. The Nasdaq Biotechnology Index dropped about one point, before beginning to recover. Big pharma stocks like Pfizer Inc., Merck & Co. Inc. and Bristol-Myers Squibb Co. each fell about 1%.

The market reaction was less volatile than it was when Trump attacked drug prices in a news conference Jan. 12 and accused industry of "getting away with murder." Investors may be growing less concerned that Trump's statements on Twitter will be translated into policy or simply becoming more used to the way the president uses Twitter.

The problem for industry is that no one seems to know what Trump might be referring to when he talks about a "new system" or more "competition." He previously said he would require the government to negotiate drug prices, but it wasn't clear what he meant since the government already negotiates drug prices under Medicare Part D. The big fear among pharma and investors is a policy that would control how drug companies can set or raise prices, which almost everyone unilaterally agrees would curb investment in the high-risk field.

Nonetheless, concern among executives that Trump might try to push a sweeping pricing overhaul appeared to have subsided more recently, as attention turned to who might be appointed FDA commissioner. To begin with, the Republican-held House and Senate seem like a strong safety net since Republicans have never been interested in pursuing drug pricing controls. Industry's leading chief executives also appeared reassured after they met with Trump at the White House in January, mollified by his promises of tax relief and deregulation as a tool to help speed up development.

Jobs were also discussed. Investing in US jobs could end up being the industry's main leverage when it comes to negotiating with Trump, given his focus on job creation during the campaign.

MEETING HOUSE DEMOCRATS

But Trump, considered more of a populist than a traditional republican, has indicated he won't always stick to the Republican script. High drug prices could present an opportunity for him to work across the aisle. Indeed, a few hours after the tweet, Rep. Elija Cummings (D-Md.) announced that he will meet with Trump March 8 to discuss lowering drug prices, joined by Peter Welch (D-Vt.) and Redonda Miller, president of Johns Hopkins hospital.

"The president promised – both during the campaign and after – that he would support efforts to stem the skyrocketing prices of prescription drugs, so I am looking forward to discussing ideas he said he supports," Cummings said in a statement. "Our hope is that the president will make good on his promise and join us in convincing congressional Republicans to finally start helping American families who rely on these life-saving medications."

'Our hope is that the president will make good on his promise and join us in convincing congressional Republicans to finally start helping American families who rely on these life-saving medications'

In an email to investors following Trump's tweet, Evercore ISI analyst Umer Raffat said, "The question really is: what does this mean?"

As he pointed out many therapeutic areas with largely interchangeable brands are already under Part D and have formulary tiers.

"Is the president referring more to Part B (where no formularies exist currently)? Reality is, we just don't know until something definitive is put out," he said.

Industry leaders at the BIO CEO & Investor conference in February also discussed potential changes to Medicare Part B as an alternative to price controls.

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Brexit And International Reference Pricing To Cost Companies Billions

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Companies could lose hundreds of millions of dollars thanks to the impact of Brexit on international reference pricing. Brexit has other market access implications too, for example on the ebb and flow of parallel trade.

The UK's decision to leave the European Union is going to be costly for companies. The pharmaceutical industry will have to deal with the fallout from international reference pricing (IRP), which according to one big pharma company could cost it $200m. Brexit may also cause a headache for company market access strategies as it could impact marketing authorization timelines and parallel trade.

"That is a really big impact for one decision. If you multiply that out across the whole industry, then Brexit has a huge implication from an IRP perspective"

Exchange rate fluctuations are for companies one of the perils of international reference pricing, and since the UK decided to leave the EU, the value of sterling has dropped against the euro. This is problematic because the UK is a popular country for other markets to reference when setting their own prices – some 15 EU member states include the UK in their price comparison baskets. So when the pound drops in value against the euro, or other currencies, markets looking at UK prices see those prices fall relative to their own and at some point they review their own prices and adjust them downwards to reflect the drop.

One pharma giant could stand to lose up to $200m in a worst case scenario, it commented at the 2017 World Pharma Pricing and Market Access Congress in London. "That is a really big impact for one decision. If you multiply that out across the whole industry, then Brexit has a huge implication from an IRP perspective. We somehow need to manage all that," said the company. It told *Scrip* that there were many unpredictable moving parts that could impact the size of losses, for example how foreign exchange rates play out, and the point in time when different markets reference prices. The company said it would likely see different markets respond sensibly to UK prices, but added that the reference price differentials would provide big opportunities for lower prices.

"Countries referencing UK prices may well cut their prices in response to a relative decline in prices in the UK … That is an immediate effect. "said Neil Grubert, global market access consultant and trainer in an interview at the conference with *Scrip*. If after Brexit European markets continue to reference UK prices, there could be downward pressure on prices across Europe if the pound does not recover, he said. He explained that different markets use different methodologies for calculating their prices, which means currency fluctuations have different effects. For example, some use an average of all the prices in their baskets, while others use the lowest basket prices to set their own. The former methodology dilutes the impact of price drops elsewhere, while the latter maximizes it.

However, in the longer term the UK's role in reference pricing is uncertain, said Grubert, as it is not clear whether EU member states will keep the UK in their reference pricing baskets. Grubert points out that there is an "unwritten convention" among member states that sees them reference primarily other EU member states, although there are some exceptions and a small number of markets do look at countries outside of the EU.

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PARALLEL TRADE, AUTHORIZATIONS AND HTA

Aside from reference pricing, Brexit has plenty of other headaches in store for companies. The biggest unsolved question about Brexit and market access, says Grubert, is the relocation of the European Medicines Agency away from London. If not managed properly, this could mean delays in marketing authorization, he says.

Another by-product of Brexit for companies to grapple with is very possibly the rise and fall of parallel exports from the UK. Some years ago the UK switched from being a net parallel importer to a big parallel exporter as UK prices fell in relation to those on the continent. Some drug classes have seen a growth in parallel exports and Grubert expects this to increase in the short term as the pound drops in value compared to the euro. However, over the longer term, parallel exports to Europe could end altogether if a hard Brexit means the UK leaves the single market.

Brexit could also have implications for EU HTA projects and the direction of future initiatives on collaboration and harmonization, says Grubert. NICE is a very influential HTA body and has taken part in a number of European initiatives to promote greater collaboration on HTA, for example it has been one of the leading agencies involved in the European network for Health Technology Assessment, EUnetHTA. NICE's role in HTA initiatives after Brexit is unclear, but the UK's EU departure could have broad implications for Europe's HTA climate, says Grubert. The UK very much favors a cost-effectiveness driven approach to HTA, while other big hitters, particularly the G-BA in Germany and HAS in France, have eschewed cost-effectiveness in favor of evaluating additional benefit. "Without the UK we may see a shift that is potentially significant for movement towards greater collaboration and harmonization and centralization on European HTA."

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Humira's Inevitable Decline: What's Waiting In The Wings?

There are 20 biosimilar adalimumab drugs in development – including one from Amgen that has already been approved but not yet launched. Biotechs and big pharma companies alike are lining up their candidates in preparation for when AbbVie's world-leading inflammation and immunology product Humira loses patent protection.

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Biosimilar versions of the world's best-selling drug, AbbVie Inc.'s *Humira* (adalimumab), are lurking all over the globe in shadows cast by the originator product, ready to hit the market as soon as patent protection is lost for the drug, which is the major engine driving AbbVie's revenues and profits.

Humira, a tumor necrosis factor (TNF) inhibitor approved for several inflammatory indications, is still the main source of growth for AbbVie, posting sales of $16.1bn for 2016 alone – almost 15% growth from 2015. $10.43bn of 2016 sales for the drug were recognized in the US, while $5.65bn was achieved internationally last year.

Humira generated 63% of AbbVie's 2016 sales and will continue to make up a large portion of its revenues for the foreseeable future as the company pushes the drug into emerging markets and adds label extensions in new indications, such as the product's 2016 approval for uveitis. But analysts at Informa Pharma Intelligence's Datamonitor Healthcare expect sales of Humira to peak at $17.1bn in 2018 before entering into a substantial decline. The drug is also expected to fall from its top spot as the best-selling branded pharmaceutical product worldwide by 2020.

Analysts from Credit Suisse expect Humira sales to peak at $18.7bn in 2018 before starting steadily to lose value; they cite pricing pressures and competition from other branded drugs as the major near-term threat. Even with the possible entry of biosimilars at the earliest predicted date of 2018 (in Europe), Credit Suisse has forecast that sales of Humira will remain above $10bn through to 2022 when it anticipates loss of US patent protection – still a higher sales figure than all of the top 10 best-selling drugs in 2015, except for Gilead Sciences Inc.'s *Harvoni* (ledipasvir/sofosbuvir) – that booked sales of $13.9bn – and Humira itself.

The question of when exactly Humira will face biosimilar competition is a tricky one to answer. AbbVie is battling several patent lawsuits globally to retain intellectual property protection for Humira and the company believes the drug is safe until 2022 in the US. However, some analysts predict Humira will lose its key patent protections in 2018 – an event that will take a toll despite AbbVie's attempts to stem the loss with other pipeline opportunities and its hepatitis C portfolio. Datamonitor Healthcare predicts, based on the speed of current patent litigation over Humira, that the first adalimumab biosimilar will be launched by 2019 in the US.

Credit Suisse expects direct biosimilar competition for Humira in Europe in the fourth quarter of 2018, but it agrees with AbbVie that the drug will be covered in the US until 2022.

One product that AbbVie hopes will help offset Humira's eventual decline is its interferon-free hepatitis C combination, glecaprevir/pibrentasvir. This is set to be the company's principal growth driver in its infectious diseases portfolio, with peak sales reaching $4.1bn in 2022. However, this represents less than a quarter of the sales achieved by Humira at its peak. AbbVie's new hep C drug will bring another set of challenges for the company, meanwhile, as Datamonitor analysts expect the product to cannibalize AbbVie's hep C patient share in all treatment settings for its already marketed treatment *Viekira Pak* (ombitasvir, paritaprevir and ritonavir tablets with dasabuvir).

BIOSIMILARS IN WAITING

Amgen Inc.'s biosimilar adalimumab, known as *Amjevita*, is leading the pack of Humira copycats, having already won approval in the US with Europe set to follow suit: it has received a positive opinion from the European Medicines Agency and is awaiting confirmation of market approval from the European Commission. But Amgen is not expecting to launch Amjevita until 2018 at the earliest because of ongoing patent litigation against AbbVie, it noted in its fourth-quarter earnings report in February.

