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Elias Zerhouni

Sanofi R&D Chief Zerhouni: How I'm Doing More With Less

Elias Zerhouni says Sanofi's ongoing R&D revamp has produced improved innovative results with controlled spending, in part by emphasizing cutting-edge product development ahead of research.

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Sanofi 's head of global research and development Elias Zerhouni feels the outside world – meaning analysts and investors – have yet to fully appreciate the pipeline progress and future promise generated by his ongoing revamp of the French group's R&D process, but he is confident that will soon happen, helped by further expected success developing multi-specific therapies.

A native of Algeria, Zerhouni was appointed to his current position in 2011 by former Sanofi CEO Chris Viehbacher. Remaining in that role under current CEO Olivier Brandicourt, Zerhouni has been vigorously remolding the company's early and mid-stage pipeline so the company can replace revenues lost from patent expiries for blockbusters like platelet anti-aggregant *Plavix* (clopidogrel) and *Lantus* (insulin glargine).

The initial R&D strategy revamp began even earlier in 2009 when Zerhouni was a consultant to Sanofi; it gained steam when he joined Sanofi in his present position.

"I structured the strategy for Sanofi in two phases. The first phase was how do we build a pipeline to be delivered in 2015, 2016, 2017 when we had loss of exclusivity on key products, with Lantus being the last major drug after Plavix and others that lost their patents. The goal was how to do it without breaking the bank," Zerhouni told *Scrip* in a recent interview.

That initial revamp involved overhauling the pipeline and trimming 19 Phase II and Phase III programs from Sanofi's R&D pipeline between 2009 and 2012. Some of the programs missed Phase II endpoints. Others were discontinued because the value proposition wasn't there from either the patient or payer perspective.

"I modified the strategy in a big way, by putting development first: we have to take care of development and underneath all that, start to fix research, not the other way around. Most heads of R&D, are heads of R&D; I said, 'No, I want to be a head of D&R,' rather than R&D at Sanofi," Zerhouni explained.

IMPROVED PRODUCTIVITY

The second phase of the revamp is focused on early research and is ongoing.

Zerhouni says the pipeline turnaround can already be seen in new drug launches.

"Between 2008 and 2012, Sanofi launched three drugs. Between 2012 and 2017 - provided we get FDA approval for dupilumab at the end of this quarter that we hope for - we will have had 13 launches. So, by numbers, it's doing well," Zerhouni said. He said that in terms of sales for 2016, new drugs represented €2.7bn

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from the editor

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In January *Scrip* reported on the launch of the new Coalition for Epidemic Preparedness Innovations, which aims to drive development of DNA/RNA-based vaccines against emerging infectious diseases, and reduce the risk of a new crisis like that of Ebola, which had languished in pharma R&D owing to a lack of commercial incentives.

Now, a new index mapping how companies are performing in driving access to vaccines in high-need countries has been published by the Dutch non-profit Access to Medicine Foundation, which has been producing the Access to Medicine Index since 2008.

The Access to Vaccines Index maps how eight key companies are performing against 13 metrics, and the evidence shows they are doing a lot. The authors suggest the index can help identify opportunities to improve vaccines access, and where new incentives are needed. In fact, it identifies the actions and omissions specifically of industry and does not explicitly propose external incentives. Companies are expected to be morally motivated to do more, aided by the new benchmarking tool. Like it or not, the gauntlet is thrown down, and the onus is now on major vaccines players to pick it up.

exclusive online content

Keryx Looks To Label Expansion To Drive Auryxia
Keryx plans to expand Aurexia's label to treat iron deficiency in pre-dialysis patients while searching for additional nephrology assets during 2017.
http://bit.ly/2mMvaif

Beyond Belviq: Reinventing Arena To Focus On Phase II Candidates
Dr. Amit Munshi, new CEO of Arena Pharmaceuticals, has already made several changes in the company's focus and direction as it reduces its commitment to Belviq. He talked to Mike Ward about progress to date.
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Teva Catches A Break On Copaxone 40mg, But For How Long?

An FDA warning letter cites deficiencies at the Pfizer-owned manufacturing facility poised to produce a Momenta/Sandoz generic competitor. It's unclear how long Pfizer might take to resolve the violations, which include particulates in finished products.

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Teva Pharmaceutical Industries Ltd. has gotten some breathing room with news that the launch of a generic rival to the important 40mg version of its blockbuster multiple sclerosis drug *Copaxone* (glatiramer) has been delayed due to a manufacturing issue.

An FDA warning letter, made publicly available Feb. 28, cites several manufacturing violations at the Pfizer Inc.-owned facility in McPherson, Kan., that was poised to produce the 40mg product on behalf of sponsors Sandoz Inc. and Momenta Pharmaceuticals Inc. The two drug makers had been planning to launch the generic imminently after a district court invalidated several patents protecting the newer formula, which is administered three times a week, rather than every day like the older 20mg formula.

Momenta announced a delay in the launch Feb. 21 because of the manufacturing violations, but didn't offer many details on the contents of the letter. CEO Craig Wheeler said at the time the company was still hopeful the launch could occur in 2017.

For Teva, the delay is a positive turn at a pivotal time, when the Israeli drug company is facing backlash from investors over slow generic growth, an expensive merger and the disappointing patent ruling. The ongoing challenges have resulted in two high-profile leadership departures at Teva: former CEO Erez Vigodman, who left the company in February, and generics head Sigurdur (Siggi) Olafsson, who stepped down in December. The company has appointed an interim CEO, Yitzhak Peterburg, while it searches for a fulltime replacement and conducts a thorough business review.

