How Will Pharma M&A Change?

Consultants predict more deals, higher prices and asset swaps as repatriated cash burns holes in US pharma's pockets **(p4)**

Can Pharma Keep Up?

The digital revolution is transforming the world of healthcare, which is awash with new technologies and floods of data **(p12)**

Raymond Schinazi's Story

Recently associated with hepatitis C cure, Schinazi tells *Scrip* why he has no intentions of stopping **(p16)**

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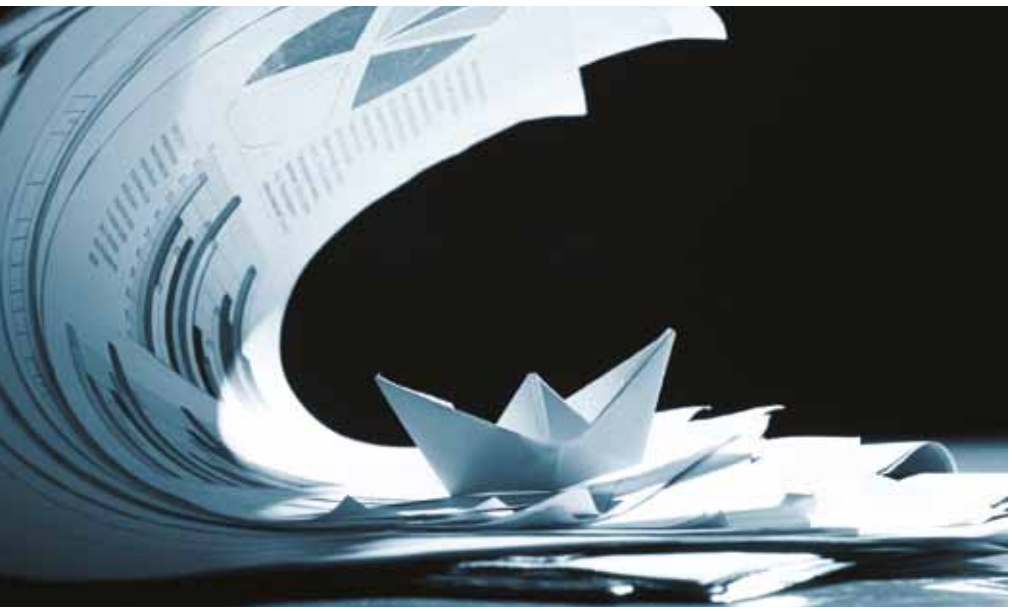

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Sweeping FDA Changes Could Have 'Disastrous Consequences'

JESSICA MERRILL jessica.merrill@informa.com

Lowering the bar on drug approval standards would create a challenging environment for biotech investors, warned Jonathan Leff, a partner at the health care investment firm Deerfield, during the BIO CEO & Investor Conference.

Deerfield partner Jonathan Leff issued a serious warning to the biotech industry during a policy panel at the BIO CEO & Investor Conference Feb. 14, declaring that sweeping changes to the FDA's drug approval standards under a new administration and a new commissioner could have "disastrous consequences" for biotech investment. "FDA as we know it has been about regulating the efficacy as well as the safety of drugs," Leff said. "If that were to change it would mark a fundamental difference to how we think about developing drugs, marketing drugs in this country."

"A major change like that would have very negative and potentially disastrous consequences for biotech investment in the biotech industry," Leff said.

The dismantling of FDA drug approval regulations has become a concern under the new Trump administration. Many of President Trump's cabinet appointees are skeptics of the agencies they've been tapped to run, with the intention being to shake up the status quo. Many in the industry have voiced concerns about a similar situation arising at the FDA, especially since some of the names that have been floated for FDA commissioner do not have industry experience. The one name industry appears to be comfortable with for the commissioner role is former FDAer and physician Scott Gottlieb, currently an American Enterprise Institute fellow.

Leff said most people in the industry agree at the macro level at least that the FDA works, and industry has shaped its drug development processes to fit the FDA's mold.

"As an investor in early-stage biotech, it would become exceedingly difficult to invest in great science if you didn't have a basic belief that great science leads to more efficacious treatments ," Leff said. "If you eliminate the requirement to prove efficacy of drugs, it becomes a wild west where snake oil can compete with real science-driven therapies, and that makes it awfully hard to think about how to invest in the sector."

Leff urged industry to be active in informing policy makers of the important role the FDA plays, and that while rolling back regulations in some sectors might stimulate growth and drive job creation, the same is not necessarily true in the drug industry.

"Some of the statements [Trump] has made suggest that…if you roll back the requirement for an efficacy standard you will unleash growth and investment and job creation in biotechnology. I think it falls to all of us to make the case as forcefully as we can that very much the opposite is true," Leff said.

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from the editor

eleanor.malone@informa.com

One of the stand-out moments at last year's Scrip Awards was the standing ovation for the winner of the Lifetime Achievement Award, Professor Raymond Schinazi, following his inspirational acceptance speech. *Scrip*'s Jo Shorthouse caught up with him to hear his extraordinary story, which saw him come through exile from his home country to developing key drugs that would transform the treatment of HIV and hepatitis. See p16.

Meanwhile, it's international Rare Disease Day next week, on Feb. 28. Rare diseases were once a rare sighting in the pharma industry's pipeline development programs, but – thanks in large part to effective incentivization programs by governments – that is no longer the case. As our infographic on p5 shows, more than two fifths of the new drugs approved in the US last year were orphan drugs, and there are more than 4,500 drugs in active development for rare diseases. Next week we will be exploring the orphan drug topic further, and finding out from different stakeholders how they perceive conversations around price and value will develop over the coming years.

exclusive online content

China's CBMG Aims For Large-Scale CAR-T Capacity
CBMG exec Tony Liu looks to differentiate CAR-T offerings partly based on ability to produce at a large scale in China, at a standard that matches the US.
http://bit.ly/2lmsKDh

Shield Pilots Ironclad Specialty Future With Feraccru
Bolstered with a successful launch in Germany and the UK of its anemia treatment Feraccru, Shield Therapeutics is looking to expand both the label and its market reach.
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Second Genome CEO Predicts Paradigm Shift With Microbiome Discovery
California biotech, which has backing from major pharmas, explains the application of its microbiome discovery platform to multiple disease types.
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Another Nail In Amyloid Hypothesis Coffin?

In another blow for the amyloid hypothesis in Alzheimer's disease, Merck ended its pivotal EPOCH study for the BACE inhibitor verubecestat based on an interim assessment that there was "virtually no chance of finding a positive clinical effect" in the nearly completed Phase II/III clinical trial.

MANDY JACKSON mandy.jackson@informausa.com

Merck & Co. Inc. revealed on Feb. 14 that it has ended the Phase II/III EPOCH clinical trial testing the BACE inhibitor verubecestat in mild-to-moderate Alzheimer's disease based on lack of efficacy, seeming to put another nail in the coffin for the amyloid hypothesis, although the company's Phase III trial in prodromal Alzheimer's is ongoing with results expected in Feb. 2019.

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An external data monitoring committee determined after an interim safety analysis that verubecestat (MK-8931) had "virtually no chance of finding a positive clinical effect" on cognition and function in EPOCH, which is not entirely surprising given the long and growing list of disappointing results for drugs that target the amyloid protein in Alzheimer's disease (AD). Also, unlike the ongoing Phase III study for the competing BACE inhibitor AZD3293 from partners Eli Lilly & Co. and AstraZeneca PLC, Merck did not prescreen EPOCH enrollees for the presence of amyloid in the brain.

Drugs that inhibit beta-site amyloid precursor protein cleaving enzyme (BACE) are different from biologics that target amyloid directly, like Lilly's antibody solanezumab, which worked to clear already developed amyloid plaques from the brain and failed in a closely-watched third Phase III clinical trial in November. Lilly revealed in its fourth quarter 2016 earnings report that it has since suspended its Phase III EXPEDITION PRO trial testing solanezumab in prodromal Alzheimer's after a review of EXPEDITION3 data left little hope of success in the earlier form of the disease.

Lilly and others working in the Alzheimer's field have held out hope that BACE inhibition would prove to be a more potent and effective means of targeting amyloid to treat the disease. Small molecule BACE inhibitors work to stop the formation of amyloid – preventing rather than removing the troublesome protein. It's a path that's discouraged other biopharmaceutical firms in the past; the Biomedtracker database shows that at least eight BACE inhibitors have been tested in AD by Lilly, AstraZeneca, Pfizer Inc., Roche and others before those companies suspended development.

Evercore ISI analyst Mark Schoenebaum said in a Feb. 14 note that expectations for success in Merck's EPOCH trial, from which final data were expected in the second half of 2017, were low despite analyst consensus that verubecestat could bring in peak annual sales of $1.3bn.

Schoenebaum noted that analysts and investors were not optimistic about EPOCH, because verubecestat was being tested in Alzheimer's patients who already were showing cognitive and functional declines upon enrollment in the study and because of the lack of pre-screening for amyloid at baseline, "which has led to the inclusion of non-AD dementia patients in other late-stage trials (thus potentially obscuring results). We will need further analysis of the data from Merck to know if this was a problem in the EPOCH trial; the ongoing prodromal study (APECS) does screen for amyloid."

Investors showed only mild doubt about whether Merck's BACE inhibitor or some other amyloid-targeting therapy would ultimately be successful in any form of AD based on the verubecestat update after the stock market closed on Valentine's Day. Merck fell 1.8% in after-hours trading on Feb. 14 to $64.51, while Lilly initially saw a small stock price increase before breaking even at $78.81.

Biogen, whose aducanumab is the latest-stage amyloid-targeting antibody in development after solanezumab's failure, had a small 14-cent decline to $285. The company presented evidence for its Phase III biologic in December that it cleared amyloid from Alzheimer's patients' brains and improved cognition in an early-stage study. Aducanumab is designed to clear amyloid plaques while Lilly's solanezumab targeted soluble amyloid.

However, the next big set of Phase III Alzheimer's data will be reported by Axovant Sciences Ltd. for its serotonin 5-HT6 antgonist intepirdine (RVT-101) – a drug in development to treat Alzheimer's symptoms, not to slow AD progression. That program appeared riskier recently after Lundbeck Inc. and Otsuka Pharmaceutical Co. Ltd. delivered a second Phase III failure for idalopirdine in the same drug class.

Merck's decision to terminate EPOCH may not kill the amyloid hypothesis, but it certainly adds more doubt to whether any company will be able to significantly reduce Alzheimer's symptoms and slow the progression of the disease by targeting amyloid with either an antibody or a small molecule.

"An ongoing debate in AD research surrounds the timing of treatment: it remains unclear whether AD-related damage to the brain can be reversed through clearing plaque (as some anti-amyloid antibodies do) or preventing the creation of additional plaque (as with a BACE inhibitor)," Schoenebaum wrote. "Instead, the argument goes, efficacy with these drugs may require treatment before the development of damage – hence the ongoing prodromal study. While it remains possible that BACE inhibition may still have a place in AD treatment, the failure of this [EPOCH] study for futility will dampen investor enthusiasm for the mechanism."

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How Will Pharma M&A Change In 2017?

LUCIE ELLIS lucie.ellis@informa.com

Industry consultants survey the landscape for pharma deal making in 2017. More deals, higher prices and asset swaps as repatriated cash burns holes in US pharma's pockets are just for starters.

In October 2016, US companies unleashed an unprecedented wave of deals, making it the busiest month ever for domestic M&A, despite what had been a lackluster start to the year in M&A. This momentum is expected to continue into 2017 and, according to a recent report from Deloitte, which surveyed 1,000 executives to gauge their expectations for M&A activity, the magnitude of individual transactions this year will exceed the size of deals seen in 2016.