However, Datamonitor analyst Armando Uribe told *Scrip* that even when IP situations are resolved, Amgen will need to "focus on introducing doctors and patients to what biosimilars are", as well as dealing with various pricing negotiations for the product with different systems such as PBMs [pharmacy benefit managers; third-party administrators of prescription drug programs] in the US and health technology appraisal bodies in Europe. "It is very uncertain how receptive the US market as a whole will be to these new biologics," he noted, adding that being the first with a Humira biosimilar may slow down the whole process of launching Amjevita for Amgen.

Ready to follow in Amgen's footsteps is Boehringer Ingelheim GMBH, which has already filed its Humira biosimilar in the US. An FDA review for this product, BI695501, is expected in the third quarter of this year.

Humira is currently priced in the US at around $2,750 per kit of two 0.4ml, prefilled syringes, but Uribe expects that the first Humira biosimilar to launch will do so at a 30% discount to the price tag on AbbVie's product. He expects this to drop to around a 50% to 55% discount once more biosimilar options enter the market. "Over a long period of time the impact to Humira's sales will be significant," he said. Uribe added that the uptake of biologics in Europe has been faster than in the US, but the process is still less than streamlined.

Humira, the first fully-human therapeutic monoclonal antibody to be approved by the FDA, was authorized in in 2002 as a treatment for rheumatoid arthritis (RA). It has since been recommended for use in juvenile RA, Crohn's disease, psoriatic arthritis, psoriasis, axial spondyloarthritis, ulcerative colitis, hidradenitis suppurativa and most recently uveitis. The drug is also approved for Behçet syndrome outside the US and Europe.

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View Biosimilar Humira Products And Their Next Steps here: **http://bit.ly/2miMNI0**

BMS M&A Q&A: Is IO Player Now In Play?

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Will activist investors succeed in unlocking Bristol-Myers Squibb's shareholder value - or instead orchestrate a takeover worth more than $100bn?

Developments in the lung cancer market over the next 12 months will be crucial to the future of beleaguered Bristol-Myers Squibb Co. and help investors determine whether shareholder value – and thus satisfaction with its management – can be unlocked, or whether activists, which include Carl Icahn and JANA Partners, will instead push for quicker profits via a rival takeover of the company worth more than $100bn.

That's the current view of many analysts and investors who are trying to make sense of BMS' situation following months of uncertainty, a sagging share price following PD-1 inhibitor *Opdivo's* failure last autumn in the CheckMate 026 study in first-line non-small cell lung cancer (NSCLC) and news Icahn - a known advocate of mergers and acquisitions – used the lower BMS share price to take an unknown stake in the group.

"While the numbers may make sense, we see an acquisition in the next 9-12 months as unlikely until we get more clarity on some of the large unknowns in the lung cancer market and macro issues such as the possibility of corporate tax reform and the political environment in the US."

Bristol's pace in the areas of cancer immunotherapy has flagged in the period between *Opdivo's* (nivolumab's) CheckMate 026 disappointment last October and the group's decision this past January not to seek accelerated approval in that setting for its proprietary combo regimen of Opdivo with its CTLA-4 inhibitor *Yervoy* (ipilimumab). Meanwhile, Merck & Co. Inc.'s PD-1 inhibitor *Keytruda* (pembrolizumab) won approval in first-line non-small cell lung cancer and Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab) entered the second-line setting, eroding Opdivo's once dominant position.

That sequence of events has been reflected in BMS' share price, which saw highs of around $75 per share in 2016 but currently stands at around $57. Most analysts view that level as seriously undervaluing the company.

ICAHN'S INTENTIONS?

Savvy serial investor Icahn was clearly attracted by those levels, and acquired a stake in Bristol-Myers Squibb, according to the Wall Street Journal which Feb. 21 said Icahn sees BMS as a potential takeover target. The WSJ at the time said the exact size of Icahn's stake wasn't known, only that it was a 'big' one.

M&A rumors have subsequently spread, fanned by reference to his previous operating style of putting pressure on the management of companies in which he has invested to do what he wants them to do, and his reputation for promoting mergers and acquisitions. Icahn's last big biotech target was Biogen Inc. in 2007, but the sale he sought didn't happen so he pushed for and won board representation and then used his voices to influence the company's strategy and actions.

Still, some analysts say Icahn might prefer to take a 'longer view' with BMS and see how the drug maker's pipeline of oncology, immune-science, and cardiovascular products performs.

BMS recently decided to appoint three new independent directors to its board as part of a settlement with activist investor Barry Rosenstein's JANA Partners, which had been lobbying for changes in its oversight structure. JANA owns less than 1% of BMS though.

Analysts say those recent changes imply scenarios comprising either getting BMS sold to another big pharma, or convincing its management to make strategic acquisitions, or to invest in its business to diversify its therapeutic operations. But there is much uncertainty over which option is likely to be chosen.

POSSIBLE PREDATORS

A number of possible suitors with deep enough pockets to afford buying BMS are being mentioned, composed of Pfizer Inc., Novartis AG, Gilead Sciences Inc., Roche, Amgen Inc., Sanofi, Johnson & Johnson, ahd Merck & Co. Inc.. Analysts say BMS would likely fetch more than $100bn if bought outright.

"There are a lot of desperate buyers out there with low cost of capital," analysts at BMO Capital Markets said in a Feb. 21 note. They added that "however, fundamental concerns, particularly regarding the IO franchise, lead us and most investors to believe that such a $100bn-plus deal would be less likely."

Analysts at Credit Suisse agreed: "While the numbers may make sense, we see an acquisition in the next 9-12 months as unlikely until we get more clarity on some of the large unknowns in the lung cancer market and macro issues such as the possibility of corporate tax reform and the political environment in the US."

BMO expects the oncology market "will become increasingly fragmented" with more personalized and targeted treatments. Also, "the relatively rapid pace of development in IO from multiple large players, and seemingly similar clinical profiles of the anti PD-1s, lead us to believe that price pressure is inevitable."

Ongoing uncertainty over US tax reform is an issue too. So the financials behind a merger for US-based companies could depend on whether they could efficiently repatriate cash held outside the country.

"Does this mean that a deal with an ex-US based company is more likely? Perhaps; however, this does not negate our fundamental concerns," the BMO analysts said.

COMING CATALYSTS

The situation could be influenced by clinical and regulatory events over the next 12 months, analysts note, such as a further shake up in the front-line non-small cell lung cancer market, including potential accelerated approval for Keytruda in combination with Eli Lilly & Co.'s *Alimta* (pemetrexed) in front-line NSCLC by May, progression-free survival data from AstraZeneca PLC's MYSTIC trial by mid-year in which the anti-PD-L1 durvalumab and anti-CTLA-4 tremelimumab are being evaluated in NSCLC patients; pivotal I-O plus chemotherapy data from Roche on PD-L1 inhibitor Tecentriq in the third quarter and then data from BMS' CheckMate 227 trial early in 2018.

"We struggle to see how a company would be willing to make a $100bn-plus deal prior to seeing at least some of the upcoming data," Credit Suisse analysts said in a note."

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CONTINUED FROM COVER

R&D expenditures across the 15 companies "would have saved US patients, businesses, and taxpayers approximately $40bn in 2015," the researchers point out (the US premium was $116bn that year, when R&D spending was $76bn that year). By comparison, the Centers for Medicare and Medicaid Services (CMS) reported that total US spending on pharmaceuticals was $325bn in 2015.

> 'Our analysis cannot inform the question whether or not it is appropriate for US patients, taxpayers and businesses to bear the burden of funding pharmaceutical research for the world'

Amgen Inc., Biogen Inc., Pfizer Inc. and Teva Pharmaceutical Industries Ltd. generated "more than double their global R&D budgets" through higher pricing in the US, the researchers reported.

Three companies covered, or nearly covered, their research spending through premium pricing for their top-selling product: AbbVie Inc. with *Humira* (adalimumab), Biogen with *Tecfidera* (dimethyl fumarate), and Teva with *Copaxone* (glatiramer acetate), the study found.

However, results varied among the companies. The premium earned in the US by Bristol-Myers Squibb Co. was less than its global R&D budget in 2015 and for Novartis AG and AstraZeneca PLC, the premiums essentially matched global R&D spending.

The analysis "does not address whether prices in European countries or in the US are appropriate," the researchers state. Nevertheless, they suggest European pricing may more closely reflect product value.

"We do know that all of the European countries included in our analysis use pharmacoeconomic analyses in their price negotiations, while this cannot be said of the US." Nevertheless, the researchers point out, "our analysis cannot inform the question whether or not it is appropriate for US patients, taxpayers and businesses to bear the burden of funding pharmaceutical research for the world."

List prices in the studied countries average 41% of US net drug prices for the select companies; the UK had the lowest average at 38% and Denmark came in highest at 52%.

'MISLEADING NARRATIVE'

The Pharmaceutical Research and Manufacturers of America (PhRMA) disputed the study's implications in an emailed statement. A spokesperson emphasized, "We have always said many factors may go into the price of a medicine, including a medicine's clinical merits, unmet need and R&D."

PhRMA pushed back against the notion that the dynamics of the US market can be

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Revenues Earned From US Premium Pricing And Global Spending On R&D Of The 15 Pharmaceutical Companies Responsible For The World's 20-Top-Selling Products In 2015

COMPANY	INT'L PRICE/US PRICE	US PREMIUM PRICE %	US SALES (2015, $M)	REVENUE FROM US PREMIUM ($M)	REVENUES FROM US PREMIUM AS % OF GLOBAL R&D
AbbVie	48%	52%	$13,561	$7,092	166%
Amgen	43%	57%	$16,523	$9,355	239%
AstraZeneca	36%	64%	$9,474	$6,078	101%
Biogen	25%	75%	$6,546	$4,934	245%
Bristol-Myers Squibb	45%	55%	$8,188	$4,516	76%
Celgene	45%	55%	$5,525	$3,020	148%
Roche (Pharma Div)	45%	55%	$17,782	$9,759	119%
Gilead	75%	25%	$21,200	$5,200	173%
GlaxoSmithKline (ex consumer)	48%	52%	$10,188	$5,300	114%
J&J (Pharma Div)	39%	61%	$18,300	$11,127	163%
Merck	39%	61%	$17,519	$10,649	159%
Novartis	52%	48%	$18,079	$8,678	97%
Pfizer (ex consumer)	21%	79%	$19,906	$15,735	219%
Sanofi	28%	72%	$12,625	$9,123	163%
Teva (specialty meds)	22%	78%	$6,442	$5,018	263%
AVERAGE 41%					

CONTINUED FROM PAGE 7

compared to Europe or Canada. "This study advances a misleading narrative by understating how the competitive marketplace for medicines in the United States helps control costs and provides patients with access to innovative treatments and cures faster than in many parts of the world."