Teva issued financial guidance in January forecasting a revenue reduction of $1bn to $1.3bn in 2017 if one or two generic competitors to Copaxone 40mg were to hit the market. Sandoz/Momenta already market a generic version of the once-daily version of Copaxone called Glatopa, which the Pfizer plant has been producing for commercial use since April 2015. Teva's success transitioning patients to the 40mg version ahead of the Glatopa launch has been one of the bright spots for the company.

A REPRIEVE MEASURED IN MONTHS

But how much of a break Teva will get is unclear. Pfizer said in a statement that it submitted a corrective and preventive action plan to FDA in May 2016 and is "diligently" implementing the commitments made to FDA. However, the latest warning letter says Pfizer's actions are inadequate and lays out further actions.

The FDA letter cites five manufacturing violations, including the presence of visible particulates in several sterile injectable products, which the agency said represents "a significant loss of control in your manufacturing process and represents severe risk of harm to patients." As examples, the letter cites vials of the antibiotic vancomycin hydrochloride and the non-steroidal anti-inflammatory ketorolac tromethamine.

It's not clear how quickly the problems might be rectified, but in a same-day email to investors, Evercore ISI analyst Umer Raffat said the median time to resolve manufacturing issues on finished pharmaceuticals is 13 months. He analyzed data over 20 years and found the minimum time to resolution is five months and the maximum 47 months.

He also pointed out that the letter was addressed to Pfizer CEO Ian Reed rather than a lower-level manager. "When FDA addresses the letter to the senior most person, it is trying to make a statement," he said.

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Other drug manufacturers also pose a threat to Teva. Aside from Sandoz/Momenta, several other generic drug manufacturers also have ANDAs at FDA pending for the 40mg Copaxone dose, including Amneal Pharmaceuticals LLC, Dr. Reddy's Laboratories Ltd., Mylan NV and Synthon Pharmaceuticals Inc., which is partnered with Pfizer on the marketing.

Although Teva is the world's largest generic drug manufacturer, it also markets a substantial specialty drug portfolio, focused in multiple sclerosis and respiratory disease. The company has hoped to build the specialty portfolio through new launches, like SD-809 for the treatment of chorea associated with Huntington's disease and the movement disorder tardive dyskinesia.

The company announced Feb. 28 that SD-809 was granted a priority review for tardive dyskinesia, and the application has a Prescription Drug User Fee Act action date of Aug. 30. But Copaxone makes up more than half of Teva's specialty sales; Teva reported $4.22bn in Copaxone revenues in 2017 in an $8.67bn specialty segment.

Pfizer acquired the manufacturing facility in McPherson with the acquisition of the sterile injectables specialist Hospira Inc. in September 2015 for $17bn.

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What Will Happen Next In Orphan Drug Pricing?

Feb. 28 was Rare Disease Day. To mark the occasion, Scrip asked experts the question: Do you see orphan drug pricing coming under pressure over the next five years?

REPORTING BY Joseph Haas, Sten Stovall, Mandy Jackson, Cathy Kelly, Lucie Ellis, Francesca Bruce, Eleanor Malone and Maureen Kenny.

Having their say:

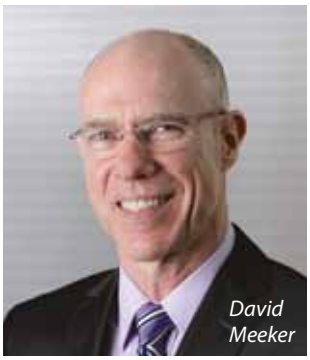
- *Companies:* Genzyme, Sanofi, Akari Therapeutics, Vertex Pharmaceuticals, MyoKardia, Shire
- *Trade associations:* EFPIA/EuropaBio Joint Task Force on Orphan Medicinal Products and Rare Diseases
- *Health technology assessment bodies:* UK's NICE
- Datamonitor Healthcare

The orphan drugs business is seen as one with high margins, high entry barriers and limited competitive pressure. But as the field matures, will those dynamics change? To mark Rare Disease Day on Feb. 28, *Scrip* asked experts the question: Do you see orphan drug pricing coming under pressure over the next five years?

We received a broad range of answers from an equally broad range of stakeholders – from the grandfather of orphan drug companies, Genzyme Corp., to newcomers such as Akari Therapeutics PLC and MyoKardia Inc., from industry groups EFPIA and EuropaBio to the G-BA, which decides on health insurance coverage in Germany, from patient organization alliance EURORDIS to US pharmacy benefits managers Express Scripts and Humana Pharmacy Solutions.

DAVID MEEKER

Head of Sanofi Genzyme


David Meeker

First, all pricing, including orphan drug pricing, is under pressure. Historically orphan drugs have in some situations or countries been carved out from a general pricing mandate but that is no longer the case.

Second, if you are in an orphan disease serving a population of 100,000-200,000, the pricing dynamic or mechanics of that population are very different than if you're serving a population of 1,000-5,000. And that's where the debate gets lost a bit, because people don't recognize that orphan is an arbitrary definition and rarity is a continuum.