In the report titled *M&A Trends: Year-end Report 2016*, Deloitte found that 75% of respondents expected deal activity to increase this year. Executives surveyed also flagged divestitures as a major focus, with 73% highlighting that they planned to shed business in 2017; up from 48% in a mid-year 2016 survey.

The report also found an even split among corporate respondents who said they would be seeking major, transformational deals and those seeking smaller strategic ones, with 27% of executives picking one or the other. One in five respondents were on the fence, saying they'd respond reactively to any opportunities that arose. Deloitte notes that all survey participants work in either private or public companies or private equity firms with annual revenues of $10m or greater.

In keeping with expectations for increased M&A across multiple sectors, *Scrip* has asked consultants from Informa Pharma Consulting, Novasecta Ltd and HireRight for their opinions on how the pharma M&A environment will develop this year.

ALL EYES ON THE US

Timothy Pang, director of healthcare consulting at Informa Pharma Consulting, flagged the new US president as a catalyst for M&A on that side of the Atlantic. "President Donald Trump has promised to let US companies with global operations and significant cash piles outside the US repatriate that cash at lower tax rates than before – this could trigger a new wave of deal making by US-based behemoths such as Pfizer Inc., Merck & Co. Inc. and Johnson & Johnson, all of which have cash mountains they've never been keen until now to repatriate," Pang noted. He expects firms such as these to continue to shop to fill pipelines or add bolt-on assets if they can do so tax efficiently.

Pang also said the evolution of pharma to become more of a service provider rather than just a product provider will impact some deal making decisions and spike change across the sector in 2017.

Informa Pharma Consulting's global director Christian Neckermann said that a change in US FDA approval processes could impact M&A. However, he is skeptical that recent proposals to allow products to market sooner with increased post-marketing surveillance would be accepted due to safety concerns. But approving products sooner "would arguably reduce costs to get to market and allow smaller biotechs to commercialize their own products rather than sell them to big pharma," Neckermann noted.

Susan Danheiser, also a director of healthcare consulting at Informa Pharma Consulting, added that in 2017 she expected to see expansion and restructuring by pharma to support evidence-based strategy development, in both the pre- and post-launch phases. "Evidence generation is becoming increasingly important for competing in the marketplace with regard to reimbursement and pricing," Danheiser said. "The additional resources for planning and executing the requisite clinical studies will add significantly to overall costs of drug development and marketing."

Ed Corbett, engagement manager at specialist pharmaceutical strategy consultancy Novasecta, told *Scrip* that M&A was hot for pharma right now because there is cheap capital around. However, he also noted that overspending for assets, particularly in the oncology space, is on the rise. "The cost of M&A is going up but whether companies are getting a return is another thing," Corbett said.

"Does that mean companies will stop doing M&A deals? It's a bit of an arms race," Corbett said. He added that when one pharma backs out of a deal due to a high price disproportional to an asset, it opens the door for competitors with more cash to burn. This competitive action is spurring high deal prices that are expected to continue in 2017. However, Corbett noted that there was still cheap capital around in a lot of development areas, especially outside of oncology.

Meanwhile, Corbett thinks asset swaps, like the GlaxoSmithKline PLC and Novartis AG megadeal in 2015, will become much more common in the pharma industry this year. He is also expecting to see more capability swaps come into play. "Company A has a geographical presence in a particular market that Company B values and Company B has got a product or a R&D capability that Company A wants, so a deal can be done. These actions are becoming increasingly attractive because it's a very win/win situation, usually comes at a much lower cost to traditional M&A and frequently the value is realized much more quickly," he said.

Looking at Europe, Steve Girdler, managing director for the EMEA region at human resources specialist HireRight, believes M&A in 2017 will be controlled by companies seeking a stronger global presence. "The world is changing so much, politically, geo-politically and economically," he said. "The businesses that will be successful in this new world will be the ones that take the bull by the horns and say 'I need to be a global business with a stronger foothold.'"

LOOKING AHEAD

Further ahead than 2017, Pang said that the application of artificial intelligence would be critical for pharma – noting that companies may need to seek deals outside of the pharma & biotech sphere for success.

"AI is on the cusp but hasn't yet hit as big as many have hoped," Pang said. However, he noted that the biggest impact would be the spread of medical decision making using AI.

Neckermann also highlighted Big Data as a continuing target for pharma. Big Data is heavily linked to the still elusive goal of real personalization of medicine, he noted. "Billions of dollars are spent amassing data but we are still not at the point where data is integrated well across sources so that analytics are able to make an interpretation easily," Neckermann said.

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ORPHAN DRUGS FOR RARE DISEASES

Rare diseases are defined as those that affect fewer than 200,000 patients in US, or fewer than 5 in 10,000 (about 250,000) in EU, or fewer than 4 in 10,000 in Japan[1]

7,000
THE NUMBER OF RARE DISEASES

>232
Rare disease indications for which drugs have been launched[2]

~950
Number of unique orphan drugs launched[2]

41%
Of the 22 new medications approved by the FDA in 2016, 9 were orphan drugs[1]

4,549
RARE DISEASE DRUGS IN ACTIVE DEVELOPMENT[2]

TOP 10 Originators Developing Drugs For Rare Diseases[2]

top 10 order | # of unique drugs | Originator

1	58	Sanofi	6	19	Johnson & Johnson
2	51	GlaxoSmithKline	7	18	Serum Institute of India
3	27	Novartis	8	17	TB Alliance
4	26	Medicines for Malaria Venture	9	17	Bharat Biotech
5	22	China National Pharmaceutical	10	17	Microgen

Number of drugs receiving orphan status in US, EU, Australia/ New Zealand, Japan, South Korea and Mexico[3]

2013	299
2014	326
2015	394
2016	369

Nine orphan drugs were approved in the US in 2016[4]

9 Orphan Drugs	6 Fast-track	3 Breakthrough	8 Priority review	5 Accelerated approval	8 US was 1st approval market
Anthim	✔				✔
Defitelio	✔		✔		
Exondys 51	✔		✔	✔	✔
Lartruvo	✔	✔	✔	✔	✔
Netspot					✔
Ocaliva	✔		✔	✔	✔
Rubraca		✔		✔	✔
Spinraza	✔		✔		✔
Venclexta		✔		✔	✔

50%
Half of all people affected by rare diseases are children[5]

30m
Americans have rare diseases **(1 in every 10 People)**[1]
25m-30m in Europe

Sources: [1]National Organization for Rare Disorders, [2]Pharmaprojects, October 2016, [3]Pharmaprojects, [4]FDA, [5]Global Genes

J&J's Stoffels On Actelion's 'Exquisite' Researchers

J&J's chief scientific officer Dr. Paul Stoffels tells Scrip that flexibility is a hallmark of how the company goes about its collaborations, including the new $30bn deal with Actelion. Stoffels is also hoping to progress the science for a new TB medicine via a unique collaboration in India.

ANJU GHANGURDE anju.ghangurde@informa.com

Johnson & Johnson's chief scientific officer, Dr. Paul Stoffels, says that the deal structure for the acquisition of Actelion Pharmaceuticals Ltd., which provides for a spin-out "R&D engine," is an "inventive" one that finds a solution that's good for all concerned.

He noted that Dr. Jean-Paul Clozel, chief executive officer and founding member of Actelion, and his wife Martine Clozel are "exquisite" researchers and it's their "entire passion" to continue to do the research they were doing.

"The large part of the company [the commercial part as well as the late-stage development], for them it was like this is something less of a passion - we love it but we would like to continue with our R&D. It was a very inventive deal to say 'why don't we find a solution for both,'" Stoffels told *Scrip* in an interview at the grand sea-facing Taj Mahal Palace Hotel overlooking the Gateway of India in Mumbai.

The structured transaction allows Actelion's current scientific team with Dr. Clozel as CEO to continue with basic research via a spin-out of the drug discovery operations and early-stage clinical development assets, while J&J "brings in the late stage."

J&J will also receive an option on ACT-132577 within the spin-out, which is being developed for resistant hypertension and is currently in Phase II.

"It's good for the people, for the science/the new [spin out] company and us. We have a very focused company on pulmonary arterial hypertension and eventually resistant hypertension and that is a new franchise for us. For us it was an ideal deal," Stoffels declared.

On the spin-out model being financially viable for J&J as well, Stoffels said: "Hopefully. We have a significant part in it. We have committed to be long-term partners but leave them the space to be entrepreneurial and do research and at the same time be a partner. Wherever they want to use us as a commercial partner in the world, we will be open to do it."

J&J will initially hold 16% of the shares of the spun out new R&D company, with an option to double that holding.

ARAGON-SERAGON PARALLELS?

Asked about any parallels of the Actelion deal with the spin-out model for J&J's acquisition of cancer biotech Aragon Pharmaceuticals Inc. in 2013 and the spin out of Seragon Pharmaceuticals Inc., which was later acquired by Genentech, Stoffels maintained that the two deals were quite different.

He explained that while Aragon had a product for prostate cancer, Seragon had products for breast cancer, where J&J did not have expertise. He recalled how Dr. Richard Heyman, co-founder of Aragon, "wanted to continue with his company" and so the deal that was struck allowed a spin out of the second part of the company (as Seragon).

"He went on with it and did a very good job and Roche bought it and it was perfect for us. That was exactly what we intended to do."

Seragon, founded in August 2013, was spun out of Aragon following its acquisition by Johnson & Johnson. J&J did not have an ownership stake in the spin out nor retain any rights to its products or programs. Seragon, which was developing drugs for hormone dependent cancers, was acquired by Roche's Genentech arm in 2014.

Stoffels underscored the flexible approach that J&J deploys towards collaborations. He also referred to the deal with Genmab AS for the anticancer compound, *Darzalex* (daratumumab), where the CEO of the Danish firm apparently wanted to continue research but preferred not to "spend his effort and resources on development." J&J went on to firm up a licensing deal with Genmab and globally developed the product.

"Flexibility of how we do collaborations is a hallmark of our company," the J&J CSO said.

INDIA TB COLLABORATION

Interestingly, J&J is also working on plans for a potential collaboration with the Institute of Microbial Technology (IMTECH), Chandigarh, in the area of infectious diseases, specifically tuberculosis. IMTECH is a research institute of India's Council of Scientific & Industrial Research (CSIR).

"The way we are thinking about it is to jointly work on a plan on how we can work with IMTECH on doing joint development of a new product with an institution specifically on TB – this on XDR [extensively drug-resistant] TB. Hopefully, we can pull off something special here where the company, with an institution, will jointly progress the science for a new medicine in TB," Stoffels said.

While specifics on the proposed plans are not immediately clear, what is perhaps unique is that Dr. Anil Koul, the director of IMTECH who took charge recently, is a senior director and head, respiratory infections discovery, at J&J in Belgium.

"He [Dr. Koul] took a sabbatical on his own initiative on the request of the government to come and lead that. Anil was part of the team that developed bedaquiline and other antivirals, so he has very good insight on what it takes to get from science in the lab to a product," Stoffels noted.

Koul's LinkedIn profile notes that he was awarded "The Johnson Medal" for the discovery and development of bedaquiline, which is marketed as Sirturo by Janssen.

Stoffels indicated that the proposed India collaboration is for "more than a follow-on" to bedaquiline, which is a new drug in a very complex regimen.

"TB has medicines that have been used for a long time, so when people get resistance, they get to multi-drug resistance. Then by adding bedaquiline you get to a very significant cure rate in XDR-TB. What we want to do is come with one or two additional new mechanisms of action with broad spectrum antimicrobial, anti-mycobacterium products, which we think we have a good start for."