In addition, PhRMA said, "price differences that may exist between the United States and other countries are often achieved through price controls that result in restricted access to medicines and fewer choices for patients."

Furthermore, "there are many factors that may go into a price of a medicine, including a medicine's benefit based on clinical and real world evidence. The medicine's clinical merits (e.g., efficacy, length or quality of life, reduction in other health care costs) and other factors including unmet need and R&D are considered. And the revenues from commercially successful medicines are reinvested in research for the next generation of treatments."

To conduct the study, the researchers derived a company-level average by examining the US price premium for each drug in that company's portfolio that contributed 5% or more to US product sales. The average premium was applied across each company's US pharmaceutical revenue base to arrive at a "proxy" for the amount of total US revenue that resulted from US premium pricing.

US pricing data came from July 2016 average sales price files reported by manufacturers for physician administered drugs and the September wholesale acquisition costs (WACs) for retail drugs (published in Truven Health's Redbook).

WAC prices were reduced by each company's reported average gross-to-net adjustment by incorporating, "in a pooled manner," the discounts and rebates the company provides to payers, Medicaid, 340B hospitals and the Veterans Administration as well as other channel intermediaries, the authors explain.

Ex-US pricing information came from the UK, Ireland, Denmark and Canada. The researchers used the drugs' list prices in these countries, because rebates were not publicly available. The approach "serves to lessen our estimate of the premium companies earn through charging higher prices to US patients," they point out.

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Roche In New Phase III Bet On MorphoSys' Anti-Amyloid Agent

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Roche is taking a punt on a new Phase III trial with gantenerumab in patients with mild Alzheimer's despite ending one called SCarlet RoAD in similar patients just over two years ago.

Having collated safety and dosing data on gantenerumab, which it licensed in from MorphoSys, Roche now plans a new pivotal Phase III trial program – dubbed GRADUATE 1 and 2 – for the HuCAL antibody gantenerumab in patients with prodromal to mild Alzheimer's disease, and expects to start dosing later this year.

The decision might come as a surprise to some given that back in December 2014, Roche ended a Phase III study of the experimental anti-amyloid drug in prodromal Alzheimer's disease, after a futility analysis suggested the probability of the study meeting its primary endpoints was poor.

That study, dubbed SCarlet RoAD, was started in November 2010 and was the first Phase III trial to evaluate a potential disease-modifying medicine in this early prodromal stage of Alzheimer's. It had an overall safety profile similar to that seen in a Phase I trial, Roche said at the time. While gantenerumab exerted a dose-dependent reduction of brain amyloid load, cerebrospinal fluid tau, and total tau - the first reported treatment effect on both hallmark biomarkers - that did not translate into a clinical response in SCarlet RoAD, hence the trial was stopped.

But other trials continued. A global Phase III trial trial, Marguerite RoAD, initiated in March 2014, continues to investigate the efficacy and safety of gantenerumab in patients with mild Alzheimer's disease at the same doses as those used in SCarlet RoAD. The study is expected to be fully completed in March 2019, according to Informa Pharma's BioMedTracker.

"There are open label extensions of the gantenerumab SCarlet RoAD and Marguerite RoAD studies ongoing that helped us to evaluate the safety and biological effects of higher doses of gantenerumab. Based on the open label extensions, we have decided to initiate new Phase III pivotal studies, GRADUATE 1 and 2 and anticipate FPI (first in patient trials) in late 2017," a Roche spokesperson told *Scrip*.

Gantenerumab is also involved in the ongoing DIAN TU (Dominantly Inherited Alzheimer Network Trials Unit) trial, investigating treatment options for individuals who are at risk of dominantly inherited Alzheimer's disease and also including Eli Lilly & Co.'s amyloid-beta antibody solanezumab. This trial, funded by the National Institute of Health and conducted by Washington University.

Gantenerumab is a fully humanized centrally and N-acting monoclonal antibody that primarily targets fibrillar amyloid-beta using MorphoSys AG's proprietary HuCAL antibody technology. It acts by preventing amyloid-beta plaque formation, promoting microglia-mediated clearance. This binding and clearance is essential as amyloid-beta accumulation is a hallmark feature of Alzheimer's disease, according to Roche.

MERRY MORPHOSYS

Roche owns gantenerumab through a discovery and development collaboration announced more than 16 years ago between the Swiss drug makers and MorphoSys, under which the German biotech applies its Human Combinatorial Antibody Library (HuCAL) technology to biological targets chosen by Roche. MorphoSys in turn receives pre-determined financial milestones based on clinical outcomes and, if commercialized, will receive royalties, a MorphoSys spokesperson told *Scrip* but declined to give details.

The German biotech welcomed the decision by its Swiss partner. "This is great news for MorphoSys. We are delighted by the strong commitment to gantenerumab as a potential new therapy for Alzheimer's disease", Marlies Sproll, MorphoSys' chief scientific officer said in a statement. "The HuCAL-derived antibody gantenerumab has properties that we believe make it a promising candidate to treat Alzheimer's disease, and we look forward to learning more about these new Phase III trials".

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Pfizer Takes Step Back With Avelumab

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Major changes to Phase III Lung 100 study of PD-L1 inhibitor avelumab mean a big delay for development in first-line lung cancer, but, separately, Pfizer advances in allogeneic CAR-T therapy with partners Servier and Cellectis.

Pfizer Inc. has taken a step backward with the development of its PD-L1 inhibitor avelumab in lung cancer, the most valuable indication for checkpoint inhibitors, but the firm's efforts to build in immuno-oncology are advancing in another important area through an IND for an off-the-shelf CAR-T candidate, in partnership with Servier SA and Cellectis SA.

Avelumab, which is partnered with Merck KGAA's EMD Serono Inc., has trailed behind development of the leaders in the family of PD-1/L1 checkpoint inhibitors – Bristol-Myers Squibb Co.'s *Opdivo* (nivolumab) Merck & Co. Inc.'s *Keytruda* (pembrolizumab), Roche's *Tecentriq* (atezolizumab) and AstraZeneca PLC's still-unapproved durvalumab.

Avelumab is now under review for second-line treatment of metastatic bladder cancer, with an Aug. 27 user fee date, as well as the rare skin cancer Merkel cell carcinoma, which is expected to clear FDA in May.

Avelumab development generally, however, took a big step back in development in the most valuable indication of first-line non-small cell lung cancer with major protocol changes to the JAVELIN Lung 100 study, which tests avelumab as a single agent against chemotherapy. Changes recently posted on the Clinicaltrials.gov website include a dramatic increase in the number of trial participants and a nearly two-year delay in the study primary completion date – from August 2017 to April 2019.

Bernstein analyst Tim Anderson commented in a March 8 research note that changes to trial design were likely prompted by results from Bristol's failed CheckMate 026 study, in which Opdivo failed as a monotherapy in a broad population of patients with PD-L1 positive first-line lung cancer, and Merck's contrasting successful development program of Keytruda as a monotherapy in the KEYNOTE-024 study, which focused on those with high levels of PD-L1 expression. AstraZeneca similarly made adjustments to its MYSTIC trial of durvalumab monotherapy and combination therapy with tremelimumab, its investigational CTLA-4 inhibitor, in light of the emerging data.

Avelumab is on its way to a filing in second-line NSCLC, with top-line data due in the fourth quarter, but that space is becoming less important following Merck's move into the frontline with the approval of Keytruda as a monotherapy and with a submission for combination use with chemotherapy now under review at FDA.

The second-line setting also has become more competitive following FDA approval of Roche's Tecentriq in October 2016, as there are now three PD-1/L1 inhibitors cleared for that indication.

Pfizer confirmed in a statement that the following protocol changes have been made to the JAVELIN Lung 100 study:

- Primary study objective now evaluates both progression-free survival and overall survival as co-primary endpoints.
- Outcomes are evaluated based on different levels of PD-L1 expression in tumors, defined as "moderate to high," "high" and "any" (≥1%) level of PD-L1+ expression.
- Third treatment arm added to investigate whether higher exposure to avelumab as a first-line treatment for metastatic NSCLC has the potential to further improve clinical outcomes for patients versus platinum-based doublet chemotherapy.
- Additional patients recruited to allow for these additional analyses (from 420 to approximately 1,095 randomized patients).
- Completion date and estimated primary completion date are September 2024 and April 2019, respectively, changed from June 2023 and August 2017.

Pfizer explained to *Scrip* that the study design changes were spurred by recent analyses of the NSCLC cohorts of the Phase I JAVELIN Solid Tumor Study and the reported Phase I-III studies of other checkpoint inhibitors.

The revised protocol will enable the evaluation of avelumab in patients with NSCLC, whose tumors have varying levels of tumor PD-L1 expression, and with alternate avelumab dosing regimens, in the first-line treatment setting, the company said. Data from the NSCLC cohorts of the Phase I JAVELIN Solid Tumor study suggest a correlation between higher exposure to avelumab and higher efficacy, "with a marginal, if any, impact on safety," according to the company.

"We continuously evaluate our clinical development plan to ensure we answer clinically meaningful questions, and different options are built into our clinical program and studies," Pfizer said.

TOO LATE FOR PD-1 PARTY?

Anderson commented that Pfizer and Merck KGaA are "almost too late" to the anti-PD-L1 party to be relevant and that there has been speculation about whether Pfizer could terminate its deal with the German firm and instead acquire a leading player in the checkpoint market, notably Bristol or AstraZeneca.

Significant speculation lately has named Bristol as a takeover target, following the disappointment of Opdivo losing its leadership position in lung cancer and the subsequent acquisition of a stake in the company by activist investor Carl Icahn.

Anderson believes, however, that companies interested in an acquisition would likely wait for more clarity on the outcomes of various Phase III combination studies by the checkpoint sponsors. "Only then will it become clearer how market shares will be allocated among the various participants. A good portion of this information comes in 2017. At the moment, PFE and Merck KGaA are running no Phase III combination studies in lung cancer," he pointed out.

Data from AstraZeneca's MYSTIC study of durvalumab/tremelimumab and Roche's IMpower 150 study of Tecentriq with the anti-VEGF *Avastin* (bevacizumab) and chemo are expected in the second half. Data from Bristol's CheckMate 227 study of Opdivo with the CTLA-4 inhibitor *Yervoy* (ipilimumab) are expected in the first half of 2018.

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Scientific And Pricing Challenges Can't Slow New Immuno-Oncology Therapies

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Scrip spoke with executives from five companies about challenges that remain for the burgeoning – but still young – immuno-oncology field in Part 2 of a wide-ranging roundtable discussion.