Third, I actually feel that pricing in the ultra-rare orphan sense will be under less pressure because there is an understanding of the importance of the business model to the willingness of people – investors, companies – to invest in potential treatments or cures. It's a high price because there are so few patients; for any given patient it's perhaps not affordable for the patient, but at a systems level that's a small fraction of the population and the total amount spent on managing that disease is extremely low. With time they've come to understand that. What payers are pushing back on is "don't apply that same basic philosophy across the full spectrum."

But we shouldn't be hiding behind the orphan designation. To me your pricing is a function of the value, the rarity of the population you're addressing, the investments that you made to get to market. We have to recognize that it's a continuum, that competitive forces will come into play the larger the population being served, and that phenomenon is accelerating everywhere. And it will accelerate within the orphan drug envelope too. And it has nothing to do with orphan or not orphan, it has simply to do with what is the target population, and can it support lower prices?

We're in endless discussions on a regular basis around the world about pricing. The discussion has become more intense and the pressures have become more, but the substance of those conversations hasn't changed over the 20 years we've been doing this.

[We need] to help people think about orphans not as one bucket… to really get people refocused on this idea of a continuum and [on the fact] that the pricing is really very much about the rarity, and that within the orphan drug there's a large range, or continuum, of rarity.

ELIAS ZERHOUNI

Global President of R&D, Sanofi

The real question is going to be the value that you provide for each [product] and there's not a one price fits all.

So in orphan diseases what is the rare disease? Look at Genzyme. It's a rare disease company... At most, it's taking care of eleven thousand, twelve thousand patients. Well, it has six thousand employees so you can see that for every two patients we have an employee. If you say, 'I want to cut the price,' to such an extent that you cannot sustain that innovation, you would dry out the well for rare diseases.

It's very, very hard to maintain the machine behind these patients that provides not only the innovation but also the support, the manufacturing and so forth.

The business model, I think, of where there was an understanding that you needed to take the risk to develop drugs for five or six thousand people, that's what it takes for that to happen. The problem that you have is when it's used for a very different purpose, when these prices are not applied to very reduced populations.

GUR ROSHWALB,

CEO of Akari Therapeutics, a UK-based rare disease specialist

Not really. Take PNH [paroxysmal nocturnal hemoglobinuria], for example. Before Alexion Pharmaceuticals Inc.'s drug *Soliris* (eculizumab) came to market, people with PNH would die within five to ten years. That drug's appearance gave people with PNH back a normal life span, and these patients during those five to 10 years before its arrival were not leading a normal life. They were severely anemic and had a lot of medical problems. They are often diagnosed in their 30s and 40s and so this drug has really changed the path of these people and given them another 30 to 40 years of life. That's worth a significant sum of money.

And on the flip side, from the payer point of view, you're usually not talking about that many patients. These diseases are very rare, so for any given payer you might only have two or three, so that $1


Gur Roshwalb

million line item is just not something they're going to fight over. Also, a lot of medical innovation results from rare orphan disease. For example, the immune system part that we're targeting to treat PNH, called the complement pathway, the immune system does two things in the body – it identifies foreign stuff and it kills it. The complement pathway is one of the bridges between identification and the destruction, and in auto-immune diseases, complement plays a large role in doing the destruction.

Innovating the first complement therapy and hopefully bringing others to the market... can have a profound effect on the millions of people with auto-immune disorders over time. That first drug is expensive, but being able to innovate in that area will make a tremendous difference over time. So, while it's true that any initial drugs in orphan areas might be expensive, it pays for very important innovation that brings important results further down the line. So I feel there's a consensual balance currently between orphan drug innovators, government authorities and payers in accepting that that effective ecosystem permits rare disease innovation to trickle down over time into broader therapeutic areas.

STUART ARBUCKLE

Chief Commercial Officer, Vertex Pharmaceuticals Inc., a US-based specialist company with a focus on cystic fibrosis

With the recent explosion in understanding of the biology of disease, we have a new opportunity to fundamentally change the course of human health. Still, developing a transformative treatment for a rare disease requires a huge investment in terms of both money and countless hours from talented, dedicated scientists. If we are to fully grasp the opportunity in front of us, society needs pricing policies that incentivize this tremendous effort and ensure companies have the resources necessary to fund the next set of breakthrough medicines.

EFPIA/EUROPABIO

EFPIA/EuropaBio Joint Task Force on Orphan Medicinal Products and Rare Diseases, a European alliance of over 45 companies committed to the development of orphan medicinal products

The price of medicines, whether orphan-designated or not, is a topic of debate. In Europe, society shares the burden of disease and public budgets, including for health, are under unprecedented pressure with spending being carefully scrutinised.

Today, it is estimated that the budget impact of orphan medicinal products (OMPs) is approximately 4-5% of the total pharmaceutical spending in the largest EU countries that have the best access to rare disease treatments. This is less than 1% of the overall health expenditure. As more OMPs are developed, this figure may increase, but estimates show it should still remain a small portion of health spending in Europe. Also, as most OMPs were developed post-2000, we expect generic and biosimilar competition to grow, benefitting budgets.

The European Orphan Medicinal Products Regulation was developed on the belief that patients suffering from rare conditions should be entitled to the same quality of treatment as other patients. Since 2000, the Regulation has been successful in incentivizing research and development of OMPs. Prior to the regulation, only eight orphan-like therapies were approved compared to the 130 currently approved. There seems to be a concern that the Orphan Regulation incentives are misused. We believe that the incentives are well balanced, with very stringent criteria for orphan designation based on distinct orphan conditions.