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Read Five Big Picture R&D Questions For J&J's Stoffels, Novartis's Narasimhan here: **http://bit.ly/2kDNWYA**

CONTINUED FROM COVER

The BIO panel touched on other policy issues like drug pricing, which has come under attack by Trump, who raised industry alarms with statements about requiring the government to negotiate on drug prices.

ACTION POINTS

BIO senior VP-federal government regulations Jeanne Haggerty said there are a lot of efforts underway to educate the president about the intricacies of drug pricing and how Medicare Part D works. "He is starting to understand them a little bit better," she said.

The new administration may be more likely to make changes under Medicare Part B, which covers drugs like oncology and anti-inflammatory agents that are administered by physicians, than to make changes to Medicare Part D, she said. Those comments are interesting since last year, the Centers for Medicaid & Medicare Services tried to make changes to Medicare Part B drug reimbursement under a controversial demonstration program. CMS ultimately scrapped the plan after Tom Price was nominated as HHS secretary; Price, who has since been confirmed, was an outspoken critic of the program.

Eli Lilly & Co. former US president Alex Azar, who recently left the company and formed a new strategic consulting company, Seraphim, also anticipates changes to Medicare Part B. For example, he said it might make sense to allow pharmacy benefit managers to negotiate drug prices with Medicare Part B as an alternative to the current payment system of Average Sales Price (ASP) plus 6%.

Most importantly, the administration should focus on the affordability of medicines for patients rather than list price, he said.

"Things that disrupt the market, that reduce choice, that disrupt the one government program that is actually working quite well, Part D, that actually won't change the question of the patient who has a Part D plan is in their deductible phase or donut hole and the fact they have to pay too much when they go to the pharmacy," he said.

Patient affordability is one of industry's typical talking points when it comes to debates over drug pricing. But it doesn't address the issue of how much the health care system spends on drugs. Azar suggested faster generic drug approvals could have an impact on the cost of drugs, and pointed to other options that could be explored, like reevaluating some of the policies of high deductible health plans. One suggestion he mentioned was allowing copay cards to be used in Medicare Part D and B; they are currently allowed to be used only in commercial plans and are controversial in that while they lower the cost of the drugs for patients, insurance companies still foot the bill for what they say is a more expensive drug.

> 'If you eliminate the requirement to prove efficacy of drugs, it becomes a wild west where snake oil can compete with real science-driven therapies, and that makes it awfully hard to think about how to invest in the sector'

ACTIONS WILL COME

Nonetheless, Azar speculated that "something" will happen with drug pricing this year, but he said it might not have anything to do with Medicare Part D negotiations as industry thinks of them. "When the president says something, eventually the government will do something," he warned.

"In the policy world, we hear negotiate drug price, we go right to a certain place. That may not be where the president means when he uses those words."

Azar also forecast that Congress will pass legislation repealing the Affordable Care Act this year. The question, he said, is how they will go about it. Deerfield's Leff agreed a repeal seems likely given the platform Republicans ran and won elections on.

"From an investor point of view, there is a right way to do it and a wrong way to do it," Leff said. "Uncertainty can have a negative impact on investor appetite. The right way to do repeal and replace is to know what you are replacing it with at the time that you repeal it."

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Siliq Approval To Make Little Dent In Valeant Debt

A Black Box warning on suicidal ideation and behavior, a REM program and a Medication Guide may hold back the sales growth of Valeant's new psoriasis therapy in the US, Siliq, following its Feb. 15 approval, although the drug has been associated with high levels of total skin clearance, a finding that could differentiate it from competing products.

At last, some good news for hard-pressed Valeant Pharmaceuticals International Inc., with the US FDA announcing the approval of the psoriasis therapy, *Siliq* (brodalumab), on Feb. 15. The Canada-based multinational said it would start marketing Siliq in the US in the second half of 2017.

Brodalumab was approved in the US for the treatment of adults with moderate-to-severe plaque psoriasis, in patients who are candidates for systemic therapy or phototherapy and have failed to respond, or have stopped responding, to other systemic therapies.

Although only modest sales might be expected from the product because of its risk/benefit profile and the fierce competition in the psoriasis market, Valeant's share price rose 5.51% to $16.86 on the day of the approval, buoyed by the rare positive news from Valeant, a company with a multi-billion dollar debt pile.

The approval is a boon too for one of the drug's original developers, AstraZeneca PLC, which will share profits on the US sales of the product with Valeant, and has also received a $130m milestone payment after Valeant gained its first regulatory approval for brodalumab.

The US labeling for the interleukin-17 blocker includes a Black Box warning on the risk of suicidal ideation and behavior with the drug, although this will be no surprise to Valeant. The company announced in November 2016 that the US review goal date for brodalumab was being extended to Feb. 16, 2017, to resolve questions about the "product labeling and a REMS program."

john.davis@informa.com, 16 Feb 2017

Triple Immunotherapy Combos Enter The Ovarian Cancer Fight

JOHN DAVIS john.davis@informa.com

Immunovaccine's investigational cancer vaccine combined with an immunomodulator and a checkpoint inhibitor or other similar type of agent could have a synergistic beneficial effect on tumor cells, and lead to triple-drug combinations being evaluated in other cancers.

Numerous clinical studies of dual combinations of checkpoint inhibitors are underway, with or without conventional chemotherapy agents, but one of the first Phase Ib studies of a triple combination of immunotherapies in ovarian cancer that includes an investigational cancer vaccine is expected to report initial results in March 2017, and a Phase II trial of another similar triple combination should start in the next several months.

Both triple combinations involve Immunovaccine Inc.'s potential cancer vaccine DPX-Survivac to induce T-cell activation, low doses of cyclophosphamide that have an immunomodulating effect, and a checkpoint inhibitor/IDO1 inhibitor to unmask the tumor. The Halifax, Canada-based company is hoping the use of three immuno-oncology agents with different mechanisms-of-action will produce a synergistic effect with fewer side-effects than those seen with dual combinations of other agents like checkpoint inhibitors.

In the Phase Ib study, Immunovaccine is collaborating with Incyte Corp. on the use of Incyte's oral indoleamine-2,3-dioxygenase (IDO1) enzyme inhibitor, epacadostat, combined with DPX-Survivac and low-dose cyclophosphamide, in patients with recurrent ovarian cancer. "Interim results from this first triple combination study should be released at the end of March," Immunovaccine's CEO Frederic Ors, told *Scrip*.

But slightly more advanced is a Merck & Co. Inc.-funded and clinical investigator-sponsored Phase II study of a combination of Merck's checkpoint inhibitor *Keytruda* (pembrolizumab), DPX-Survivac, and low-dose cyclophosphamide at the Princess Margaret Cancer Centre in Toronto, Canada, in patients with recurrent, platinum-resistant ovarian cancer, which is due to start soon after clearance by regulators.

This non-randomized open-label trial will evaluate the triple combination in 42 ovarian cancer patients with overall response rate (ORR) as the primary endpoint, and progression-free survival, overall survival and potential side-effects as secondary endpoints.

"The involvement of Merck in the study gives Immunovaccine a certain amount of credibility and indicates the value attached to DPX-Survivac and its target, and the use of a triple combination of immunotherapeutic agents," Ors said. The vaccine targets survivin, a protein that regulates cell proliferation at the beginning of life but is usually absent in mature healthy cells. However, survivin is highly expressed in cancer cells and seems to suppress apoptosis (cell death) and leads to the development of treatment-resistant cancer.

"Immunovaccine showed in a study conducted in 2011 that low-doses of cyclophosphamide can enhance the immune response produced by DPX-Survivac," Ors said. A further potential benefit of DPX-Survivac, according to Ors, is that DPX-Survivac is formulated in oil, without water, that has a depot effect when injected into patients. The formulation, DepoVax, is patented. "If antigenic peptides in solution are injected into the body, they are fragile and degrade quickly, but formulating those antigens in oil traps them and protects them from degradation."

The antigens are taken up by phagocytosis and eventually reach the lymph nodes where they elicit an immune response, and this process means that they are associated with a prolonged immune response. This is exactly what is wanted when treating a bulky solid tumor, Ors noted.

NASDAQ LISTING?

If these clinical studies are successful, Immunovaccine will be at an inflection point. The company has a cash runway of around two years, and its shares are already listed on the Toronto Exchange, TSX, but it might find itself in a position to list on Nasdaq, Ors remarked.

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Ipsen Shores Up Primary Care Business

Ipsen has picked up five of Sanofi's consumer healthcare products in certain European markets to enable the larger company's deal with Boehringer Ingelheim to proceed. Despite moves by Ipsen to bolster its cash-generating primary care business, some analysts still believe a sale could make good business sense.

Ipsen of France is buying five consumer products from Sanofi that the latter had to divest in order to complete the acquisition of Boehringer Ingelheim's consumer healthcare business.

In a recent interview with *Scrip*, Ipsen's CEO David Meek affirmed the company's commitment to its smaller, primary care business amid a flurry of activity in its larger specialty care division. A primary care deal with Italian company Akkadeas Pharma soon followed.

But this hasn't stopped analysts from speculating about Ipsen's plans for its primary care business. "Does this move say anything about Ipsen's commitment to primary care? We do not believe it does," said Eric Le Berrigaud of Bryan, Garnier & Co in a research noted dated Feb. 13. "In any case it makes sense i.e. to keep a stronger CHC (consumer healthcare) business or to divest a more attractive unit... Our view is not that Ipsen will divest the whole primary care business but more likely pieces of it to keep the best of it in selected countries and targeted fields."

Ipsen is paying €83m in cash for the five Sanofi products, and the deal is expected to close in the second quarter.

The most significant product covered by the deal is Prontalgine, an analgesic for the treatment of moderate to severe pain, which has grown at double-digit rates over the last four years and is available only in France, according to Ipsen. The deal also includes Buscopan, an antispasmodic; Suppositoria Glycerini, a laxative; and Mucothiol and Mucodyne, expectorants for cough and flu. Combined, these brands span a geographic scope of eight European countries.

sukaina.virji@informa.com, 13 Feb 2017

Ardelyx Challenges Phosphate Binders

The emerging data package for Ardelyx Inc.'s first-in-class NH3E inhibitor tenapanor looks competitive with phosphate binders for treating hyperphosphatemia and bodes well for a new Phase III study coming up, analysts say. Ardelyx is positioning tenapanor for hyperphosphatemia, or high levels of serum phosphorus, associated with end-stage renal disease (ESRD), among other indications. The company describes tenapanor as a minimally absorbed small molecule, with a "unique mechanism of action that limits the amount of dietary phosphorus that can then pass between cells in the gut through the blood. Importantly, these effects appear to be selective to sodium and phosphorus." In a top-line release Feb. 15, Ardelyx announced that the drug met its primary efficacy endpoint in a study of 164 ESRD patients and was also well-tolerated. The study had been designed with input from FDA; originally it was a Phase II trial that was changed and repositioned as the first of two registrational studies. Ardelyx is planning to start a second Phase III study in hyperphosphatemia associated with ESRD patients on dialysis in the middle of the year that will include a 26-week treatment period and a 26-week extension study.