In Part 2 of *Scrip*'s IO Roundtable, executives from Tocagen Inc., CytomX Therapeutics Inc., Trillium Therapeutics Inc., Xencor Inc. and Poseida Therapeutics Inc. talk about what's still unknown in cancer immunotherapy and the challenges that lie ahead, including pricing and reimbursement for novel therapies.

Mandy Jackson moderated the discussion with Tocagen vice president of business development and marketing Nicholas Boyle, CytomX chief medical officer Rachel Humphrey, Trillium president and CEO Niclas Stiernholm, Xencor president and CEO Bassil Dahiyat, and Poseida CEO Eric Ostertag while in San Francisco for the J.P. Morgan Healthcare Conference in January. Part 1 of the roundtable centered on differentiation of emerging immuno-oncology (IO) platforms and the vigorous appetite for deal-making in this arena.

SCRIP: *What do you see as the biggest challenges in this field, because relative to other areas like maybe neuroscience or antibiotics, IO looks easy.*

BASSIL DAHIYAT: There's a lot to try.

NICLAS STIERNHOLM: There's 12,000 combinations and they're growing. So we have to do exactly what Bassil said – we have to invest in understanding biology. The problem is that you have investors that want to see [complete responses (CRs)] in your first human trial and not do those [exploratory] studies that you really should be doing, and that's the struggle that we have. People aren't going to sit around and wait for biology for two years, so we've got to at the same time do something to satisfy the people that want to see some human clinical benefit.

NICHOLAS BOYLE: Another important challenge in IO and in cancer therapy in general is patient participation in clinical trials. It's a well-known problem that a small percentage – a single-digit percentage of patients – actually participate in trials, yet that really is where the best outcomes often can come from.

In brain cancer, which is our initial focus, it is no different; there's about 6% participation in clinical trials. [The challenge is] innovative ways to get patients and their caregivers motivated, because it's often a complex conversation deciding on participation in trials. Obviously, you need the sites motivated – not just the [principal investigator (PI),] but the study coordinators and all the support staff have to be engaged. Without this, all the things that collectively we want to do in IO is going to take a lot longer.

[There] are things that we'd struggle to fix, but it is a problem facing the industry of what's going to motivate that community physician to refer one of their patients to an academic center or a local center that is offering clinical trials. What's going to motivate them to even have the conversation about clinical trials with their patient, because the surveys show most patients only spend five minutes in their entire disease course talking about clinical trials with their physician?

BASSIL DAHIYAT: My wife's a physician at UCLA; she's a pathologist, so whenever something comes up with a person we know or if someone we're somewhat familiar with has cancer, her first question when they say, "What do you think?" is "Do they have insurance and how educated are they and how much of an advocate can they be? Because [insurance coverage and education] are the two best predictors of your outcome in cancer. If you don't have insurance you're, frankly, dead; it's very sad and it's a horrible element of the system we have here. But the other one – how do you advocate for yourself – those are the guys getting into clinical trials; those are the people that are looking at the billboard on the freeway saying, "City of Hope Cancer Center: We make cures here."

SCRIP: *Is it a problem right now of the industry eating its young, in a sense, because you've got Merck and others running hundreds of IO clinical trials?*

DAHIYAT: That's making the problem manifest more clearly, but no, that's not the problem. The problem is that you've got a lot of cancer patients in a community doctor's office, who is really busy and who needs information and he needs a place send them in, but he or she is not greatly financially incentivized to refer them out [to participate in a study].

RACHEL HUMPHREY: I think there's a fair number of those physicians who are not treating with immunotherapy now.

DAHIYAT: A ton of them, I'm sure.

HUMPHREY: To your point, I suspect the size of the market is grossly underestimated and as we all build safety efforts it may expand further.

And, in terms of the patients, if you look at all of the studies that are open, I don't know what the pace of your enrollment was [at Tocagen], but in my experience at Bristol-Myers Squibb Co. and AstraZeneca PLC and even now, it looks like the patients are plentiful. You'd expect them to compete with each other, but the incoming from all over is impressive.

ERIC OSTERTAG: In our experience in CAR-T, even though we haven't started the trials yet, we've lined up five sites. And very consistently, across the board, every site has said the demand for CAR-T far exceeds the supply. There are more patients that want to get in than there are companies able to deliver it.

HUMPHREY: You'd think that as the number of opportunities grows there's a saturation. I think that everybody's feeling that the saturation hasn't happened and they're throwing their very reasonable creative hats into the ring, because it's still doable. It may stop being doable, but as long as we're generating data – and soon fantastic data, no doubt – that excitement will continue. And I suspect the patient base and the physician base will also expand.

BOYLE: And imagine if we were able as an industry to double participation in clinical trials.

HUMPHREY: I wonder if it's gone up, because the interest I'm seeing is [high]. I'm in the industry 20 years on the clinical side and the enrollment up front is just very different. It used to be hockey sticks – the first [*Yervoy* (ipilimumab)] Phase III study [conducted by Bristol] that ended up changing the world had almost no patients in the first year, and then it had a hockey stick where they all came on in the last hour.

SCRIP: *How much of that is because of patient access to information now versus what it was 20 years ago?*

HUMPHREY: I think it probably helps, because we're getting input from patients and their caregivers and the web is such a replete source of, hopefully, accurate information.

BOYLE: I'm fascinated by the system in the US – I'm from the UK, so I had a different experience growing up – [where] those decisions are made about treatment pathways and the insurance companies play a very significant role in that. Imagine if the insurance companies were the ones saying, "Well hang on, have you considered a clinical trial?" It has to be a win-win for everybody. Insurance companies would need to be convinced that if patients did participate in trials then their outcomes may well be better and ultimately cost less.

DAHIYAT: At least it's free enrolling in a trial.

HUMPHREY: You know, the [National Comprehensive Cancer Network (NCCN)] guidelines used to say that you should enroll in a clinical trial in the first line across the board. With the immunotherapies out there, they're actually not saying clinical trials up front, they're saying give them the PD-1 or whatever. So part of the challenge – and it's a legitimate challenge – is that penetrating the first line can be more difficult. But the more successful you are in first line, the more available the patients are in the second line. At the beginning of my career, lung cancer had no standard of therapy; it was universally a fail. Nowadays, we're on the fourth line now, and the fourth line never existed, the third line never existed and even the second line didn't exist. So, it's a very interesting trend as patients become more available on the post-treatment range.

SCRIP: *So in your mind, what are some of the biggest needs? Is it just information, more data on mechanisms and pathways and targets, or is it having the dollars to do what you want to do?*

HUMPHREY: I think it's [a need for even more] good ideas.

DAHIYAT: I think it's actually some data. I think it's actually seeing out of this mass of, at the moment, equivalently exciting sounding ideas, which ones actually deliver some efficacy results? What is the safety cost of those results and where? And, hopefully, we can glean mechanistic understandings from that, because I think mechanistic understandings as to how these incredible therapies work is very dim, and why they don't work in most patients is very dim. We just need a lot more data, which is why it's great we're doing all these trials. I could actually see in the timeframe of my career, as it remains, an enormous change in how much we understand what's going on in the molecular level of the immune system against tumors. That's amazing.

STIERNHOLM: Patience [is a problem]. PD-1 was discovered by [Japanese immunologist Tasuku] Honjo when I was in grad school. It takes a long time [to then develop drugs].

HUMPHREY: That's right, CTLA-4 was discovered in 1994.

DAHIYAT: The IND for ipilimumab was opened in 2001 … and approval was in 2011.

HUMPHREY: I supervised [clinical development at BMS through] that whole period. Back in the day, when immuno-oncology [was young,] they handed me $100m and sent me in the back room, never believing it was going to work. [In terms of clinical trial enrollment, there were] so many years where you just didn't get the patients, because something else was sexy. Once ipilimumab opened the door a crack, I think what followed is much faster.

And, in retrospect, I sat in on meetings where people would stand up – [Richard Pazdur, director of the US FDA's Oncology Center of Excellence] was speaking and somebody stood up and said, "How come we didn't approve ipilimumab earlier? We had data from Phase II; why do you need to wait all the way to Phase III?" The answer was a fair one, which is to say, "We don't understand it well enough; we really need to get a risk/benefit story in a controlled setting."

I think as our hurdles drop [development programs move faster]. I think for [*Opdivo* (nivolumab)], once BMS got it started, it was approved in a very short period of time, and the new IO drugs are going even faster.

DAHIYAT: I think also that's the difference between the infrastructure and resources and skill sets at [smaller companies.] The early development of ipilimumab was at Medarex, a mouse antibody company that was doing clinical trials, and the later development was at BMS.

HUMPHREY: It wasn't that much later, we picked it up early.

SCRIP: *How many innings are we in the immuno-oncology ball game at this point? Do you think it's still the first?*

DAHIYAT: Bottom of the first.

OSTERTAG: I would agree.

HUMPHREY: Someone asked me if immunotherapy was going to cure cancer at a talk I gave some time ago … and I said, "Absolutely not." [There are] just a host of things we haven't learned yet and I suspect we're going to overshoot very soon; it's already happened.

There's a bit of a pendulum coming back and forth as we turn in the most effective things and patients get into trouble, which is why [Poseida has] an off switch for your CAR-T and why [Xencor is] paying attention to what you're doing at the Fc domain – so that we can make it safe – and [Trillium has] a magical way to get the cancer activated. There are plenty of examples we're going to see where the drugs are just extra potent, so we're still calibrating.

OSTERTAG: My Lyft driver asked me the same question.

HUMPHREY: Really, and what did you say?

OSTERTAG: I said I think we will cure some cancers in some patients, but clearly not all cancers in the next 10 years. The first CAR-T patient's still cancer-free four years out, so I think there will be clear wins.

[Editor's note: The discussion has been lightly edited for length and clarity.]

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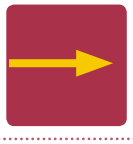


Click here for a background on the companies: **http://bit.ly/2mSelBQ**

BIG PHARMA OUTLOOK TO 2025

Big Pharma **prescription drug sales** grow to **$464bn** by 2025.

Pfizer sustains top ranking in prescription drug sales.

Humira will continue to be the highest selling product with global sales forecast at **$11bn**

Big Pharma's launch portfolio is set to add **$134bn** in revenues.

2015 Infectious diseases → 2020 **Oncology** will supplant Infectious diseases as the most valuable therapy area in Big Pharma.

REVENUES

2020: Big Pharma will add $17.8bn in sales, similar in magnitude to growth between 2010 and 2015, which saw a $15.3bn gain.