There is still enormous unmet medical need in rare diseases. Moving forward, it is important that the rare disease community build on the success of the European OMP Regulation and work closely together, including with payers, to continue supporting patients.

TIJANA IGNJATOVIC

Lead analyst for market access at Datamonitor Healthcare

Getting a successful reimbursement outcome for highly priced orphan drugs will get more difficult in the future. We have already seen some cases of this so far, with the recent restriction of reimbursement for Alexion Pharmaceuticals Inc.'s *Strensiq* (asfotase alfa) in the UK for hypophosphatasia. While the UK may be one of the most challenging markets, the difficulty Alexion has experienced with the reimbursement of *Kanuma* (sebelipase alfa) in France indicates that this is unlikely to be a trend confined to the UK. Kanuma was also recently rejected by NICE [the National Institute for Health and Care Excellence] due to its high price for use on the National Health Service in England and Wales to treat infants, children and adults with the rare inherited genetic disorder lysosomal acid lipase deficiency (LAL-D). NICE was not convinced the high cost of the drug – nearly £500,000 per patient – could be justified by its long-term treatment benefits in LAL-D patients.

The advent of multiple early/conditional market authorization pathways is resulting in reimbursement barriers for all drugs approved through these routes and orphan drugs are more likely to pursue these pathways. Consequently, they undergo health technology assessment (HTA) processes without full, mature datasets, resulting in uncertainty in the determination of their clinical effectiveness and also cost-effectiveness. Hence, managed entry agreements – which have already been put in place for some orphan drugs – are likely to be used more as a means to address the residual uncertainty. Meanwhile, small patient populations and treatments being available in specialist centers render these drugs highly suitable to participate in such schemes without requiring onerous administrative costs. Some payers (for example those in the Netherlands) have had mixed experiences with risk-sharing schemes for orphan drugs, but for many this approach will provide a compromise between ensuring patient access and value for the healthcare system.

In Germany, orphan drugs hold an advantage over other drugs in that by law they have to get an added benefit under the AMNOG early assessment, though it can be reassessed if their expenditure exceeds €50m per year. Recently, several groups including the German HTA body IQWiG have called for this rule to be abolished under AMNOG reforms, which signals another potential risk for the commercial success of orphan drugs in the future and the need to have a strong evidence base.

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Click here to see what G-BA (Germany), Humana Pharmacy Solutions, Express Scripts, Bay Life Science Advisors and EURORDIS had to say: **http://bit.ly/2lRpGPV**

Chi-Med Roll Continues With Positive Fruquintinib

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Chi-Med's China-focused strategy is paying off with positive Phase III top-line results for its home-grown VEGF inhibitor fruquintinib, keeping it on track to for a filing this year. But competition looms.

The first look at Phase III data for Chi-Med (Hutchison China MediTech Ltd.)'s new highly selective VEGF inhibitor fruquintinib show encouraging efficacy on both primary and secondary endpoints in third-line colorectal cancer, leading the way to a filing in China mid-year and a possible launch in 2018.

Top-line results from Chi-Med's first pivotal trial, FRESCO, in 416 patients with locally advanced or metastatic colorectal cancer in China who have failed at least two prior chemotherapies, including fluoropyrimidine, oxaliplatin and irinotecan, show a significant improvement in overall survival compared with placebo when given on top of best supportive care (BSC).

A significant improvement in the key secondary endpoint of progression-free survival was also seen, and no new or unexpected safety issues arose. The full results are expected to be reported in the middle of the year, most likely at ASCO.

The data are another positive step on the Chi-Med's path towards becoming a fully integrated global pharmaceutical company, taking its lead from the major Japanese companies and staying based in its home market of China. The company is hoping that recent changes to the Chinese regulatory environment particularly for innovative domestic treatments for clear unmet medical needs will help propel the product more swiftly through the regulatory process than has previously been the case; it is hoping for approval in early 2018 with a launch soon after. Chi-Med says CRC is the second most common cancer type in China, with about 380,000 new cases per year, according to CA: Cancer Journal for Clinicians 2016.

The FRESCO results follow the recent report of promising Phase II data for another of its key assets, savolitinib, which is partnered with AstraZeneca, in papillary renal cell carcinoma (the second most common subtype of renal cell carcinoma); patient-selected Phase III trials of the c-Met receptor tyrosine kinase inhibitor are now planned. These were the two biggest milestones for its pipeline of eight drugs that Chi-Med had previously penned in for early 2017.

"The success of the FRESCO trial is an important milestone not just for CRC patients and Chi-Med, but also for Chinese innovation," said Chi-Med chairman Simon To. "We believe this is one of the first home-grown, China-discovered and developed, mainstream innovation in the field of oncology to succeed in a pivotal Phase III registration trial. It shows that China has the resources, capability and perseverance to emerge as an innovator in the global oncology field."

The company says it is well positioned to market the product at home, with about 2,000 sales reps covering not just the hospitals in China's provincial capitals and medium-sized cities, but also in the majority of county-level hospitals.

There are no drugs currently approved in third-line CRC in China, and BSC is the general standard of care. Analysts at Deutsche Bank say they believe fruquintinib would be the first tyrosine kinase inhibitor by a domestic company to be launched in China targeting this population – they believe the drug is likely to capture peak sales of approximately CNY1bn ($145m) following a launch in the second half of 2018.