emily.hayes@informa.com, 17 Feb 2017

Axovant Plans Nelotanserin Phase III

Swiss biopharma Axovant Sciences Ltd. reported on Feb. 13 positive interim Phase II data for the first 11 Lewy body dementia patients to complete its study for dementia drug nelotanserin – results that have prompted the company to take the drug into Phase III this year. But its plans to use the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III for a primary endpoint have piqued analysts' interest as the only other Phase III study to use this scale as endpoint in dementia failed last year. The double-blind, randomized, placebo-controlled Phase II trial includes patients with either dementia with Lewy bodies or Parkinson's disease dementia (PDD) who experience frequent visual hallucinations with a score of 18 or higher on Mini Mental State Examination (MMSE). Previously, Axovant had said it would predominantly evaluate nelotanserin for the treatment of visual hallucinations in dementia patients. However, in the Phase II trial, changes in the frequency and severity of visual hallucinations was relegated to a secondary endpoint, while extrapyramidal signs as assessed using the motor subsection of UPDRS Parts II and III was used as the primary endpoint.

lucie.ellis@informa.com, 14 Feb 2017

AstraZeneca/Chi-Med Set For 'Selective' Pivotal Renal Cell Cancer Trial

"We are delighted to report this highly encouraging progression-free survival data in Met-driven papillary renal cell carcinoma (PRCC), a disease with no approved treatment options," said Christian Hogg, CEO of Hutchison China MediTech Ltd. (Chi-Med). "With development of the companion diagnostic assay to screen Met-driven disease now also complete we are preparing for the initiation of our global Phase III study, the first global registration trial for savolitinib." The positive Phase II data of savolitinib in PRCC and other savolitinib data were presented last week at the 2017 Genitourinary Cancers Symposium sponsored by the American Society of Clinical Oncology (ASCO-GU). PRCC is the second most common subtype of renal cell carcinoma (RCC) – accounting for 10-15% of RCC – and is associated with alterations in the c-Met gene. It is linked with significantly worse prognosis and treatment outcomes than other forms of RCC. Therapies that are currently available for RCC patients have demonstrated only modest benefit in PRCC and there are no therapies specifically approved for this subset of patients. This patient selection approach would make it the first ever molecularly selected trial in RCC. The study will be conducted with Chi-Med's partner AstraZeneca PLC. The companies have also stated that over the course of 2017, they will be conducting a molecular epidemiology study of around 300 PRCC patient samples to further understand the correlations between c-Met alterations and patient outcomes, including any predictive biomarkers.

sukaina.virji@informa.com, 15 Feb 2017

Lynparza's Wider Prospects Boosted

News that *Lynparza* (olaparib) works better than standard of care chemotherapy in treating a group of patients with HER2-negative metastatic breast cancer harboring germline BRCA1 or BRCA2 mutations has lifted hopes for the first-in-class drug – which is already been approved in the US for ovarian cancer – as well as for AstraZeneca PLC's overall DNA Damage Repair portfolio. AstraZeneca announced Feb. 17 that Lynparza showed a statistically significant and clinically meaningful improvement in progression-free survival in patients with germline BRCA mutated breast cancer in its Phase III OLYMPIAD trial comparing the PARP-inhibitor – taken in tablet form of 300 mg twice daily – to physician's choice of a standard of care chemotherapy. The trial data will likely be presented at ASCO later this year. Lynparza works by blocking pathways in the body whose function is to repair damaged DNA within malignant tumors, without which the tumors cannot continue to grow. Lynparza – which AstraZeneca once shelved due to uncertain prospects during development – is now the foundation of the UK group's portfolio of compounds targeting DNA damage response mechanisms in cancer cells.

sten.stovall@informa.com, 17 Feb 2017

ViiV/Janssen's Double-Edged HIV SWORD

ALEX SHIMMINGS alex.shimmings@informa.com

Data from ViiV Healthcare and Janssen's SWORD studies point the way to a two-drug future in HIV for Tivicay/Edurant, but will doctors want to rock the boat, especially with Gilead's bictegravir impressing in Phase II?

The possibility of a two-drug regimen for HIV maintenance therapy has come further into view with the full data for the SWORD studies showing that patients can be switched from a three- or four-drug regimen to ViiV Healthcare's *Tivicay* (dolutegravir) plus Janssen Inc.'s *Edurant* (rilpivirine) without sacrificing any anti-HIV efficacy. The companies are planning regulatory filings for the two-drug regimen as a single tablet this year.

The dolutegravir and rilpivirine regimen achieved non-inferior viral suppression (HIV-1 RNA <50 copies/mL) at 48 weeks compared with a three- or four-drug regimen in both pooled and individual analyses of the SWORD 1 and SWORD 2 studies, according to data presented Feb. 14 at the Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle. The 148-week studies are ongoing.

ViiV's chief scientific and medical officer John Pottage said the studies could change the understanding of how HIV can be managed. "For more than 20 years, we thought that three or more drugs were required to maintain virologic suppression, but the SWORD studies provide compelling data that suppression may be maintained with a two-drug regimen of dolutegravir and rilpivirine. These data mark an exciting first step towards making two drug regimens a reality in HIV treatment," he said.

The main benefit to patients would be a simplified treatment regimen, particularly compared with commonly used used second-line and beyond integrase strand transfer inhibitors (INSTIs)/protease inhibitor (PI)-based regimens which require boosting agents (e.g. *Truvada* + *Prezista* + *Norvir*; Truvada + *Reyataz* + Norvir; Truvada + *Isentress* + Norvir).

The advantages could transfer to payers too. "The combined cost of dolutegravir/rilpivirine would be much cheaper than the cost of commonly used regimens, and given that the drugs are intended to be taken for life, the accrued savings could make a big impact on payers' budgets," commented Datamonitor Healthcare senior analyst Michael Haydock.

Overall, Haydock was encouraged by the SWORD data but said some doctors might be cautious. "These are really promising data for the two-drug regimen given that the standard of care for HIV treatment is currently to use three or four drugs to maintain virologic suppression. It is quite an ambitious approach because reducing the number of antiretroviral agents runs the theoretical risk of resistance generation and therefore virologic failure – so physicians are generally reluctant to rock the boat," Haydock noted.

"But encouragingly, the rates of virologic failure were comparable between both arms (<1% for dolutegravir/rilpivirine and 1% for other arm). This is no doubt because of dolutegravir's very high barrier to resistance (rilpivirine belongs to the NNRTI class which have quite poor barriers to resistance), as demonstrated by the fact that no INSTI resistance-associated mutations were reported in the dolutegravir/rilpivirine arm."

BENEFITS LIMITED?

Jefferies analyst Brian Abrahams also wondered whether doctors and patients would be tempted to change the status quo. "Overall, we see little incentive for patients to switch to a dolu/rilpivirine dual-regimen," he said in a research note, adding that the SWORD data were of little threat to ViiV's major HIV rival Gilead Sciences Inc.'s long-term prospects in the disease.

Now that Gilead has its better-tolerated Viread (TDF) successor tenofovir alafenamide (TAF), he thinks the benefits for the dolutegravir/rilpivirine combo are limited. "A dual regimen would also have a theoretically lesser cushion for noncompliance vs. a triple regimen, something that would be difficult for GSK to disprove in a clinical trial setting-- though dolu does have a very high barrier to resistance, which could mitigate this concern a bit." Abrahams said. "In fact, in SWORDs, resistance development was low, but one patient who did not adhere perfectly to the dual regimen did develop a resistance-associated mutation (through they were re-suppressed)."

BICTEGRAVIR IN THE WINGS

Moreover, Abrahams pointed to new Phase II data also presented at CROI for Gilead's new once-daily INSTI bictegravir.

The study compared a combination of bictegravir (75 mg) and emtricitabine/tenofovir alafenamide (200/25 mg) versus dolutegravir (50 mg) and emtricitabine/tenofovir alafenamide (200/25 mg) in treatment-naïve, HIV-1 infected adults and both regimens both demonstrated high virologic response rates at weeks 24 and 48.

"The high virologic response rates seen in this study show that the pairing of bictegravir with emtricitabine/tenofovir alafenamide could potentially offer patients and physicians a new HIV treatment option with preclinical data supporting few drug interactions and a high barrier to resistance," said lead investigator Paul Sax, clinical director of infectious diseases at Brigham and Women's Hospital.

Based on the data, bictegravir was rapidly advanced into four Phase III trials as part of a single tablet regimen in combination with emtricitabine/tenofovir alafenamide for the treatment of HIV (bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg). The studies are fully enrolled and Gilead expects to see data later this year.

Abrahams commented: "With hints today that Gilead's own integrase, bictegravir, may actually have some modest advantage vs. dolutegravir, we see little incentive to switch to this dolu/rilpivirine dual or to start with/switch to GSK's other dual dolu/lamivudine, unless GSK prices more aggressively and payers become more proactive managing HIV formularies."

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Read how Gilead's Bictegravir Data Could Mean Continued HIV Sector Dominance: **http://bit.ly/2m8q6Bg**

Shire's Sales, R&D Heads Shed Light On The Post-Baxalta Road Ahead

Shire's Perry Sternberg and Phil Vickers are optimistic about recent launches and products in late stages of development in key rare disease and specialty therapeutic areas, many of which come from Baxalta and other high-profile acquisitions.

MANDY JACKSON mandy.jackson@informausa.com

There probably are few things that pharmaceutical sales representatives like more than new products to pitch to doctors and Shire PLC's Baxalta Inc. buyout last year gave the company's reps plenty to be happy about.

The excitement is palpable when talking to US Head of Commercial Perry Sternberg about the eight products that Shire recently launched or expects to launch in 2017. Meanwhile, the company's head of research and development Philip Vickers is looking forward to delivering more internal and externally developed drugs to the market this year and in the years ahead.

Scrip spoke with Sternberg and Vickers last month during the J.P. Morgan Healthcare Conference in San Francisco about their view of Shire's prospects now that the integration of Baxalta's marketed products and its R&D pipeline is complete.

"We have seven products mid-launch and hopefully one more this year," Sternberg said.

The eighth launch would be for SHP465 in the treatment of adults with attention-deficit/hyperactivity disorder (ADHD). The US FDA acknowledged the receipt of Shire's resubmitted NDA for SHP465 in January and the agency is expected to make an approval decision by June 20. The resubmission provides new data requested by the FDA a decade ago.

"I'm excited about this product, because it goes after the shape of the market right now – adults are the fastest growing part of the ADHD market," Sternberg said. "We are actively gearing up our plans to bring this product to market."

SHP465 is an important asset for Shire, since it will add a new product to the company's established ADHD portfolio – one of its specialty pharmaceutical areas. *Xiidra* (lifitegrast) for dry eye disease is another key specialty pharma product and it has garnered a significant share of the market since its third quarter 2016 launch, Sternberg said. Other recent legacy Shire approvals and launches include the ADHD drug *Vyvanse* (lisdexamfetamine dimesylate) for binge-eating disorder in Canada and *Lialda* (mesalamine) for ulcerative colitis in Japan.

Recent approvals and launches for legacy Baxalta products include *Cuvitru* (human immune globulin 20%) for primary immune deficiency, *Onivyde* (irinotecan liposome injection) for second-line metastatic pancreatic cancer in the EU, Vonvendi (recombinant von Willebrand factor) for adults with von Willebrand disease, and pediatric and surgery indications for the recombinant factor VIII product *Adynovate* (recombinant antihemophilic factor) for patients with hemophilia A.

Sternberg said Shire demonstrated its ability to take on a portfolio of products in new therapeutic areas and execute the combined company's business plan while the integration was under way. Shire launched Xiidra, Vonvendi and Cuvitru during that process.

"Hemophilia, immunology and oncology were new areas for us, but ophthalmics was new to Shire and the Xiidra launch went well," Sternberg said.