2025: Big Pharma will add $39bn in revenues out to 2025, generating $464bn in prescription pharmaceuticals sales.

2016 2017 2018 2019 2020 2021 2022 2023 2024 2025

2016-2018: Stagnant revenues are expected owing to the onset of biosimilar competition.

2020-2025: Growth is expected to decelerate owing to maturing portfolios.

REGIONAL GROWTH

Big pharma will have a 0.8% CAGR out to 2025 in the **5EU*** region. Novartis is forecast to maintain its leadership in the 5EU out to 2025. AbbVie will exhibit the most growth. Humira will sustain its status as the region's leading product.

Several companies will see declining sales in **Japan**, where the overall Big Pharma CAGR will be 0.4% out to 2025.

The **US** region will grow at a CAGR of 1.6% as payer concerns intensify. Gilead will lose its number one spot by 2025 as Roche and Johnson & Johnson share the top spot.

The **RoW** region will be the only regional drag on Big Pharma leading up to 2025, with a 0.5% negative CAGR.

Big Pharma is poised for growth because of strong launch portfolios, the availability of high-potential pipeline assets, and a focus on high-performing markets. This outlook has been created using in-house sales forecasts from the 16 companies that form **Datamonitor Healthcare**'s Big Pharma peer set.

PRODUCTS

By 2025

Big Pharma will have

62 new blockbusters NEW

BUT

55 products will lose blockbuster status

Entresto will make inroads into the heart failure market with sales of

$6bn

Humira

will retain top spot as AbbVie continues to invest in its flagship product.

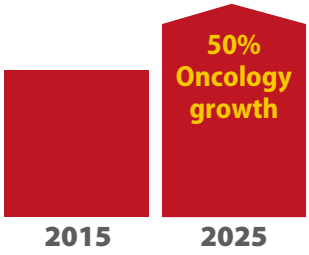
Humira sales

will decline at a CAGR of -2.1% as it navigates biosimilar entry.

THERAPIES

Oncology will account for the largest proportion of Big Pharma prescription sales in

2025



Big Pharma will add

$34.4bn

in oncology sales.

A number of large product launches in the **metabolic market** will result in this market overtaking infectious diseases by

2023

*EDITOR'S NOTE: For more information, see Datamonitor Healthcare's in-depth **Big Pharma Outlook** report, go to: http://bit.ly/2ndw6cm*

Datamonitor Healthcare
Pharma intelligence | informa

The **infectious diseases market** is set to decline by

$11.5bn

from 2015 to 2025.

The **immunology** and **inflammation therapy area** will remain stagnant as major biosimilar threats are thwarted by innovative product launches.

*5EU = France, Germany, Italy, Spain, UK. Sources: PharmaVitae Analytics, Datamonitor Healthcare

Takeda Pits Staff Against Dragons

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Takeda is embracing a "Dragon's Den" style initiative to seek digital ideas from its employees as part of the company's greater ambition to be a fully digital business.

Shutterstock: Lightspring

Takeda Pharmaceutical Co. Ltd.'s recent deal with brain testing experts Cambridge Cognition, which covers a pilot clinical study testing wearable technology as a tool for measuring symptoms and changes in patients with major depressive disorder, is one example of the big pharma's recent transformational pledges to become a digital health-based business.

Chief digital officer at Takeda, Bruno Villetelle, told *Scrip* in a recent interview about the company's plans to include digital techniques into aspects of its everyday business and how he is encouraging employees to bring forward digital ideas for the enhancement of the company via a Dragon's Den style setup.

Villetelle wants Takeda to work like a start-up when it comes to assessing digital tools. As such the company has created an internal fund to finance the best ideas from employees for incorporating digital techniques into the workplace. So far, more than 40 projects have been given the greenlight within Takeda for testing. Each digital project is run like a new startup business, Villetelle said, allowing for quick and agile decision-making.

"I want to empower small, lean teams within the company to experiment with and develop ideas to use digital to enhance Takeda's healthcare offering," Villetelle said. "You could call it a shark tank or Dragon's Den type of process. The aim is to provide a good technology that can be scaled up to be used within the wider company."

Ideas given the greenlight receive seed funding from an internal money pot set up by senior management, as well as coaching and help with project management. Digital ideas are tested within small groups before selecting the best successful projects for expansion across the business. "In my mind this is not a process that will stay for the long run, it's about showing the potential of digital and exposing employees to a new way of working," Villetelle said. "The startup way of working is novel to some, it's fast and it teaches you how to be ready for potential failure and how to move on again with a stronger hypothesis."

He added that the beauty of the setup is that next time those who have used the Dragon's Den process get a good idea, they will give it a shot on their own, "eventually this way of thinking and working becomes part of the company's DNA," he said.

Villetelle cited a current digital partnership Takeda has with IBM Watson in Japan. The two firms are developing an artificial intelligence (AI) program to provide information to medical providers on Takeda products 24 hours a day, seven days a week – an idea that originated from the internal funding initiative.

COGNITION KIT

Another recent digital experiment at Takeda is its partnership with Cognition Kit, part of Cambridge Cognition – a neuroscience digital health company that markets software products. Together, Takeda Pharmaceuticals US (a wholly-owned subsidiary of Takeda Pharmaceutical Company) and Cognition Kit Limited (a joint venture between Cambridge Cognition Holdings PLC and Ctrl Group Limited) have launched a pilot study to test a specially designed app on the Apple Watch wearable device to monitor and assess cognitive function in patients with major depressive disorder (MDD).

The study will involve 30 participants, aged 18-65, with a clinical diagnosis of mild to moderate depression who have been prescribed an antidepressant for MDD. It aims to evaluate feasibility and compliance, as well as increase understanding around how measures of mood and cognition on wearable technology compare to more traditional neuropsychological testing and patient reported assessments. The output of the study is expected in the first half of 2017.

Nicole Mowad-Nassar, vice president and head of US business operations and external partnerships for Takeda US, told *Scrip* this study is "designed to intersect healthcare and digital technologies at the patient and healthcare provider level."

The study will act as a "hypothesis generating" experience that will contribute to internal decision-making at Takeda for future clinical studies and the use of wearable technologies to measure outcomes.

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Allergan Exits Noctiva Deal

Serenity Pharmaceuticals LLC gained FDA approval of its urology drug *Noctiva* (desmopressin acetate) as the first approved drug therapy for nocturia due to nocturnal polyuria, but it lost Allergan PLC as a marketing partner. The US FDA approved Noctiva nasal spray March 3, but with a boxed warning and a narrower indication than Milford, Pennsylvania-based Serenity initially sought. The approval followed a less than enthusiastic endorsement by FDA's Bone, Reproductive and Urologic Drugs Advisory Committee Oct. 19 as to whether the drug provided a therapeutic benefit for patients suffering frequent nighttime urination. Serenity said in a March 6 release announcing the approval that it and Allergan had agreed to terminate their partnership, signed in April 2010, leaving the privately held biotech responsible for commercialization and continued development of Noctiva following a 90-day transition period. Serenity declined to comment on whether it might seek a new marketing partner for the product. Allergan called the decision a "mutual termination" in a statement provided to *Scrip* and said the firm's reasoning was due to "a shift in Allergan's commercial priorities." Allergan, however, maintains an ongoing urology business, into which Noctiva might have fit seamlessly. The unit includes *Botox* (onabotulinumtoxin A) and *Sanctura* (trospium chloride) for overactive bladder and *Rapaflo* (silodosin) for benign prostatic hyperplasia. Safety issues and a more limited patient population than sought as well as pricing and reimbursement challenges due to off-label use may have contributed to Allergan's exit. Drugs approved for overactive bladder (OAB) in the US often are used off-label to treat nocturia and nocturnal polyuria, but reportedly with little efficacy. Serenity has maintained that while most OAB therapies either shrink the prostate or create a neurological block on the bladder, its drug works by reducing kidney function overnight, stopping frequent instances of nighttime urination until the medication wears off. There are other formulations of desmopressin on the market in the US, which also have been used to treat nocturia off-label.

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Post-Lung Transplant Market For Breath Therapeutics?

Breath Therapeutics has been spun-out from German firm Pari Pharma GMBH with a €43.5m series A round led by Gimv and Sofinnova Partners, and including Gilde Healthcare. Graziano Seghezzi, partner at Sofinnova, told *Scrip* that Bronchiolitis Obliterans Syndrome (BOS), a lethal orphan respiratory disease mainly affecting lung transplant patients, is currently the company's sole target indication. Discussions are ongoing with US and European regulators on designing the protocol for a Phase III trial. BOS is commonly understood as chronic graft rejection and is the main reason for the poor five-year survival rates after lung transplantation. There are no approved drugs for the indication and a search of Informa Pharma Intelligence's Pharmaprojects database revealed only one drug in clinical testing: Orbis Sciences' ORB-101, a formulation of prednisone that is currently in Phase I. Based on work by Pari Pharma and lung transplantation expert Dr Aldo Iacono of the University of Maryland in the US, Breath Therapeutics is developing a drug/device combination that puts a formulation of liposomal cyclosporine A into a high-performance nebulizer, which enables remote adherence monitoring. This approach is expected to ensure a safe, well tolerated and targeted delivery of immunosuppressive medication directly into the lungs. "BOS is one of the most devastating lung diseases and still today, no effective therapy is available. Our strategy is to deposit high concentrations of an immunosuppressive agent directly into the small airways of the lung," said Jens Stegemann, CEO of Breath Therapeutics, in a statement.

sukaina.virji@informa.com, 9 March 2017

Vertex Plays Defense In CF With Concert Deal

Vertex Pharmaceuticals Inc. has acquired worldwide development and commercialization rights to Concert Pharmaceuticals Inc.'s edited version of its own market-changing cystic fibrosis therapy *Kalydeco* (ivacaftor) in a move to defend its market-leading CF portfolio. The transaction takes away Concert's rights to its lead development program, but the deal is transformative for the company in another important way: Concert will use the proceeds to finance its operations into 2021, including clinical development for another of its pipeline programs. Cystic fibrosis treatment has changed significantly since the approval of Vertex's standard-of-care-altering drug Kalydeco in 2013; and the specialist drug developer now rules the CF market place, with a second treatment-enhancing product approved, *Orkambi* (lumacaftor/ivacaftor), and a busy pipeline of drug candidates targeting different patient populations based on mutation types. *Orkambi*, approved in the US in 2015, is expected to become the most prescribed CF therapy in the country by 2025, with a predicted market share of 28%. The asset purchase agreement for Concert's mid-stage asset that was announced March 6 falls into the latter category and has been labeled a "defensive strategy," by Datamonitor Healthcare lead analyst Daniel Chancellor. Vertex acquired Concert's CTP-656, an investigational cystic fibrosis transmembrane conductance regulator (CFTR) potentiator that has the potential to be used as part of future once-daily combination regimens of CFTR modulators that treat the underlying cause of CF.

lucie.ellis@informa.com, 6 March 2017

Nine Leadership Lessons From The Biotech Front Line

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After six years as CFO of Algeta and two years as CFO and CEO of Targovax, Øystein Soug has learnt some things along the way, good and bad. Here are nine of his leadership lessons to date.