Nonetheless, this market is expected to become much more crowded. The Deutsche Bank analysts say there are five other innovative small-molecule drugs in late-stage development in China, while Avastin biosimilars are likely to be launched in China in 2H18/1H19.

"As such, we expect competition in the medium term. For chemical drugs, a Phase III trial for regorafenib [*Stivarga*] from Bayer AG was completed and it is pending for manufacturing approval," they said, adding that other competitors in Phase III targeting the third-line CRC market include Taiho Pharmaceutical Co. Ltd.'s TAS-102, Sino Biopharmaceutical Ltd.'s anlotinib, Suzhou Zelgen's donatinib, and Hengrui Therapeutics Inc.'s famitinib.

Chi-Med, however, is dismissive of its domestic VEGF rivals. Executive director and CEO Christian Hogg said most were first-generation multi-kinase inhibitors with their attendant off-target toxicities. "They don't concern us one bit."

He admits competition is more likely from Bayer's Stivarga, but here Hogg believes they have advantages. "Fruquintinib is designed to be globally best in class. Being where we are with the Phase III data, we are confident it is a better drug than Stivarga, both for efficacy and tolerability." He also noted that Stivarga costs about $14,000 per month, and the market in China would not bear even half that amount.

FULLY INTEGRATED

Chi-Med is already planning trials of fruquintinib in the US to take the product to the rest of the world in due course. Its joint development partner, Eli Lilly, currently only has an interest in China, but retains an option to obtain global rights. Under the companies' deal, Lilly has two windows of opportunity to exercise this option: a two-month window that started with the release of the CRC top-line data to gain global rights for $50m up front plus development, regulatory and approval milestones, plus royalties, and be responsible for 100% of ex-China clinical trial costs; or it can wait until up to two months after the release of data from fruquintinib's study in third-line non-small cell lung cancer (FALUCA) in about a year's time, but here the up-front fee would rise to $75m.

Fruquintinib is in two ongoing clinical studies in lung cancer, including the pivotal Phase III FALUCA study in a planned 520 patients in China (topline results expected in early 2018), plus an open-label Phase II study of it in combination with AstraZeneca PLC's *Iressa* (gefitinib) in first-line advanced or metastatic non-squamous NSCLC with EGFR activating mutations.

A pivotal Phase III registration study is expected to start during the first half of 2017 in gastric cancer after a successful Phase I/II dose finding study of fruquintinib in combination with paclitaxel, which established a combination regimen that was well tolerated.

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CONTINUED FROM COVER

of the total €33.8bn generated last year, up sharply from the €1.4bn in 2015 and €498mn in 2014 that new drugs generated. Dupilumab - an interleukin-4/IL-13 inhibitor which has the brand of Dupixent - is the first biologic to treat the condition of atopic dermatitis, having been granted a priority review by FDA. It is being co-developed by Sanofi and Regeneron Pharmaceuticals Inc..

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BIOLOGICS AND PARTNERING

"What I've tried to do is, firstly, to move our portfolio towards biologics, and not be shy about partnering when we needed to - but also not abandoning what I call the fundamental strategy, which is support the franchises Sanofi is already in, and then create new franchises."

Sanofi's seven therapy areas of focus are diabetes, vaccines and infectious diseases, rare diseases, immunology and inflammation, cardiovascular and metabolism, cancer, and multiple sclerosis and ophthalmology. Late-stage biologic drugs currently comprise some 60% of its pipeline.

Underscoring Sanofi's optimism in its pipeline and anticipation of future demand for new biologics, Sanofi recently entered a joint venture whereby Lonza Group Ltd. will build a large-scale mammalian cell culture facility for monoclonal antibody production in Visp, Switzerland, with completion of the facility set for 2020.

Zerhouni says the future "is going to belong to smart combination therapies targeted to very clearly identified populations in need", meaning precision therapies with combination medicine.

"The challenges for R&D heads are that they've got to manage the complexity of biology on the one hand and precision on the other hand. There are very few conditions that you can address with one target."

Sanofi's aim is to go from mono-targeting to multi-targeting, by inventing molecules that can do not just one thing at a time but a number of things.

"You can see it already with MRNAs (Messenger RNA) where you can affect two or three pathways at once with one molecule. The key is that mixing molecules, having a cocktail of different molecules, is not the same as having a smart, multi-targeting molecule. It's almost like a missile with three warheads. Multi-specifics. That's where the long term is going," he said.

Duplimumab illustrates that approach.

"I tend to look for what I would call the hub molecule strategy, where you try to pick a molecule when it intersects multiple disease pathways. The iconic example would be dupilumab because it does affect atopic dermatitis, it affects asthma, it affects chronic sinusitis, it's what I mean by saying dupilumab is a pipeline in a single drug. That's what I'm looking for."

Duplimumab is unusual in being a monoclonal antibody that has a dual action, acting against both the IL4 receptor and the IL13 receptor.

"The reason why I picked that with our colleagues at Regeneron is because we bet that it would be more effective because both of these receptors act differently on the same pathway but they are synergistic in their action in the same pathway. I believe it's going to be the same in many other diseases," Zerhouni said.

Isatuximab, an anti-CD38 monoclonal antibody currently being trialed for multiple myeloma, is another example. "It's one antibody but it has multiple actions and multiple pathways."