He noted areas within the legacy Shire portfolio that overlapped with the acquired Baxalta specialties, such as the company's hereditary angioedema (HAE) franchise and immunology. Similarly, Shire's lysosomal storage disease business overlaps with hemophilia. Oncology – an area that the company has wanted to break into since at least 2014 – has less overlap with Shire's legacy assets, but it expects to apply its rare disease and specialty pharma expertise to cancer drugs.

CEO Flemming Ornskov noted during his J.P. Morgan presentation that Shire is on its way to exceeding the company's goal – established when it revealed the $32bn Baxalta deal – of becoming the leading rare disease biopharmaceutical company with $20bn in revenue by 2020 with 65% of its revenue coming from medicines that treat rare diseases. Ornskov said on Jan. 10 that Shire derived 63% of its worldwide sales revenue from rare disease drugs and 37% from specialty medicines in 2016, but the company now expects that ratio to be 70% and 30% by 2020.

Growth between now and 2020 will be driven by a mix of newly launched products and drug candidates in the pipeline, including Baxalta's R&D programs after Shire shed the acquired firm's biosimilar product candidates. The company also sold its messenger RNA platform to RaNA Therapeutics Inc. in January for undisclosed upfront and milestone fees.

Vickers said Shire has finished its portfolio prioritization following the RaNA transaction and noted that the process of divesting ancillary assets after a big merger usually takes years for biopharma companies to complete. The combined R&D pipeline is expected to achieve several milestones in the year ahead as the company also faces new competition in areas where it or Baxalta has been the market leader.

"A few years ago, we had a gap in our late-stage programs," Vickers said. "Those have progressed that were in the early stage and we've brought in new products." Nine of the 12 Shire drugs with major milestones in 2017 that Ornskov highlighted during his J.P. Morgan conference were developed by acquired companies.

The company has said for the past year, however, that in light of the Baxalta and $5.9bn Dyax Corp. acquisitions it will not make any additional large purchases for the foreseeable future, though smaller buyouts and licensing transactions remain on the table.

"For sustained growth, we will have to bring things in from the outside," Vickers said. "Our in-licensing continues unabated."

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View the 12 Shire drugs with major milestones in 2017 here: **http://bit.ly/2kQ8p7A**

Can Pharma Keep Up With The Challenges Of Digital Healthcare?

By Kevin Grogan & Lubna Ahmed

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

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

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

Digital integral to healthcare

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

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

Pharma doing enough to embrace the digital age?

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

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

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

Pharma should not fear disruption

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

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

Partnerships best path to take

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

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

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

Respiratory ripe for digital deals

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

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

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

Beyond respiratory

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

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

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

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

Safe and secure

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

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

Pharma must take care to pick the right partner

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

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

For patients, privacy is paramount

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

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

Regulation no excuse to do nothing

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

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

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

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

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

Change just not fast enough

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

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

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

Cinven's M&A Ambitions Under Scrutiny

Having "crunched its numbers" and done initial due diligence, private equity group Cinven has approached troubled Stada Arzneimittel AG with a takeover offer of €56 per share that observers believe aims to create value through industry consolidation, using the German target as a core structure around which future acquisitions would coalesce. But while Stada seems relatively easy prey after board-level changes at the group last year, the subsequent arrival upon the scene of Advent International and later a third, as-yet-un-named party on Feb. 16 as rival suitors, has made Cinven Partners LLP's plan more difficult. The third party – identified by Bloomberg as Bain Capital – has made an offer of €58 euros a share, €2 more than that initially offered by Cinven, according to Stada. The three approaches are non-binding offers. Analysts have said CVC and Permira are also keen onlookers who could eventually throw their hats in the ring.
sten.stovall@informa.com, 13 Feb 2017

ArQule Shifts Focus After Tivantinib Flop

ArQule Inc. is focused squarely on plans for early-to-mid-stage assets following the hard-to-explain failure of tivantinib, which is partnered with Daiichi Sankyo Co. Ltd., in the Phase III METIV-HCC study in second-line liver cancer with high expression of the biomarker MET. The companies announced Feb. 17 in a joint statement that tivantinib failed to meet the overall survival primary endpoint in the Phase III study of the drug as a second-line therapy compared to best supportive care in 340 patients with MET-overexpressing liver cancer. ArQule had previously announced that it needed to reduce dosing in the trial for safety reasons, as a decline in white blood cells was reported. ArQule found the failure hard to explain during a Feb. 17 investor call. "We are certainly disappointed that the METIV-HCC trial did not replicate the results from the Phase II HCC trial on which it was based and did not demonstrate an improvement in overall survival for these patients selected with the biomarker population," CEO Paolo Pucci told investors during the call. Data will be presented at an upcoming scientific forum, he added. The company is expected to terminate development in the US; the drug had also been in development for a range of other indications, including pancreatic and colorectal cancer. But a second Phase III liver cancer study in Japan – JET-HCC sponsored by Kyowa Hakko Kirin Co. Ltd. – will continue. Ethnicity matters and it's unclear if results will pan out better in Asian populations, according to ArQule.
emily.hayes@informa.com, 17 Feb 2017

Takeda Extends PRA Alliance To Japan With New JV

Following its unveiling of a major global R&D overhaul last year, Takeda Pharmaceutical Co. Ltd. is further strengthening its alliance with contract research organization PRA Health Sciences Inc. through the planned formation of a new joint venture in Japan. The equally held operation will provide clinical development and pharmacovigilance services in the country to Takeda, managing a broad portfolio of studies across the Phase I to IV (postmarketing) spectrum, and offering other services for both the development and marketed portfolios. This set up closely mirrors the two companies' worldwide relationship announced last September, under which PRA will manage a broad range of human studies for Takeda and provide regulatory, pharmacovigilance and other operational services for pipeline and marketed products. Under its wide-ranging R&D shakeup, unveiled last July, Takeda is looking to transform its global R&D organization to improve flexibility and R&D productivity while reducing fixed costs. The Japanese firm is essentially outsourcing much of its development activities, and around 300 of its employees will be given the chance to "transition" to work with PRA in the US and Europe.
ian.haydock@informa.com, 15 Feb 2017

Inovio Strikes First Partnership For Lead Product

Beijing-based ApolloBio Corp. has acquired exclusive rights to develop and commercialize Inovio Pharmaceuticals Inc.'s cervical dysplasia DNA vaccine VGX-3100 in mainland China, Hong Kong, Macau and Taiwan. The new deal, worth $15m in upfront and near-term payments, gives Plymouth Meeting, Pennsylvania-based Inovio its first partner for the first-in-class immunotherapy product, the most advanced therapeutic vaccine globally for precancerous cervical lesions caused by human papillomavirus (HPV). Beijing-based ApolloBio will bring to the table "significant capabilities and expertise" in the development and regulatory landscape in China, Inovio president and CEO Dr. J. Joseph Kim said in a statement. ApolloBio, meanwhile, gains an innovative project in Asian markets increasingly afflicted by cervical cancer, which has already become China's second most prevalent malignancy in women aged 15-44, with an estimated 130,000 newly diagnosed cases in the country every year, accounting for nearly 30% of the global total. CEO Dr. Weiping Yang - a former executive for Fresenius SE & Co. KGAA in China - said the agreement "marks our determination to introduce late stage innovative new drugs to meet severely unmet medical needs within the Greater China region." ApolloBio's basic business model is to in-license innovative medicines with market potential in China in the fields of oncology, liver disease, and cardio-cerebrovascular disorders. The pact includes a $3m signing fee and a $12m milestone payment if a current pre-Phase III initiation clinical hold is lifted by the US FDA.
ian.haydock@informa.com, 14 Feb 2017

Where There's A Cure There's Controversy: Raymond Schinazi's Story

It is thought that more than 94% of HIV-infected individuals in the US on combination therapy take at least one of the drugs Raymond F Schinazi has invented. Most latterly associated with hepatitis C cure sofosbuvir, Schinazi tells Jo Shorthouse why he has no intention of stopping any time soon.

JO SHORTHOUSE jo.shorthouse@informa.com

"All these controversies do not compare to what I had to go through to get to where I am today," says Professor Raymond F Schinazi, the serial academic entrepreneur who led the original group that created the cure for hepatitis C (HCV), Sovaldi (sofosbuvir), as well as many hepatitis B and HIV drugs now on the market.

In 2013, the FDA approved Sovaldi and news of the high price tag placed on it by Gilead Sciences shocked many politicians, media commentators, and patient advocates. By association, Schinazi's scientific breakthrough was tainted with claims of pharmaceutical company greed. Dr Schinazi led the original chemistry group at Pharmasset Inc. – a company he co-founded with Dennis Liotta (a fellow chemistry professor at Emory University and co-inventor of the HIV drug emtricitabine alongside Woo-Baeg Choi and Schinazi) in 1998 – that created the precursors to Sovaldi, PSI-6130 and PSI-6206. Gilead Sciences Inc. bought Pharmasset in 2012 for $11.2bn.

An interview with Schinazi encompasses many topics that cannot be ignored, but equally cannot be comfortable for the Egyptian-born Italian chemist and virologist, to discuss.

EXILE FROM EGYPT

Life for the Schinazi family prior to 1962 was relatively stable in Egypt. A well-established Jewish family, originally from Livorno, Italy, they lived in the port city of Alexandria and owned three trading businesses. Then everything changed. After a day at the beach the family came home to find their house sealed, cars taken, business closed and bank accounts sequestered. The family of four were given an allowance of their own money of Egyptian £20 a week to live on, but the situation made it impossible for the family to stay in Egypt.

This may not have come as a huge shock. Earlier, in 1956, at the height of the Suez Crisis when France, the UK and Israel coordinated their attack on Egypt in an attempt to gain control of the Suez Canal and oust President Nasser from power, the Schinazi family had witnessed their French relatives thrown out of Egypt and returned to France. Bombs dropped by the British fell on nearby buildings and churches. The six-year-old Raymond learnt a lesson he still puts into practice today, never place a bed next to a window. The shattered glass from the bomb is still fresh in his mind, memories of his "little traumatic adventures" when he was still a child.

Raymond F Schinazi

Forward to 1962, finding themselves as refugees, the family of four boarded a ship to a refugee camp in Naples. Once in Italy Schinazi's father, a "smart businessman," found work with the meat industrialist Campofrio in Spain and his son was sent to a Jewish private school called Carmel College in England, enabled by a fund that lent money to British-educated students from Egypt wishing to study in the UK. Schinazi says that he has no anger toward the Egyptian people and that he cried when he heard the news of President Nasser's death in 1970. "He was like a father figure to us, even though he had done enormous harm to my family, I was very upset; it is part of my life," he explains.

The charity that was shown to his family left a huge impression and Schinazi credits his moral obligation to create new drugs to these early experiences. However, he also discusses his Anglo-Egyptian education that may explain his unapologetically entrepreneurial nature. He recalls: "In Egypt you learn early how to negotiate and you learn how to become a businessman, in a way, and you learn to find solutions very early in life if nothing is available."

Schinazi has since gone back to Egypt, albeit 40 years after his exile, to facilitate negotiations between the Egyptian government and foreign companies, including Gilead for Sovaldi, an experience he describes as emotional. "I never worked or consulted for Gilead. I worked for humanity, I worked for my university; and in that capacity I tried to advise the Egyptians and that helped a lot," he says.

"Today they have cured HCV from over 600,000 people using generic and proprietary drugs in Egypt; they are relatively cheap but in those days it was life and death. Everybody wanted that drug, the people lined up for miles trying to get it. Every family in Egypt was affected," he explains. "That's the irony of things,

it's remarkable. We were kicked out by the military and now I'm shaking hands with the military. Now I'm helping to cure Egyptians infected with HCV."