Targovax CEO Øystein Soug

Øystein Soug has first-hand experience in many of the corporate and developmental procedures that leading a biopharmaceutical company needs. He has taken a product from Phase II through Phase III, started five new trials on a shoestring, secured a partnership deal, registered a product with the FDA and EMA, established proprietary production, established a US organization and sales force, and launched an oncology product in the US market. In the boardroom he has built an organization from 25 to 200 people, a finance/HR department from zero to 18, raised more than $250m in the capital markets, conducted a trade sale with subsequent integration, merged two small biotech companies, conducted hundreds of investor relations meetings and attended more board meetings "than is healthy".

Clearly, this is a lot of material to reflect on and he would never claim to have done all this by himself. "Mostly I was merely taking part or trying to help from the sideline – but nevertheless I was close enough to be able to reflect on what would have been helpful to know," he says.

Be careful when guiding. You will be forgiven for conservative guiding, but not for failing to fulfil your promises

- Selling a biotech equity story is all about creating expectations. Investors particularly crave to hear when trials are starting, how they are recruiting and when data is coming. It is tempting to assume that things will happen as planned. Boards and bosses always push for speed. Don't fall for the temptation of being optimistic. Be extremely careful and build in more buffers than you think you need. Assume trials will start later than the CMO is telling you and always assume paltry patient recruitment speed.
- Over-delivering is also nice.
- Never guide in quarters. Half-years are short enough.

Do a lot of IR. It's the easiest way to spread your story

- As a CEO or CFO the easiest way to spread your story is via investor relations. IR is a self-perpetuating machine where brokers want to take you out, investors want to learn about your market and technology (and maybe even your company) and you want to spread your story.
- If investors buy into your story, they will discuss it with analysts and analysts will discuss with key opinion leaders (KOLs) and other investors. If you do a lot of IR, you may start a virtuous circle in which you will eventually inculcate KOLs with your story. This may have real life consequences – not only on capital raises and the share price, but also on your ability to conduct trials and launch products.

Raise as much cash as you can, when you can

- When I first heard this, I thought it pretty tabloid and – if a truth at all, at least one with many caveats. After all, dilution is bad, right?
- My experiences have shown that the statement is always correct. I cannot think of one instance where raising less cash or waiting to raise cash would have been beneficial for existing investors. Some boards and shareholders want to be smart and only raise at higher prices, but, alas, it is rarely possible in real life.
- Biotech is all about creating data and you need the security of cash not running out in order to do that.
- One would think that everyone understands it is better to own 1% of Pfizer than 85% of a one-trick-pony. Although boards and shareholders say they do, they don't always grasp the implications. Brace yourself!

Take corporate governance seriously

- Early stage, when the shareholder register is small and transparent, getting things through the AGM is easy.
- When the market cap grows and international funds start owning significant shares of the company, you will see that the PMs don't even read your AGM notice, but send it off to proxy companies who advise on (dictate) voting. Their advice is according to stringent rule books, often stricter than national corporate governance guidelines. Make sure you establish contact with these proxy companies, understand how they are thinking and understand their rule books. If you don't, you will get a nasty surprise one fine AGM morning.

Structure partnerships in a way that ensures aligned interests

- For a small but proud biotech, it is tempting to fight for a big role in a partnership.

Soug's Résumé

Øystein Soug, CEO of Targovax ASA since November 2016 after serving as its CFO, has spent the past 20 years in international banking and industry, including six years at Algeta ASA.

He is the former CFO of Algeta, a Norwegian oncology biotech company which was sold to Bayer AG for $2.9bn in 2014. Prior to joining Algeta in 2008 Soug worked for six years at Norwegian conglomerate Orkla, lastly as CFO of Orkla's Russian division.

Soug started his career as a banker with Credit Suisse and with the European Bank for Reconstruction and Development. He received an MSc in Economics and Financial Markets from Universität St. Gallen in Switzerland in 1997.

It is always painful to give up control of products and programs, but you are better off if the partner does the heavy lifting, even if it means you must take the back seat.

- If you have too much say and too big a role, you probably also have to pay for it, co-financing Phase III trials, for example. That may shackle the product and impede its development if you can't raise the money.

Don't talk about the plumbing unless you have to

- Investors are primarily interested in value bumps from data. Executives and boards know that chemistry, manufacturing and control (CMC), as well as logistics and other technical aspects of the business, are almost as important (late product development equals late pivotal trials/launches in the future).
- Unless investors really demand updates about CMC, logistics, QA and other technical things that have to be in order, don't play the card. When you start telling them about what you are doing within these areas, they will lock onto the risks as they have already discounted in the upside.

Always be nice to people and don't get emotional

- All organizations are political and sometimes people clash.
- The biotech industry is small. We circulate and we are bound to meet again.
- Don't get emotional. Try to be nicer to adversaries than you really would like to be. In two years, that adversary may be your boss or counterpart.

Mergers are all about psychology

- Mergers are planned with spreadsheets. Integrations are done rationally. But if people feel lost, if they feel their concerns are not addressed, they will leave.

Women do not have a prostate

- In my very first IR meeting, I informed the investor that prostate cancer is a lot more prevalent in men than women! CFOs should know their stuff before they open their mouths…

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From the editors of *Start-Up*

Merck's Biosimilars Business: What's For Sale And Who Will Buy It?

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Merck KGaA is getting out of biosimilars – a unit that CEO Stefan Oschmann called the company's now redundant back up plan – to instead focus on its growing oncology pipeline, which includes recently acquired pipeline candidates from Vertex Pharma.

Merck KGaA is in "advanced discussions" to divest its biosimilars business unit – which includes a copycat version of AbbVie Inc.'s best-selling immunology drug *Humira* (adalimumab) – as part of an ongoing restructuring process, the company announced during its March 9 annual results presentation. The divesture of this unit would also cut down on R&D costs to the company, which said it spent around €130m on biosimilars in 2016; mostly on R&D, as well as on manufacturing work and preparation for commercialization.

At present, Merck has no revenue streams from its biosimilar drugs but its biosimilar adalimumab product, MSB11022, is in Phase III trials for rheumatoid arthritis and psoriasis.

Merck's website lists only MSB11022 under the tab for biosimilars in development. But rumors of a potential divestment of the unit started late last year, with reports valuing Merck's biosimilar portfolio as high as $1bn – though these estimates came from anonymous sources. This high price suggests there is more to Merck's portfolio than just a Humira copycat that would be sold at a cut price on the market against many other biosimilar options, the originator drug and other branded therapies.

In 2014, the company initiated a deal with Bionovis to develop biosimilars for the Brazilian market; and in the same year Merck said in a presentation that it had licensed another biosimilar. The company did not disclose which product this was a biosimilar of but it is speculated to be a version of Roche's *MabThera* (rituximab).

Merck's chair and CEO Stefan Oschmann said during the company's earnings call that the biosimilars program was "initiated at a time when our pipeline looked much less attractive." He said Merck expected to divest this unit to focus more on its innovative pipeline. "In a way us getting into biosimilars was a plan B," he said, noting that the company's shift to focus on branded pharmaceuticals only should be interpreted as a vote of confidence from the firm in its innovative pipeline.

In parallel to the divestiture of its biosimilars unit, Merck said it expects to spend more on R&D in its pharma business this year. Oschmann did not confirm a total R&D budget for the group, but he said market forecasts claiming that Merck will spend €150m to €200m more on R&D in 2017 were "not illogical." Merck's 2016 healthcare R&D costs were around €1.5bn.

In 2017 the German firm will be advancing R&D for six new molecules in oncology that it acquired from Vertex Pharmaceuticals Inc. earlier this year; as well as making significant investment into its other key pipeline cancer drug avelumab.

POTENTIAL BUYERS

Morning Star senior equity analyst Michael Waterhouse suggested Teva Pharmaceutical Industries Ltd. as one company that might be interested in Merck's biosimilars portfolio, in a Mar. 9 note. However, Datamonitor Health analyst Armando Uribe ruled out the generics giant, telling *Scrip* that Teva didn't have the funds and had other things to focus on following its $40.5bn acquisition of Allergan PLC's generics business in 2016. "It would be very risky to for Teva to take on another acquisition right now," Uribe said.

A buyout from a company without an established biosimilars arm could be on the cards. All the big biosimilar players are knee-deep into development for copycat versions of Humira and MabThera – the most advanced or key products in Merck's portfolio. It is unlikely versions of these drugs from Merck will grab their attention. However, a readymade biosimilar portfolio could greater benefit a mid-sized or big pharma looking to move into or bulk up its offering in the biosimilar space.

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Akcea Faces Tricky Risk/ Benefit Scenario

Ionis Pharmaceuticals Inc. subsidiary Akcea Therapeutics Inc. now has Phase III efficacy data in hand for volanesorsen in familial chylomicronemia syndrome (FCS), but market analysts are mixed on the implications of safety data showing frequent instances of reduced platelet counts, potentially leading to thrombocytopenia. FCS, a rare disease affecting an estimated 3,000-5,000 patients worldwide, results in extremely high triglyceride levels and can lead to recurrent and potentially fatal pancreatitis. In the Phase III APPROACH study, Akcea revealed March 6 that volanesorsen achieved statistical significance compared to placebo for mean reduction of triglycerides, with a number of other treatment benefits seen, but 10% of volanesorsen patients discontinued treatment due to declines in platelets. Another 10% stopped treatment because of injection-site reactions. Akcea noted during an investor call to review the data that its understanding of FCS and how volanesorsen treats the disease has evolved over the clinical development program and that it now believes that platelet-count decreases can be a by-product of how the drug works, and that the reductions are manageable. The company added platelet monitoring after becoming aware of the issue, and noted that no patients discontinued treatment with volanesorsen during the last six months of the study after platelet monitoring was fully implemented. Wall Street reactions to the data were decidedly mixed, while parent company Ionis' stock price closed trading on March down 8% to $50.18 per share. Eun Yang of Jefferies Equity Research rated the Ionis stock "underperform" in a March 6 note and said volanesorsen's safety profile suggests "limited commercial potential" for the drug.