Another example of Sanofi's multi-specific therapy approach is its GLP-1 GIPR dual-agonist for type II diabetes.

The appointment of immunology expert Yong-Jun Liu, who in March 2016 was lured away from AstraZeneca PLC where he was head of research at the MedImmune biologics business, underscores the importance of exploring and developing multi-specific drugs. At Sanofi, Liu is now working as head of research for global R&D, under Zerhouni. "He has a systems view of biology. So do I," Zerhouni said, adding: "the combinatorial game is what is going to make us successful ... or not successful - but that's what is worth trying."

R&D SPENDING TO RISE

Zerhouni says the multiple-targeted therapy approach could ultimately help reduce cost burdens on healthcare systems by restraining drug prices.

"Pricing of drugs is going to be helped by that combination approach, because it's not tenable to have stacked drugs, like in cancer, for multiple vendors at very high prices: at some point we have to be smarter than that."

Zerhouni says his R&D strategy's success in generating a promising portfolio has happened while keeping spend in a reasonable proportion of overall sales.

"If you look at our R&D spending relative to other companies; it is still low at 14% or 15%. It's a spend which has helped, actually, the overall efficiency of R&D and its productivity."

He stressed that R&D annual spending should not be viewed in isolation.

"You shouldn't look at it in one year, you should look at it over a period of years, so when you look at that, it's more in the 14.5% - 15% actually. … You have an under-spending which you'll see next year is going to be overspend. So, you've got to look at an average."

But Sanofi's R&D spending will need to rise going forward, with a target of €6bn set for 2020 measured in constant exchange rates. "We do see the need to invest more in R&D and we have a pipeline that is extremely promising, that requires that investment."

He said Sanofi under its new CEO Brandicourt is now aligning its marketing and the business units globally.

"Before, the organization was more regionally focused, essentially country-

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based. But when you have 13 launches in three or four years, it does require a different view of the business, because you have to grow big products in every geography. So, it's really a business idea of having franchises that are vertically coherent from top to bottom in the US, Europe, and Japan where most of the market is."

He added that it's not enough to get an approval for drug. "You have to also strategically align it with a market and to getting market access. So it is necessary to align very precisely the research, development, commercial, medical affairs and market access for a product along those vertical business units."

'Pricing of drugs is going to be helped by that combination approach, because it's not tenable to have stacked drugs, like in cancer, for multiple vendors at very high prices'

"PEOPLE TALENT"

Asked for comment on the Britain's decision to leave the EU and US President Donald Trump's stated views on immigration, Zerhouni replied: "I can't comment on Brexit or any particular policy but I can tell you this: R&D is a global enterprise and today R&D talent is at a premium."

"Any barriers to the exchange of ideas in science is not a good thing for humanity and so, to me, I can't predict what Brexit is going to do, what Trump Administration policies are going to do - but I can tell you with a lot of experience behind it that restricting scientific exchange restricts progress in biomedical research or any research.

"You don't know where talent comes from; it can come from anywhere, anytime – and if you restrict it, you lose human potential."

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Spring Break: Novo's US Head Resigns After Rough Winter

Novo Nordisk's executive VP and head of North American operations, Jakob Riis, has resigned from the company – a move not completely out of the blue considering recent rumors of conflict within the diabetes drug developer's US operations and a lackluster 2016 financial performance for the whole group.

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Jakob Riis, Novo Nordisk's head of North American operations, has resigned from the company following a tough 2016 and rough winter period for the Danish firm – which reported earnings last month 2% below analyst's estimates for 2016.

Riis, who has been with the company since 1996, was previously considered the heir-apparent to recently replaced CEO Lars Rebien Sørensen, who stepped down early from leading the business in September last year. Sørensen was instead succeeded by Lars Fruergaard Jørgensen, the company's former head of corporate development.

Overlooked for the top job, Riis took on the role of North American head last year, but *Scrip* reported in December that Novo Nordisk's US operations were struggling and conflict had risen due to supposed differing management styles. At the time, *Scrip* was told of strong "cultural differences" between Novo Nordisk's European and American management teams.

A tough year for the Danish firm, 2016 saw Novo Nordisk twice cut its long-term growth targets, its then-CEO Sørensen pulled forward his retirement by two years, and the company slashed 1,000 jobs from its workforce – half of these job losses were recognized in Denmark and most of the rest focused on the US. Novo Nordisk's stock on NYSE has been in steady decline over the last year, falling from a price of $53.15 on March 1, 2016, to $35 pre-market opening on the same date this year.

Also, during its third-quarter earnings presentation last year, Novo Nordisk highlighted the US as its biggest concern for 2017 and the reason for lowering its growth expectations – resulting in a long-term growth forecast cut from 15% to 5%. The US accounts for around half of the insulin maker's pharmaceutical sales.

Jakob Riis

Riis – who will remain with the company for a transition period before taking on the role of CEO at Danish emergency services group Falck – will be replaced by Doug Langa, former senior vice president for market access at Novo Nordisk. The change in leadership is effective immediately, the company said, and Langa's title will be senior vice president, head of North America operations and president of Novo Nordisk Inc.

Relatively fresh blood for Novo Nordisk, Langa joined the company from GlaxoSmithKline PLC in 2011 as senior director of managed markets. Prior to GSK, Langa spent much of his career at Johnson & Johnson, where he held various roles within managed markets, sales leadership and marketing.