This situation is one that Schinazi would never have imagined as a 13-year-old boy. Once settled in Britain and flourishing at school, his dream of becoming a nuclear physicist was soon smothered and instead his attentions turned to chemistry. He attended Bath University studying chemistry at undergraduate level, followed by a PhD in organic chemistry. Frustrated by the siloed nature of the sciences department, Schinazi sought to bring chemistry, biology and pharmacology together.

However, the language of chemistry was soon left wanting and Schinazi decided to broaden his scientific horizons to drug development. "The glory is in the biology not in the chemistry, so that's where everything changed. I was motivated to develop something useful, there's no point in making these compounds, publishing and showing how clever you are, but no use to anybody."

He recalls a very stark lesson in the application of medicine two years before leaving Egypt. His mother suffered a miscarriage and her womb became infected with fungi. "At that point everybody thought she was going to die," he says, the family knew there was an anti-fungal drug that was available in the US, but not in Egypt, so Schinazi's grandfather managed to get a TWA pilot to buy the drug, mycostatin, in the US which was used to cure Schinazi's mother. "I said, 'Wow, this is pretty good. You have a little pill, you take it and it cures you. How wonderful, let's do that, let's save people's lives, that's a great thing.'"

Today, Schinazi is associated with 15 New Drug Applications (NDAs), and has published more than 500 peer-reviewed papers, authored at least 100 US patents and seven books. Although his name has most recently associated with Sovaldi, as a world leader in nucleoside chemistry, Schinazi has been a pioneering influence in virology. He has founded five biotechnology companies including Pharmasset, Triangle Pharmaceuticals Inc. and Idenix Pharmaceuticals Inc. He is an inventor or has been associated with several medicines, including the HIV drugs stavudine, lamivudine and emtricitabine, and the hepatitis B treatment telbivudine. More than 94% of HIV-infected individuals in the US on combination therapy take at least one of the drugs he invented.

SUCCESS AND CRITICISM

It is probably because of his huge success and continued commitment to work that he is able to be so candid about the criticism he has received over the funding and pricing of Sovaldi. "The bottom line is, I'm the guy who founded Pharmasset with my own credit card; I hired all the chemists, I hired all the biologists and the management including the last CEO, I had a vision and I executed the vision successfully. So, you are being criticised for doing what is really public good and saving lives."

There have been accusations that he benefitted from government funding to develop sofosbuvir while working as professor of pediatrics at Emory University and at the Atlanta Department of Veterans Affairs, an Emory-affiliated hospital. When Gilead Sciences bought the company he co- founded, Pharmasset, in 2012 for $11.4bn, he pocketed more than $400m. He claims he has never received VA or NIH funding in support of his work on HCV and disclosed his activities at Pharmasset as chairman and director to both Emory and the VA. It is mainly the rubbing together of Schinazi's public and private interests that have called into question how much civic time and money went into developing blockbuster drugs that some members of the public simply cannot afford without health insurance coverage.

Batting away the controversy, Schinazi simply puts the claims down to jealousy. The fact is that without Pharmasset, there would be no Sovaldi and its precursors, he says. "Without Sovaldi there would not be a high cure rate for HCV as early as 2013. Yes, there are good drugs now for HCV other than Sovaldi, but somebody had to be the pioneer."

When discussing the furore surrounding the pricing issue, he parks the issue firmly at the Gilead marketing department door. When Gilead launched Sovaldi it didn't use the word 'cure' in campaigns, he says, and the difference between a treatment and a cure is very significant. Pricing for the latter of those options is a lot less controversial.

"When I've failed, and I've failed many times, I never gave up," he says. "Admittedly, Gilead may have made a mistake by charging initially about a $1,000 per pill, but the reality is that nobody has ever paid that price. It's a misconception." Although Schinazi had no involvement in setting the pricing of Sovaldi, Gilead's pricing methodology is based on the GDP for the country and the price of similar, less effective and older HCV medicines, he says. The current HCV treatments have fallen in price, but initially they were based on the cost of interferon treatments which were painful, long (a year), rarely effective and still costly.

"And you have to amortize it," he continues. "Because even if you calculate the price of a treatment – for an innovative treatment not a generic, but something that took years and years of hard work and many failures to get to that point – I never ever imagined that we would have a drug that cures at a 95% rate. Show me one viral disease where you have a cure. It's remarkable, for the first time in the history of humankind, you have a drug that actually cures a viral disease."

FINDING A CURE

It is not just HCV that Schinazi is connected with, of course, but also his pioneering scientific breakthroughs in HIV. He is positive that finding a cure for HIV will happen, despite the ethical issues surrounding a process whereby a drug-stabilized patient has to stop treatment for the disease to rebound.

In practical terms, finding a cure for hepatitis B has most recently taken up a lot of Schinazi's time. HBV affects more people than HIV and HCV combined, around 450 million people globally. "We need to keep our laboratory running with all the young bright minds and future leaders and I cannot do it alone. A cure for hepatitis B; that's huge."

Schinazi spends almost $4m a year to run his Emory laboratories, mostly from royalties from his inventions. At 66, Schinazi still has a strong drive to still cure disease, he explains, and this keeps him going. "The momentum after coming out of Egypt, this momentum drove me to become who and what I am and I think this is important to have drive, to be enthusiastic and be passionate about what you want to do. There is nothing better than saving lives, and when you get a letter from a patient, out of the blue, thanking you for what you've done, it's so gratifying. I respond to every single one of them."

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UC's CRISPR Licensees Unbowed By Losing Initial US Patent Office Ruling

STEN STOVALL sten.stovall@informa.com

The US patent office's initial ruling on CRISPR patents that granted the Broad Institute a victory at the expense of the University of California caps the first major skirmish in what will be a long, drawn-out corporate legal battle.

Round one in the heated patent fight over rights to the genome-editing technology CRISPR/Cas9 has gone to Harvard University's and the Massachusetts Institute of Technology's Broad Institute and its intellectual property licensees, including Editas Medicine Inc. However, the University of California and its licensees says that it is far from beaten and remains confident of an eventual overall victory.

They were reacting to the US Patent and Trademark Office (USPTO) ruling Feb. 15 that said contested patents on the CRISPR/Cas9 technology do belong to the Broad Institute, dashing efforts by the University of California (UC) and its corporate allies to overturn those patents. The briefly worded legal ruling in effect means that key CRISPR patents awarded to the Broad beginning in 2014 differ enough from those applied for by UC that Broad's patents can stand.

That ruling by the US Patent and Trademark Office Patent Trial and Appeal Board (PTAB) is the first outcome in a legal battle pitting the Broad Institute against UC, the University of Vienna and the scientist Emmanuelle Charpentier over a technology that promises to let genes be altered to treat disease. The PTAB ruled that there is "no interference in fact" between patents awarded to the Broad, which are mainly licensed to Editas, and the patents sought by UC and licensed to CRISPR Therapeutics AG, Intellia Therapeutics Inc., Caribou Biosciences Inc and ERS Genomics Ltd.

The patent judges did not explain their reasoning for the ruling. The decision means that UC's claim that the Broad's patents – specifically intellectual property related to the use of CRISPR/Cas9 technology in eukaryotic, or human, cells – were "obvious," was rejected by the PTAB, thus the Broad's IP could be patented.

The dispute's roots date back to 2012, when CRISPR technology was invented. The method has since become widely used, revolutionizing the way gene editing is done, and offering its potential use in a wide array of therapies. The financial implications are therefore huge.

Intellia and CRISPR Therapeutics convened separate conference calls Feb. 16 to calm investors' nerves, during which management stressed that the PTAB decision does not judge the validity of UC's patents nor their foundational IP claims – nor does it insulate Broad from future IP litigation by UC.

> 'Nobody can block anybody for the next five years or so'

Intellia CEO Nessan Bermingham told analysts the ruling "specifically stated that its decision neither cancels nor finally refutes either party's claims. PTAB did not make a determination regarding which party in the interference first invented the use of a CRISPRCas9 genome-editing technology in eukaryotes. We believe that UC's CRISPR/Cas9 IP, which was filed in May 2012, covers the use of the technology on eukaryotic cells. This decision does not contradict this and does not change our mission. It is business as usual for us."

Analysts at Jefferies said UC and its corporate allies now have three options in response to the court's no-interference decision: UC could either appeal the decision to the Federal Circuit and expect a decision in 18 months; file for a second interference with another set of claims, a process that could take up to two and a half years; and/or seek a settlement where UC and its associated partners could move forward with their own IP, inventing around any potential restrictions on Broad's patents.

CRISPR Therapeutics chief business officer Samarth Kulkarni described that menu of tactical options as "accurate," but said the decision on what their side should do next had not yet been made. Meanwhile, plans for CRISPR Therapeutics to transition therapies for hemoglobinopathies – such as sickle cell disease and beta-thalassemia – remain on track for late 2017 or early 2018. "Nobody can block anybody for the next five years or so, while R&D is happening," Kulkarni said an interview with *Scrip*.

Kulkarni noted the issue of CRISPR patents is a global one, which adds further complexity to the issue. UC is also in the process of filing IP in Europe, which is completely separate from any IP action in the US. The UK's Intellectual Property Office has granted patents to foundational CRISPR/Cas9 genome editing technology in any non-cellular or cellular setting including in human cells to UC, Kulkarni said.

Analysts at Barclays noted that if the PTAB had instead ruled in UC's favor, then Broad's patents could have been considered invalid. Importantly, the decision also does not establish which party invented CRISPR/Cas9 technology first. "The situation as it now stands means University of California can now move forward with its patent application on the use of CRISPR/Cas9 technology to edit genes in any setting, including eukaryotic, or human, cells," they said.

They noted that even if Broad is eventually issued patents for the use of CRISPR/Cas9 in eukaryotic cells, UC could require a license from Editas "given UC's IP is broader and encompasses use in all settings. At this point, UC can seek a new interference on Broad's patents or appeal the current decision," the Barclays analysts said.

Unsurprisingly, Editas welcomed the PTAB legal ruling.

"This important decision affirms the inventiveness of the Broad's work in translating the biology of the natural world into fundamental building blocks to create unprecedented medicines," Editas CEO Katrine Bosley said in a statement, adding: "We are continuing to invest in this technology to build our business for the long-term and to create genome-editing therapies for patients suffering from genetically-defined and genetically-treatable diseases."

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AbbVie 'Disagrees' With NICE's Venclyxto Rejection

STEN STOVALL sten.stovall@informa.com

NICE has rejected AbbVie's BCL-2 inhibitor on grounds that evidence presented by the drug maker didn't adequately prove Venclyxto's clinical effectiveness, nor that the cancer product would be value for money.

AbbVie Inc. said it was disappointed by NICE's initial rejection of *Venclyxto* (venetoclax) for treating chronic lymphocytic leukaemia but has vowed to work with the UK HTA to get Europe's first approved BCL-2 inhibitor made routinely available on Britain's publicly-funded National Health Service (NHS).

AbbVie's promise followed an announcement by the National Institute for Health and Care Excellence (NICE) that it would not recommend Venclyxto within its marketing authorization as a treatment for chronic lymphocytic leukemia, as "the treatment benefits of venetoclax were uncertain." NICE in a statement also said the incremental cost-effectiveness ratios (ICERs) for Venclyxto compared with best supportive care "were higher than the normally range considered cost-effective for use in the NHS."

The US drug maker expressed "disappointment" at the NICE decision, saying in a statement: "AbbVie disagrees with the negative recommendation," but that it will keep working with NICE and the clinical and patient communities "to ensure a positive reimbursement decision for venetoclax as quickly as possible."