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TG Welcomes CLL Data – But Cloud Looms

Positive top line data for TG Therapeutics Inc.' Phase III GENUINE study of *TG-1101* (ublituximab, a monoclonal antibody that targets CD20) plus *Imbruvica* (ibrutinib) versus Imbruvica alone in previously treated patients with high-risk r/r CLL were welcomed by analysts and investors alike, ensuring the company's share price almost doubled within a week. The trial met its primary endpoint of increasing overall response rate. The combination arm had an ORR of 80% compared with 47% in the Imbruvica monotherapy arm. "We believe this data supports previous data showing that ublituximab is well-tolerated and should reduce the relapse rate," wrote Aegis Capital Corp's Jason Wittes in a March 6 note. The high risk CLL patient group is currently served by AbbVie Inc. and Johnson & Johnson's Imbruvica, Gilead Sciences Inc.'s *Zydelig* (idelalisib), bendamustine + rituximab (BR), and increasingly – following its 2016 approval – AbbVie/Roche's BCL-2 inhibitor venetoclax. "We believe the ublituximab plus ibrutinib combination label will be preferred when treating high-risk r/r CLL patients over venetoclax – the latter being more cumbersome to administer (requiring hospitalization and heavy monitoring) and risky in this patient population, thus rarely used in the community setting," Wittes wrote. "The current standard of care is ibrutinib therapy over *Venclexta* (venetoclax), given that venetoclax can rescue ibrutinib-treated patients but not vice-versa." TG is moving full steam ahead to get its product through the regulatory process. In previous discussions with the company, the FDA indicated that a 20% increase in ORR would be clinically significant and sufficient for approval. Following the release of the interim GENUINE results, TG said it was targeting full data presentation at a medical meeting in 1H17 and meeting with the FDA in 2H17 "to discuss the results and filing for accelerated approval."

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Dunsire Takes XTuit Helm

Privately-held XTuit Pharmaceuticals Inc. has tapped experienced oncology leader Deborah Dunsire as president and CEO as the company's lead drugs mature towards the clinic. The Waltham, Massachusetts-based firm, focused on developing novel drugs targeting the disease-promoting microenvironment in fibrotic diseases and cancer, expects to bring its first drug into the clinic in 2018. Dunsire has a long track record building drug companies. She is perhaps most recognized for running the cancer company Millennium Pharmaceuticals, which was sold to Takeda Pharmaceutical Co. Ltd. for $8.8bn in 2008. More recently, she led neuroscience-focused Forum Pharmaceuticals Inc., which was forced to close operations last year after its lead candidate failed in Phase III for Alzheimer's disease. At XTuit, Dunsire will return to a business area she knows well – oncology -- but XTuit also is developing drugs for fibrotic diseases, including non-alcoholic fatty liver disease (NASH) and liver cirrhosis. "I felt excited about a company that really had a platform to work in diseases of high unmet need," Dunsire said in an interview. The company, which brought in $22m in a Series A financing in 2015, was built out of science by Rakesh Jain of Harvard Medical School and Massachusetts General Hospital, Robert Langer of Massachusetts Institute of Technology and Ronald Evans of the Salk Institute for Biological Studies. Investors include Polaris Ventures, New Enterprise Associates, CTI Life Sciences, Arcus Ventures and Omega Funds. XTuit hasn't revealed exactly what drug targets it is pursuing, but the research is focused on multiple pathways that cause the disease microenvironment.

jessica.merrill@informa.com, 8 March 2017

Bristol Is Not Backing Down On Oncology

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The appointment of oncologist Thomas Lynch to succeed Francis Cuss as chief scientific officer suggests the biopharma won't be straying too far from its current focus on developing cancer drugs.

Bristol-Myers Squibb Co. tapped an industry outsider as its new research and development leader, announcing the appointment of oncologist and academic Thomas Lynch as chief scientific officer March 8. The news that Lynch will succeed Francis Cuss suggests that while Bristol wants to shake up its R&D unit after losing ground to rivals in the competitive immuno-oncology field, the company's future investment will remain deeply tied to success in cancer.

Lynch brings a strong pedigree to the position with specific experience in lung cancer, one of the biggest commercial oncology opportunities. He worked for 23 years at Massachusetts General Hospital as chief of hematology/oncology and later as CEO Massachusetts General Physicians Organization and as a member of the hospital board from 2015 to 2017. He worked outside of MGH from 2009 to 2015 as the director of the Yale Cancer Center. In 2004, while at MGH, he was part of a team credited with the discovery that certain genetic mutations in lung cancer patients caused therapies to work for some individuals and not for others.

Lynch is not entirely new to Bristol, however, having served on the company's board of directors since 2013. He will step down from that role March 15. Cuss, meanwhile, who took over the top R&D role in July 2013, will serve as an advisor to the company for the next three months. "Tom is an internationally recognized oncologist known for his leadership in the treatment of lung cancer and has made significant contributions to the field of targeted therapies throughout his career," CEO Giovanni Caforio said in a statement.

Bristol has been the early frontrunner in immuno-oncology with approvals for its PD-1 inhibitor *Opdivo* (nivolumab) and CTLA-4 inhibitor *Yervoy* (ipilimumab).

The firm should maintain a significant market share, but it faced a major setback last year, stunning investors when Opdivo failed to show a benefit in first-line non-small cell lung cancer (NSCLC) patients after racking up successes in other indications, including second-line lung cancer. The disappointment was exacerbated by the fact that Merck & Co. Inc.'s *Keytruda* (pembrolizumab) did show a benefit in first-line NSCLC and became the first immune checkpoint inhibitor to win FDA approval for the indication.

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View Bristol's Oncology Pipeline here: **http://bit.ly/2nfFgbH**

Indian Court Lifts Curbs On Herceptin Biosimilars

The Delhi High Court has, in an interim order, permitted partners Biocon Ltd. and Mylan Inc to make and sell their biosimilar trastuzumab versions, without any riders, for all three indications - Her2 metastatic breast cancer, early breast cancer and metastatic gastric cancer. On March 3, a division bench of Justices Badar Durrez Ahmed and Sanjeev Sachdeva is said to have held that since the Indian regulator had approved the package insert and the biosimilar for all three indications, "no restrictions" be imposed at this stage with regard to the second and third indication also. Biocon maintained that the division bench has not only stayed the operation of a previous order of April 2016 but also held that the biosimilar versions can use the package insert for all three indications including the "publicly available data of the reference product therein" as it has been approved by the Drugs Controller General of India. In April, last year, Delhi High Court Judge Manmohan Singh had, in a scathing order, restrained Biocon and Mylan from using the data relating to manufacturing process, safety, efficacy and tests conducted for the safety of the drugs as complained of by Roche until the final decision on the issue of the biosimilarity is made in the suit.

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Politics Dilute Germany's AMNOG Updates

New updates to Germany's healthcare reform could lead to more conservative prescribing and will open the door to AMNOG benefit assessments for drugs launched before such evaluations were introduced. Some pricing measures have been scrapped ahead of this year's general elections, however, the pricing issue is likely to fire up once the elections are over. Companies can expect debate over pricing thresholds and pricing for combination products and orphans and potentially another new law. Germany's Bundestag has passed a law updating the 2011 AMNOG healthcare reform act. This introduced tough new assessments to compare the benefits for patients of new drugs with those offered by their rivals already on the market. The drugs are scored according to the additional level of benefit they offer and those scores then inform negotiations between statutory health insurers and the manufacturer on discounts on the initial price that was freely set on launch. The new law will come into effect in April, although it looks rather different to previous drafts thanks to September's general election. However, Mueller is pleased that measures to inform doctors about the outcome of AMNOG benefit assessments have made it through. When deciding what to prescribe their patients, doctors will be alerted to the results of the AMNOG benefit assessments and how a drug compares to rivals already on the market in terms of the benefits it offers and also its price.

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Access To HCV Therapies Decreasing

The maturing hepatitis C drug space presents a conundrum in that as the cost of therapy decreases and real-world data accumulate showing that the newest treatments are working as expected, access to these direct-acting antiviral (DAA) drugs is falling off rather than improving. According to the latest findings released by Trio Health, a health care outcomes data analysis firm, failures to start prescribed HCV therapy rose from 8% in 2014 to 20% in 2015 and again to 29% last year. The company attributes approximately 90% of the non-starts to denials of coverage by private- or public-sector health care providers or to patients failing entry requirements like drug or sobriety testing. As HCV treatment has grown less lucrative for the three primary players in the HCV space – Gilead Sciences Inc., AbbVie Inc. and Merck & Co. Inc. – the companies have cited a reduction in treatment starts as the principal reason, along with pricing pushback. But Trio Health's data indicate that demand for HCV treatment actually is rising – and that denials of coverage are the main obstacle to that continued demand.

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Novartis Korea Hit With Fine

South Korea's Ministry of Food and Drug Safety (MFDS) has fined the South Korean subsidiary of Swiss-based pharma multinational Novartis AG KRW200m ($173,988) and suspended sales of selected products for three months, in response to a violation of the country's Pharmaceutical Affairs Act by providing rebate payments to doctors in return for prescriptions of the company's drugs. The MFDS's administrative measures come after local prosecutors indicted several employees of Novartis Korea without detention in August last year on charges of making illegal rebate payments. The case is still proceeding in court. At that time, prosecutors asked the MFDS as well as the Ministry of Health and Welfare to take administrative measures against Novartis Korea including business suspension, relevant drug price cuts, and reimbursement suspensions. The ministries have also been requested to suspend the licenses of the doctors suspected of receiving rebates from the company. The MFDS notes on its website that it has levied the fine in relation to 30 variations of 14 Novartis Korea products including *Galvus* (vildagliptin), *Lescol* (fluvastatin) and *Onbrez* (indacaterol) for which the subsidiary provided financial gains with the purpose of promoting sales. It has banned temporarily the sales of 12 variations of three products - *Exelon* (rivastigmine tartrate), *Trileptal* (oxcarbazepine), and *Zometa* (zoledronic acid) – for three months from March 17 to June 16.

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Kainos Opens New Era With Parkinson's Drug

Kainos Medicine's senior vice president sat down with Scrip to talk about the progress and ambitions for its first-in-class, potentially disease modifying Parkinson's disease drug candidate. If the drug candidate successfully goes through a Phase IIa in the US, it is set to draw robust interest from multinational pharmas which are already active in the area that lacks fundamental treatments.