Langa's LinkedIn page describes him as an "industry thought leader driving pharmaceutical market access innovation." Based in New Jersey and a graduate from New York's Fordham Gabelli School of Business – Langa is expected to better bridge the gap between Novo Nordisk's traditional Danish culture and its failing US business.

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Accera Posts Phase III Alzheimer's Failure

Accera Inc.'s failed Phase III clinical trial for AC-1204 is just the latest late-stage disappointment in a recent string of trial failures in Alzheimer's disease, but the company will move forward with a second Phase III study based on the drug's novel mechanism and another new formulation. Boulder, Colorado-based Accera blamed the lack of efficacy observed in its first late-stage trial on a new formulation of the drug, because low blood plasma levels of AC-1204 were observed in the placebo-controlled study. But while it follows in the fresh footsteps of Eli Lilly & Co., Lundbeck Inc. and Merck & Co. Inc., which have ended development of three different Alzheimer's therapies following Phase III crashes during the past four months, the private company hopes to forge a different path with AC-1204. CEO Charles Stacey acknowledged the difficulty of developing treatments for Alzheimer's disease (AD), but said in an interview with *Scrip* that Accera was disappointed that AC-1204 did not achieve the primary endpoint – a statistically significant improvement in cognition at 26 weeks compared with placebo as measured by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) – in the novel drug's first Phase III test. Accera said the drug was safe and well tolerated, but the company did not provide any detailed safety or efficacy results.

mandy.jackson@informausa.com, 28 Feb 2017

Merck & Co's Shingles Vaccine Clears PhIII

The first Phase III data presented for Merck & Co. Inc.'s new varicella zoster vaccine V212 show that it can prevent shingles and reduce pain and other complications of the virus in recipients of autologous hematopoietic stem cell transplants. Another Phase III trial in subjects with malignancies is ongoing. Merck already markets the live attenuated virus vaccine, Zostavax, for the prevention of herpes zoster (shingles) in individuals 50 years of age and older – currently the only shingles vaccine on the market – but this is contraindicated in immunocompromised patients. Herpes zoster is caused by the reactivation of the varicella zoster virus, the virus that causes chickenpox (varicella). Merck's new product, V212, is an inactivated varicella zoster virus vaccine for the prevention of herpes zoster and herpes zoster-related complications in immunocompromised subjects age 18 years and above. This could expand its herpes vaccine franchise in the face of looming competition from GlaxoSmithKline PLC's newcomer Shingrix. Zostavax may have enjoyed the market to itself since its launch in 2006, but its sales have never been stellar owing to its limited efficacy, particularly in the older population. Analysts expect Shingrix to hit blockbuster status. The GSK product is awaiting approval in the US, EU and Japan for the prevention of herpes zoster in adults over 50 years following strong Phase III data in which vaccine efficacy that was higher than those seen with Zostavax in its two pivotal trials, including in the all-important over-70s population.

alex.shimmings@informa.com, 27 Feb 2017

Back To The Future: Cempra's New Product/Old Antibiotic

Putting recent disappointments with solithromycin to one side, Cempra Inc. has reported positive Phase III data for its second product candidate, an old antibiotic called fusidic acid, which despite being available in Europe for decades has never received a US approval. US FDA rejection of Cempra's solithromycin in December has pushed the novel antibiotic's approval back to 2018 at the earliest, so the company's attention has turned to *Taksta* (fusidic acid). Cempra is developing the product exclusively in the US for acute bacterial skin and skin structure infections (ABSSSI) and is investigating its use for the long-term oral treatment of refractory bone and joint infections. The product, which is orally active against gram-positive bacteria, such as *Staphylococcus aureus* strains including healthcare-acquired methicillin-resistant *S aureus* (HA-MRSA) and community-acquired MRSA, was non-inferior to linezolid in a Phase III study. But analysts remain unconvinced that this is a lucrative market, given the performance of past antibiotic launches in the US. Cempra is now set to meet with the FDA to see if another pivotal trial is needed. Brian Skorney of Baird pointed out that recent launches in complicated skin and skin structure infections and ABSSSI, such as Allergan Inc.'s *Dalvance* (dalbavancin), Merck & Co. Inc.'s *Sivextro* (tedizolid), The Medicines Co.'s *Orbactiv* (oritavancin), and Theravance Biopharma Inc.'s *Vibativ* (telavancin), have on average done around $7m, $14m and $20m in their first, second and third years on the US market.

alex.shimmings@informa.com, 28 Feb 2017

Kite On Course For FDA Filing

Data from the pivotal Phase I/II ZUMA-1 trial of Kite Pharma Inc.'s CAR-T cell therapy KTE-C19 in patients with aggressive non-Hodgkin's Lymphoma will support a rolling BLA submission due shortly and a regulatory filing in Europe later this year. The latest data showed that responses achieved in patients treated with KTE-C19 at the three-month mark remained durable at six months. The news was greeted with a 16% hike in Kite's share price. "These are positive results with the ORR (overall response rate) and CR (complete response) rates only degrading slightly from the three-month interim analysis suggesting that responses are durable," according to Informa's Biomedtracker analysts.

sukaina.virji@informa.com, 1 March 2017

Immuno-Oncology 2.0 Roundtable: Emerging Players Eye Crowded Field

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Scrip spoke with five companies about their places in the crowded IO field in which big pharma and small biotech firms alike are seeking the best options for harnessing the immune system to fight cancer.