AbbVie is looking to hematology drugs like Venclyxto – which is partnered with Roche unit Genentech Inc. – and *Imbruvica* (ibrutinib) and *Rova-T* (rovalpitizumab tesirine) to lead its oncology portfolio. Venclyxto – branded as Venclexta in the US - won conditional marketing authorization in Europe for relapsed/refractory CLL patients with the 17p deletion and TP53 mutations in October 2016, and has since become the first approved BCL-2 inhibitor in Europe.

Venclyxto, which is being commercialized by AbbVie outside the US, is already approved by the US FDA for the 17p del population. AbbVie expects data later this year from the Phase III MURANO study that the company believes will offer rationale for a broader claim in CLL. A Phase III program in acute myeloid leukemia recently started, and Phase III studies are already ongoing in relapsed/refractory and first-line CLL and multiple myeloma, the company has told *Scrip*.

In disagreeing with NICE's draft ruling, AbbVie underscored that Venclyxto's potential in CLL had already been recognized by UK regulators, who designated the treatment as a Promising Innovative Medicine (PRIME) and that in Aug. 2016 the UK's Medicines and Healthcare products Regulatory Agency (MHRA) granted Venclyxto a positive scientific opinion through the Early Access to Medicines Scheme (EAMS), representing "a first in any blood cancer for the scheme".

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Five Golden Rules For Post M&A Leadership Success

Four consultants from pharma and further afield discuss their golden rules for the soft aspects of M&A. They outline best practice guidelines for managing people through mergers or takeovers and highlight the most common errors.

LUCIE ELLIS lucie.ellis@informa.com

Predictions for the pharma and biotech sectors so far in 2017 have all carried a similar tune – M&A is on the increase, both at the big pharma and mid-sized company level. Consulting firm EY highlighted in its annual *M&A Outlook and Fire Power Report* that 2017 could be a record year for M&A and the number of biopharma deals is expected to soar because companies are well funded and greatly in need of new growth drivers to offset pricing pressures.

In theme with a heavy M&A environment this year, experts from consulting businesses Deloitte, Hire Right, Informa Pharma Consulting and Novasecta share with *Scrip* their most important rules for building strong leadership teams post-merger or takeover. They also discuss common mistakes made during company integrations and how to avoid them.

LEAD WITH THE FUTURE

According to a recent Deloitte Consulting M&A survey, over 87% of merger failures are related to leadership issues.

Anna Samanta

Anna Samanta, who leads the company's Swiss integration and separation advisory team, told *Scrip* that to start the process of leadership appointments post-merger or takeover she encourages companies to be certain of their business strategy for the integrated business – as this will drive the decisions around capabilities required on the management team. "It is very important to know where you want to take your organization with the merger because this will help to highlight the capabilities you need in your leadership team to deliver on the business strategy," Samanta said. She added that once the strategy for the combined business is confirmed it is easier to assess potential candidates objectively.

Steve Girdler, managing director for the EMEA region at human resources specialist HireRight, concurred that a senior management team post-merger needs to reflect the company's evolved business. "It's about understanding not just the strength of your own organization now, or even the strength of the company you are acquiring, it's about understanding the strategy and strengths of the combined business. The senior management team needs to be reflective of that."

However, Girdler noted that the best leadership for a newly evolved company may not come from within. "It could be that the combined senior management team is not as fit for purpose as previously thought when you are a larger organization with different goals. For example, you might need to hire people with greater international experience if you have acquired a multinational company," he said. Samanta added that it is common that an integrated business may need to complement their leadership team with external candidates.

MAKE FAST, FORMAL DECISIONS

Tim Polack, head of consulting for Informa Business Intelligence, which includes Pharma Intelligence, notes that his number one rule regarding employees during a merger situation is to make leadership decisions quickly. Polack suggested that a new management team for a post-merger company should be announced within a month of the deal closing. "You want your confirmed leadership team to be driving the integration; you do not want a team of people wondering if they will still have a job or not," he explained.

Polack added that the management team in place during the early stages of integration will be responsible for setting the tone of the combined business and leading the charge for successful amalgamation, therefore this team should be the top talent a company intends to keep. "In most merger situations, there are two or more people to each available post on the new leadership team, so the longer you delay making decisions about leadership appointments the more confusion and inefficiency is caused," Polack said.

Samanta highlighted that in her experience, merger failures don't come from the deal-making phase but from poor execution of integration strategies. "There is a case for speed because you have a window of opportunity during a merger where people are expecting change and if you wait too long it can result in a lot of resistance," she said. However, she explains that structures need to be put in place to allow for fast but concise decisions. It is also important that there is executive alignment on the merger rationale and approach to allow for fast decision making. "If different executives are giving out different guidance to their teams for how to approach the merger, this creates chaos," she said.

DON'T QUIT YOUR DAY JOB

Another big challenge for companies during an integration process is keeping staff focused on the core business and day-to-day practices. Deloitte figures show that, on average, during the first four to eight months post-merger productivity is reduced by 50%.

The key to boosting productivity, from both leadership teams and staff at lower levels, during a merger is communication, says Samanta. "Communication programs need to be well planned, it can't just be an afterthought," she advised, adding that it is critical to keep external communications in line with internal communications. "I haven't been involved in an integration yet where someone has told me there was too much information given," said Samanta, who is also managing partner for talent at Deloitte. "It's a period of change that can create a lot of uncertainty." She highlighted that it is the "me questions" that need to be

answered for employees, such as 'What is happening to my title or my office?'

In order to manage these employee queries, Samanta advises companies to train their HR teams pre-merger. "I always make sure to train up the HR team very early on because this team is going to have to deal with a lot of questions and tricky circumstances when it comes to the integration of people. A lot of the time I find that HR teams are already run to the bone, if you put this extra work load onto them it becomes difficult. It can be a capacity issue or a capability issue."

Meanwhile, Polack recommends appointing a separate integration team to manage the business transformation throughout all areas during a merger. He said that this allows the rest of the company to get on with the job at hand. "I would say an unsuccessful integration is when the whole organization gets pulled into meetings and working groups, getting bogged down in that process," he said. "In these cases, you will often see companies losing customers to competitors because they are too focused on the whole integration and not the value it brings and their customers' needs."

DON'T LET TALENT SLIP AWAY

M&A almost always involved cuts, or employees that are demoted or pushed sideways into new roles. Ed Corbett, engagement manager at Novasecta Limited, a specialist pharmaceutical strategy consultancy, said that as an employee "you've only got about three mergers in you" because they can be difficult and stressful periods. "If leaders are clear as to why a merger is happening, people may not like it because they are affected by it, but at least they understand it. That understanding is incredibly important to help individuals work through the change curve."

Polack added that losing critical talent is a risk during a business integration because of the confusion large company changes can cause to employees. "People with good skill sets who are motivated and valuable to your company are also marketable and valuable to other companies. Some people won't wait around during an integration to see where they end up, they will go out and look elsewhere," he warns.

To avoid the loss of talent, Deloitte highlights five key questions for CEOs to answer to ensure their team is successful and value is captured post-merger:

1. Who should lead our business in future?
2. Who are my key integration leaders?
3. What hidden gems do I have in my talent pool?
4. How do I engage and develop the change leaders who matter most?
5. How do I build capabilities that will sustain a culture of future growth?

The consulting firm adds that companies that are most successful at retaining top talent are also more likely to focus on tactics that support relationship and career building in addition to compensation.

Samanta said that in her experience, retention of employees is not just about financials but winning the hearts and minds of people. "Very early on you need to pinpoint the key talent to retain, not just in management but further down in the organizations; and on both sides of the integration," she noted. "You should be having one-to-one conversations with these key people."

In the pharma and life sciences sectors, Samanta noted that merger decisions more frequently revolve around generating new revenue streams and pipeline innovation, as opposed to purely cost-saving efforts. Therefore, she believes it is imperative for these companies to have good leadership with a mix of both heritage companies. "Pharma and life sciences are interesting sectors where a lot of the deals are focused on growth and how to access to new potential drugs or devices to drive a business forwards. Your deal is focused on accessing innovation and R&D, it can be even more important to have team members from both sides," she said.

KNOW YOUR PEOPLE

HireRight's Girdler also noted that a big issue with mergers and takeovers is the unknowns that come with each business. He said a priority for an acquiring company should always be due diligence on the employees of a target business, especially in sectors like the pharma industry. "The nature of highly regulated sectors, like the pharmaceutical industry or financial services, mean risks effect wider groups than just that immediate company," he said.

HireRight specializes in scanning prospective recruits and Girdler said this is a step often missed out during a merger or takeover. He said that when acquiring a business, it is important to remember that


Steve Girdler

the new workforce is largely an unknown factor. How you go about mitigating risk in the case of a merger or acquisition though is complex – it is not the same or as simple as during the initial recruitment process.

His golden rule for this area of company integration is simple: "planning, planning, planning."

"The benefit of good planning means you know you have to mitigate risks and identify any other risks and you have a formal audit trail that you have taken appropriate measures to do due diligence around the business you're acquiring," he said, noting that companies often forget about the people side of things when it comes to risk. "The best way to manage this is when you are in a M&A negotiation, you say as part of that process that you require due diligence on the staff to be part of that prerequisite," Girdler said. "That is the safest way because the company can get consent from its own staff. The company can then provide the information in a redacted form, so it is not sensitive personal data."

Alternatively, a screening policy – a process that is common in the US and growing in practice elsewhere – can be put in place post-merger. "But it is very important to tick that due diligence box during M&A discussions," Girdler advised. The biggest mistake in this area is simply ignoring due diligence on the workforce of a merging business.

Another common error is being disproportionate in checking out staff from a merging firm.

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Limited Acquisition Headroom At Specialty Pharma

ANDY SMITH

Debt-fueled acquisitions helped Teva, Shire and Allergan report well-received fourth-quarter earnings. But sector circumstances have changed since 2016 and the ability to grow by debt-funded acquisition is now severely restricted.

As fourth-quarter earnings season trundles on, the focus is moving away from the financial reports of big pharmaceutical companies to their specialty pharmaceutical counterparts and then finally onto loss-making biotechnology companies. With the missed fourth-quarter sales and 2017 guidance of big pharma threatening sentiment for the rest of the sector, specialty pharma took on the role of a linebacker last week. Headline results were better than I had expected.

Teva Pharmaceutical Industries Ltd.'s fourth-quarter earnings report followed the recent departure of its CEO so expectations were not high. Despite being in the middle of the perfect specialty pharma storm with the added concern that the CEO's departure was linked to fourth-quarter sales or profit, Teva managed to pull a rabbit out of a hat and deliver reassuringly positive results.

Sales and earnings were up about 4% and 1% respectively, ahead of analysts' consensus estimates, while its 2017 projections of sales and (admittedly non-GAAP) earnings were maintained. Teva's $973m generally accepted accounting principal (GAAP) loss versus its $1.5bn non-GAAP profit was a reminder to investors to prepare for the reconciliation of these numbers when companies report. Teva should probably be given a bye in this respect since the accounting effects of its $40.5bn acquisition of Allergan PLC's Actavis generics division are still rippling through its financial statements and there are far worse and regular exploiters of non-GAAP accounting than Teva. The company's stock price ended the week up a whopping 12.8% against the more pedestrian 2.6% rise in the NYSE ARCA Pharmaceutical Index. Like its results, Teva's share price jump had a number of influences but the maintenance of its dividend featured highly. While there were obvious reasons to be cheerful about Teva's results, 2017 guidance and dividend commitment, there are also reasons to be cautious. Teva's guidance appeared not to assume further generic drug price erosion or multiple generic 40mg Copaxone (glatiramer acetate) entrants.