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Kainos Medicine Inc. is a South Korean bioventure that has come under the spotlight recently for the progress it has made with a first-in-class, potentially disease-modifying drug candidate for Parkinson's disease (PD).

So far there seems to be smooth sailing in a Phase I clinical study in South Korea with the molecule, KM-819, and the company is now gearing up protocols for a proof-of-concept Phase IIa trial in the US, a crucial stage for Kainos as success here could draw strong collaborative interest from multinationals which are already active in the PD area.

"So far we have sufficiently increased dosing [in the Phase I trial], but we haven't found particularly problematic side effects," Sungeun Yoo, senior vice president at Kainos, told *Scrip* in an interview in Seoul.

NOVEL CLASS

KM-819, a Fas-associate factor (FAF1) inhibitor, is a first-in-class, orally active small molecule that inhibits cell death and acts as a novel neuroprotective agent for neurodegeneration. In preclinical studies, it has shown protection of dopaminergic neuron cells from MPTP-induced cell death and has also protected behavioral impairment in MPTP-treated PD animal models.

Kainos originally brought in the FAF1 inhibitor from Choongnam University's Professor Eunhee Kim, who has long studies the molecule, which appears to be only one its class in development.

"We are developing this as a global drug as there is no such [FAF1] drug now," said Yoo. "If we are successful in the Phase IIa, then the world will change."

"We are targeting global markets…if we are successful in the Phase IIa, then the world will change." – Kainos SVP Sungeun Yoo

The Phase I study is being conducted at CHA Hospital in South Korea will look at the pharmacokinetic profile, safety and tolerability of the drug in healthy young individuals. It will involve single and multiple ascending doses and assessment of pharmacodynamic markers. The study is expected to be completed in August 2017 but final results are likely to become available this November or December.

PHASE II PLANS

"We are targeting global markets, so we plan to conduct a Phase II trial in the US. The Phase I is underway in Korea, but we have designed its requirements in line with global regulations, particularly the US. And we hired Parexel International Corp. as our CRO," Yoo said.

As success at Phase IIa will be significant for the company, it is making thorough preparations over the design of the study.

"We will need to analyze the Phase I results and set protocols for the Phase II, such as how we will use imaging technology and how we will select patient groups. We could select one group with PD caused by genomic factors and another group with patients caused by environmental factors. To prepare for this, we are seeking diverse collaborations," Yoo said.

The executive commented that the company has high expectations for KM-819 as success of this project will also be crucial in wider symbolic terms.

"From a business perspective, there will be a huge economic impact. But for South Korea, this will also have a symbolic meaning, for a South Korean biotech to develop such a product, even if we join hands with a global company in the later stages. So we have to succeed," declared the senior vice president.

Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's and involves gradual loss of dopamine-producing neuron cells. It can be caused by environmental factors, which account for the majority of patients, or by genomic factors. At present, there are no disease-modifying PD drugs that can stop or slow down the progress of Parkinson's.

Current drug therapies are symptomatic. They might initially manage motor symptoms but are not able to modify the disease's course. In the absence of therapies truly capable of halting or slowing down neurodegeneration, patients will continue to experience disease progression, according to Datamonitor Healthcare analyst Ines Guerra.

"Not only is this associated with increasingly higher degrees of functional disability, but patients' quality of life is also negatively impacted," the analyst observed.

Guerra said that neuroprotective treatments have emerged as the greatest unmet need in Parkinson's and Kainos is attempting to target this unmet need with KM-819.

"It appears that by inhibiting the function of FAF1, KM-819 could help prevent cell death. This could mean the therapy might do more than supplement dopamine levels – it could potentially avoid the degeneration of dopaminergic neurons, one of the main sources of dopamine," she said.

"This [approach] would certainly be of interest to a number of pharmaceutical companies already active in the Parkinson's disease market. Some of these are very big players such as Novartis AG, AbbVie Inc., GlaxoSmithKline PLC, Boehringer Ingelheim GMBH and Teva Pharmaceutical Industries Ltd., the analyst said.

"It would then make sense that Kainos would enter a strategic partnership to expand its geographic reach, and to avoid some of the financial burden associated with a global late-stage development program."

Indeed, Kainos is seeking to tie up with a global pharma for late-stage development of KM-819. "We are now engaged in technology due diligence with some global companies," Yoo said.

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From the editors of *PharmAsia News*.

(Editor's note: includes source data/analysis from Datamonitor Healthcare)

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

CLICK

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

Selected clinical trial developments for the week 3–9 March 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Array BioPharma Inc. / Pierre Fabre Group	binimetinib	NRAS-mutant melanoma	NEMO; in *The Lancet Oncology*, March 8, 2017.
OncoGenex Pharmaceuticals Inc.	custirsen	prostate cancer	SYNERGY; *The Lancet Oncology*, March 7, 2017
Updated Phase III Results			
Eli Lilly & Co.	*Taltz* (ixekizumab)	plaque psoriasis	UNCOVER 3; maintained efficacy over two years.
Eli Lilly & Co.	*Taltz* (ixekizumab)	plaque psoriasis	IXORA-S; better than Stelara on response rates .
Sun Pharmaceutical Industries Ltd.	tildrakizumab	plaque psoriasis	reSURFACE 1; maintained to week 64.
Sanofi/Regeneron Pharmaceuticals Inc.	*Dupixent* (dupilumab)	atopic dermatitis	CHRONOS; further data on efficacy .
Amgen Inc.	*Kyprolis* (carfilzomib)	multiple myeloma	ENDEAVOR, ASPIRE, CLARION; effective and well tolerated.
UCB Group/Dermira Inc.	*Cimzia* (certolizumab pegol)	psoriasis; psoriatic arthritis	CIMPASI-1, -2; RAPID PSA; further positive data .
Amgen Inc.	*Xgeva* (denosumab)	multiple myeloma, skeletal-related events	Non-inferior to zoledronic acid.
Phase III Completed			
TiGenix NV	Cx601	perianal fistula in Crohn's disease	ADMIRE-CD; effective and well tolerated.
Phase III Interim/Top-line Results			
Janssen R&D LLC /MorphoSys AG	guselkumab	plaque psoriasis	VOYAGE 2; NAVIGATE; improved skin clearance .
Aimmune Therapeutics Inc.	AR101	peanut allergy	PALISADE; screening data collected for the study.
GlaxoSmithKline PLC	*Nucala* (mepolizumab)	severe eosinophilic asthma	MUSCA; improved quality of life and lung function.
Ionis Pharmaceuticals Inc.	volanesorsen	familial chylomicronemia syndrome	APPROACH; met primary endpoint, reduced triglycerides.
Sanofi/Regeneron Pharmaceuticals Inc.	*Dupixent* (dupilumab)	atopic dermatitis	LIBERTY AD Open-Label; sustained efficacy.
TG Therapeutics Inc.	ublituximab	chronic lymphocytic leukemia	GENUINE; met primary endpoint, increased overall response rate.
Sandoz Pharma Ltd.	adalimumab, biosimilar	psoriasis	ADACCESS; equivalent to *Humira*.
Hutchison China MediTech Ltd.	fruquintinib	colorectal cancer	FRESCO; positive results .
Phase III Initiated			
Daiichi Sankyo Co. Ltd.	*Savaysa* (edoxaban)	stroke prevention	The ENTRUST-AF PCI study.
ObsEva SA	nolasiban (OBE001)	reproductive disorders	To improve live birth rates.
AB Science	mastinib	uncontrolled asthma	Uncontrolled by steroids.

Source: Biomedtracker

Bone Therapeutics, a company focused on orthopaedics and bone diseases, has appointed ***Miguel Forte*** chief medical officer. Most recently, Forte was chief operating and medical officer at a French biotech called TxCell and chief commercialization officer and chair of the commercialization committee at the International Society of Cellular Therapy. He has over 20 years of experience in medical and regulatory affairs and is an associate professor of health sciences and pharmacy at both the University of Aveiro and the University of Lisbon.

BrainStorm Cell Therapeutics Inc., a company focused on neurodegenerative diseases, has appointed ***Ralph Z. Kern*** chief operating officer and chief medical officer. Kern joins the company from Biogen, where he was senior vice president and head of worldwide medical affairs, but previously he was head of Novartis' neuroscience medical unit. In the past, Kern was also global medical director of personalized genetic health at Genzyme Corporation.

Tris Pharma, a company focused on developing therapies for Attention Deficit Hyperactivity Disorder (ADHD), has named ***Paul Rogers*** chief commercial officer to lead the its brand business. Rogers brings over 25 years' experience in clinical research and commercial roles to Tris from his time within small and large pharma companies. Meanwhile, Tris' chief commercial officer ***Sharon Clarke*** has been promoted to the newly created position of senior vice president, corporate development of pediatric business.

Pablo J. Cagnoni has joined **Lycera Corp.**'s board of directors with board member, ***Timothy M. Mayleben***, stepping down from his position. An oncologist and biopharmaceutical executive, Cagnoni is president and CEO of the immunology company Tizona Therapeutics and director of CRISPR Therapeutics and Harpoon Therapeutics. Before this he was president of Onyx Pharmaceuticals, a subsidiary of Amgen, and previously held executive global development roles at Novartis Oncology, Allos Therapeutics (acquired by Spectrum Pharmaceuticals), and OSI Pharmaceuticals (acquired by Astellas).

Tiziana Life Sciences Plc., a company creating drugs for cancer indications and autoimmune and inflammatory diseases, has appointed ***Arun Sanyal*** a member of its scientific advisory board. Sanyal is a professor of medicine, physiology and molecular pathology within the division of gastroenterology, hepatology and nutrition at the Virginia Commonwealth University School of Medicine. He is a special council board member of NIAAA (National Institute on Alcohol Abuse and Alcoholism) and has previously been president of the AASLD (American Association for the Study of Liver Diseases). Sanyal has also chaired committees at the NIDDK NASH clinical research network and the NIH hepatobiliary study section.

Avelas Biosciences Inc., a clinical-stage oncology-focused company, has name ***Dr Alexey Vinogradov*** to its board of directors. Vinogradov is currently head of Pharmstandard Ventures, a corporate venture fund of the Pharmstandard Group. He replaces Dr Andrei Petrov as a director of the company. Vinogradov was previously a board member at Argos Therapeutics and a board observer at Protagonist Therapeutics and Aquinox; currently he serves as a board observer at Allena Pharmaceuticals.

Novartis Pharma KK in Japan has announced that ***Ichinari Tsunaba*** will become representative director and president, effective April 1. Tsunaba will succeed current president Dirk Kosche who will become an advisor.

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