When Shire PLC delivered what the analysts from Citigroup called a "solid fourth-quarter and guidance," the specialty pharma trend started by Teva at the start of the week appeared to be more than a one-off. Shire's fourth-quarter sales and earnings were 1% and 3% ahead of analysts' consensus estimates, respectively. The mid-point of Shire's full-year 2017 sales guidance range was in line with analysts' consensus estimates while the mid-point of its earnings guidance range was 2% below consensus estimates.

Like Teva, Shire is something of a building site after its $32bn acquisition and integration of the sales and earnings of Baxalta Inc. and I was struck by a common undertone at both companies. The high level of debt that was needed to fund the acquisitions last year looks to have a different risk profile with two or three interest rates possible in 2017. Both companies had debt reduction narratives in their results and both calmed stock and debt holders by declaring acquisitions were not a priority in the immediate future. In Teva's case, any deterioration in its branded or generics business outside its maintained guidance could force a dividend cut – unpalatable to those investors who just basked in its maintenance – if debt covenants are not to be breached. Shire's de-leveraging plans for the year would be aided by the absence of generic competition to its ulcerative colitis drug *Lialda* (mesalamine), which the analysts from Cowen recently assumed was unlikely before 2019. The intellectual property on Lialda had seemed robust after Shire's defense last year but last week the Federal Circuit Court of Appeals reversed the lower court's earlier decision in favor of Shire and ordered that the generic version of Lialda from Actavis did not infringe Shire's patents.

The debt-mediated acquisitions of Teva and Shire may result in an uncomfortable time depending on their generic pressures in 2017 but – as both companies alluded to in their results – they have certainly limited their borrowing headroom and appetite for further substantive M&A.

Allergan – the architect of Teva's increased debt burden – reported fourth-quarter results that initiated the specialty pharma rearguard action this earnings season. Allergan's sales and earnings were 2% and 4% ahead of analysts' consensus expectations, respectively. Admittedly, Allergan's guidance on earnings growth had been reset down at the end of 2016 but its more recent results provided an opportunity to revise up 2017 sales and earnings forecasts that were, respectively, 2% and 1% above the mid-points of what had become analysts' full-year consensus estimates.

Since the divestment of its subsequently pressured generics and Anda Inc. distribution businesses – transactions that look in retrospect to be strategic masterstrokes – Allergan has been remaking itself with a large number of transactions that rival the pace of even Celgene Corp.'s deal-making activity and have cost at least $10bn in cash up-fronts alone. While many of these transactions – like the $2.5bn paid for Zeltiq Aesthetics Inc. and $2.9bn for LifeCell Corp.'s regenerative medicine business – were in Allergan's traditional specialty strategy, if I were in business development at Allergan, I would be kicking myself that the acquisition of Novartis AG's Alcon Inc. eye care business is out of reach. This is because Alcon's total purchase price was $51bn and Allergan's net debt now stands at $19.5bn in addition to its recently committed $10bn share buyback. There is probably little headroom left for a large transformative acquisition like Alcon.

If I were a healthcare investment banker I would expect that the part of my address book that listed specialty pharma CEOs will grow cobwebs over the next year or so.

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Andy Smith gives an investor's view on life science companies. He joined the commercialization, pricing and market access group of ICON PLC in February 2017. He has been the lead fund manager of four life science–specific funds, including 3i Bioscience, International Biotechnology and the AXA Framlington Biotech Fund, and was awarded the techMark Technology Fund Manager of the year for 2007.

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.

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Selected clinical trial developments for the week 10–16 February 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Suspended			
Merck & Co. Inc.	verubecestat (MK-8931)	Alzheimer's disease, mild to moderate	EPOCH; lack of efficacy at interim review. Prodromal study (APECS) to continue.
Phase III Results Published			
Beijing Biostar Technologies Ltd.	utidelone	refractory metastatic breast cancer	*The Lancet Oncology*, online Feb. 10, 2017.
Eli Lilly & Co.	baricitinib	rheumatoid arthritis	RA-BEAM; In *NEJM*, Feb. 16, 2017.
Updated Phase III Results			
Theratechnologies Inc.	ibalizumab	HIV/AIDS	Significant viral load reduction, increased CD4+ T-cells
AEterna Zentaris Inc.	*Macrilen* (macimorelin)	growth hormone deficiency	CROSSOVER; shows efficacy, company will pursue FDA approval.
ViiV Healthcare	dolutegravir (*Tivicay*) plus rilpivirine (*Edurant*), in a single tablet	HIV/AIDS	SWORD-1 and -2; two-drug regimen non-inferior to 3- or 4-drug regimens.
BioMarin Pharmaceutical Inc.	*Vimizim* (elosulfase alfa)	Morquio syndrome	Disease stabilized in long term therapy.
Phase III Interim/Top-line Results			
Pfizer Inc.	*Xeljanz* (tofacitinib)	rheumatoid arthritis	ORAL Strategy; non-inferior to *Humira* in some but not all study arms.
Ardelyx Inc.	tenapanor	hyperphosphatemia in end-stage renal disease on dialysis	Met primary endpoint, second Phase III study to start.
Merck & Co. Inc.	doravirine, a NNRTI	HIV/AIDS	DRIVE-FORWARD; met primary endpoint, lowered virus levels.
Zosano Pharma Corp.	M207 (zolmitriptan) transdermal patch	migraine	ZOTRIP; met co-primary endpoints.
Acacia Pharma Ltd.	*Baremsis* (amisulpiride)	rescue therapy of post-operative nausea and vomiting	Positive results from fourth Phase III study.
H. Lundbeck AS/Takeda Pharmaceutical Co. Ltd.	*Brintellix* (vortioxetine)	attention deficit hyperactivity disorder	Inconclusive results.
Phase III Initiated			
Tracon Pharmaceuticals Inc.	TRC105 (endoglin antibody)	sarcoma	TAPPAS; alone or with pazopanib.
Clearside Biomedical Inc.	*Zuprata* (triamcinolone acetonide)	macular edema with retinal vein occlusion	SAPPHIRE; given suprachoroidally.
Phase III Announced			
Novartis AG	QAW039	asthma	Added to existing therapies.
Pfizer Inc.	lorlatinib (PF-06463922)	non-small cell lung cancer	Versus crizotinib.
Sanofi/Regeneron Pharmaceuticals Inc.	*Dupixent* (dupilumab) monotherapy	atopic dermatitis	Patients aged 12 to 18 years.

Source: Biomedtracker

Nathalie Moll, currently secretary general of the European Association for Bioindustries, has been appointed **EFPIA**'s director general – effective April, 2017. Eric Cornut will continue to lead EFPIA as interim director general until Moll joins the organization.

Arterial Capital Management has appointed ***Markus Weissbach*** clinical trials director and to based in Dublin, Ireland. Weissbach brings years of experience in the life science industry to the company and was previously chief medical officer at Novartis Vaccines and Diagnostics, CEO of Averion International, and director responsible for clinical research and development at Takeda Europe. He is also chief operating officer at DS Biopharma in Dublin.

Karin Hoogendoorn has joined a immuno-oncology biopharma **Immunicum AB** as head of chemistry, manufacturing and controls (CMC). Most recently, Hoogendoorn was associate director regulatory CMC in the cell and gene therapy unit at Novartis AG. She also spent seven years at Janssen Biologics BV as associate director global regulatory affairs-CMC. Hoogendoorn has held various CMC roles at companies including Crucell Holland BV and OctoPlus Development BV.

NeuroVive, a mitochondrial medicine company, has named ***Philippe Gallay*** and ***Massimo Pinzani*** scientific advisors. Gallay is professor of immunology at the department of immunology and microbiology at Scripps Research Institute in California, US. Pinzani is professor of medicine, clinical hepatologist and director of the University College London Institute for Liver and Digestive Health, UK.

Pain focused **AcelRx Pharmaceuticals** has appointed ***Vincent J. Angotti*** CEO – effective March 6, 2017. He will be succeeding ***Howie Rosen***, who will continue on the company's board of directors. Angotti carries more than two decades of experience, with his most recent position being CEO of XenoPort Inc. Before this, he held senior sales and marketing positions at Reliant Pharmaceuticals Inc.

PureTech Health Plc. has named ***Atul Pande***, GlaxoSmithKline PLC's former senior vice president, head of neuroscience and senior advisor, pharmaceutical R&D, chief medical officer. Pande is a psychiatrist and fellow of several scientific societies including the America Psychiatric Association. He has previously held senior roles in Pfizer R&D, Parke-Davis/Warner-Lambert, and Lilly Research Laboratories and is on the board of PureTech's Karuna Pharmaceuticals, Axovant Sciences and Autifony Therapeutics.

Anton Ehrhardt has joined cancer focused **Mitra Biotech Inc.** as vice president of medical affairs. Before Mitra, Ehrhardt held medical affairs leadership roles at Onyx Pharmaceuticals (Amgen), Sanofi, Millennium Pharmaceuticals, Cubist Pharmaceuticals, and Bristol-Myers Squibb. Previously, he was president of the Investigator Initiated Sponsored Research Association during its integration into the Association of Clinical Research Professionals.

Symbiomix Therapeutics, a biopharma company focused on gynecological infections, has named ***David L. Stern*** CEO. With 20 years of experience, Stern is an independent board member of the California Cryobank and previously was chief commercial officer of the personalized medicine company, Celmatrix. Before this, he was executive vice president of global commercial operations for OvaScience and also held leadership positions at Merck Serono , including senior vice president and head of global business.

Scrip

ELEANOR MALONE @SCRIPELEANOR
eleanor.malone@informa.com
ALEXANDRA SHIMMINGS @SCRIPALEXS
alex.shimmings@informa.com
SUKAINA.VIRJI @SCRIPSUKI
sukaina.virji@informa.com
ANJU.GHANGURDE @SCRIPANJUG
anju.ghangurde@informa.com
MANDY JACKSON @SCRIPMANDY
mandy.jackson@informausa.com
JOANNE SHORTHOUSE @SCRIPJO
joanne.shorthouse@informa.com
FRANCESCA BRUCE @SCRIPFRANCESCA
francesca.bruce@informa.com
STEN STOVALL @STENSTOVALL
sten.stovall@informa.com
IAN SCHOFIELD @SCRIPIANS
ian.schofield@informa.com
ASHLEY YEO @ASHLEYPYEO
ashley.yeo@informa.com
MARY JO LAFFLER
maryjo.laffler@informa.com
LUCIE ELLIS @SCRIPLUCIE
lucie.ellis@informa.com
LUBNA AHMED @SCRIPLUBNA
lubna.ahmed@informa.com
PAUL WILKINSON @PAUL__WILKINSON
paul.wilkinson@informa.com
JOHN HODGSON @SCRIPJOHN
john.hodgson@informa.com
MIKE WARD @SCRIPMIKEWARD
mike.ward@informa.com
PETER CHARLISH @PETERCHARLISH
peter.charlish@informa.com
JOHN DAVIS @JOHN023DAVIS
john.davis@informa.com
EMILY HAYES @EMILYKATEHAYES
emily.hayes@informa.com
JESSICA MERRILL @JESSCIAMERRILL
jessica.merrill@informa.com
JOSEPH HAAS
joseph.haas@informa.com
IAN HAYDOCK
ian.haydock@informa.com
YING HUANG
ying.huang@informa.com
JUNG-WON SHIN
jungwon.shin@informa.com
BRIAN YANG
brian.yang@informa.com

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Customer Services
Tel: +44 (0)20 7017 5540
or (US) Toll Free: 1 800 997 3892
Email: Subscriptions@informa.com
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scrip.pharmamedtechbi.com
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christopher.keeling@informa.com

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