Executives from Tocagen Inc., CytomX Therapeutics Inc., Trillium Therapeutics Inc., Xencor Inc. and Poseida Therapeutics Inc. sat down with *Scrip* to discuss what it takes to get an immuno-oncology deal done, starting with technology that gives pharma something it doesn't have but needs to improve the efficacy and safety of existing immunotherapies.

Companies with technology ranging from monoclonal antibodies to chimeric antigen receptor T cell (CAR-T) therapies assembled for the discussion last month when the biopharma industry descended on San Francisco's Union Square for the annual J.P. Morgan Healthcare Conference. They took a break from investor meetings and dealmaking talks to share their thoughts on IO 2.0.

Scrip's Mandy Jackson moderated the discussion with Tocagen Vice president of business development and marketing Nicholas Boyle, CytomX chief medical officer Rachel Humphrey, Trillium president and CEO Niclas Stiernholm, Xencor president and CEO Bassil Dahiyat, and Poseida CEO Eric Ostertag.

SCRIP: *Ultimately your customers may very well be pharma partners or acquirers, so what is it that you're trying to tell them that you're doing differently that would add value for them?*

NICK BOYLE: The way we've been building the company since inception is to be prepared to commercialize by ourselves in the United States, so that's what we focus all of our resources and financing towards – achieving that ultimate goal for our lead product in the lead indication.

So when it comes to partnering, and what we hear resonates with pharma, they all of course want highly differentiated mechanisms of action – something that could take them beyond the current state of IO. At least with respect to the gene therapy space, people are beginning to recognize what viruses could do in immuno-oncology 2.0 or 3.0 or whatever round it would be.

We've known this for a long time and have been excited about it for a long time, but I think the industry is catching up with what viruses can do. They light the match on tumors; they do turn cold tumors hot – or at least warm – and that's exactly what our approach does. That in particular is resonating with the prospect of combination strategies, particularly with the deficiencies with the existing checkpoint inhibitors, because they may not work particularly well in some settings, or work well at all in other settings, so there's an intense interest in figuring out how to make those tumors susceptible to the burgeoning field of checkpoint inhibitors.

That's one area that I think has grabbed a lot of attention from the big pharma guys, but more specifically they think about safety a lot. They don't want to have additive toxicity on top of the [effects] of checkpoint inhibitors, so having complementary mechanisms of action that also don't add toxicity is really important. That's another key element that we've been able to differentiate on as well, and with having a 200-patient database of safety, we can actually put the data behind what we're saying.

ERIC OSTERTAG: Our differentiator is not having any virus; we don't use viruses at all, whereas most of the CAR-T companies use a virus for transduction of the T cells. I think a virus may be very good at getting into the tumor, but we do not like it for getting into T cells. Also, it creates very long timelines, it's very expensive for that use and, maybe most importantly, lentivirus doesn't get into early naive T cells.

I think everyone, at least in the CAR-T space, is realizing that the phenotype of the cells that you put in is extremely important. You can put in an effector-like product, you can get rid of the tumor quickly, but then you have relapses, so durability is an issue. Whereas, we have an almost entirely stem cell phenotype and so we get that initial killing, but then we have engraftment of the stem cells that you can differentiate into tumor effectors, so we get long-term durability and that's what we've seen in the animal models.

RACHEL HUMPHREY: CytomX is aiming to be a standalone large pharmaceutical company. We already have a lot of deals with large pharma, because at the end of the day the technology takes validated therapies and targets – be it [Bristol-Myers Squibb Co.'s PD-1 inhibitor] Opdivo (nivolumab), PD-L1, CTLA-4 – and strengthens or widens the therapeutic window. Or, it takes combinations [where] we know have good activity, but cannot be given at all, because in all cases sparing the normal tissue is important.

We're working with BMS to make a Probody form of [Yervoy (ipilimumab)]. We have our own proprietary PD-L1 agent, other checkpoint inhibitors, both with BMS and as a standalone. We're working with AbbVie Inc. in a deal that looks a lot like what you [Boyle] were talking about, which is lots of downstream value for us – combination approaches. At this point, it looks like we're already getting lots of incoming excitement, because of the needs right now of managing the safety of the agents we already know are toxic and very active, including T cell-redirecting bispecifics that couldn't be developed before, but in preclinical models have therapeutic windows of 300 or more.

NIC STIERNHOLM: I think our spiel is that the immune system is very complex and powerful and we're just scraping the surface here with PD-1. We are actually bringing in the innate immune system, because macrophages are not only good phagocytes to chew up the tumor, but they are also quite good at presenting antigens to T cells. We actually bridge an innate immune system with the adaptive immune system. We've got two arms of the immune system going, so we do prime CD8 positive T cells. That's what pharma likes at this point and I think that that's where the deals are going to go – to broaden out from just T cells.

BASSIL DAHIYAT: Our experience with what pharma wants is that they want to be able to rapidly make drug candidates, not

prototypes, not surrogates, not research reagents, but rapidly make drug candidates that can give them as many different tools and widgets as they can play with in immuno-oncology. [That may include] redirecting against many different tumor targets, because you don't know which ones are really going to be amenable, which ones are going to have the safety, which ones are going to have actually any efficacy.

They want the tools to rapidly make molecules that can target the multiple combinations of different antigens you might need to go after, whether one might be on a myeloid cell, one might be on a T cell, two might be on a T cell, one might be an agonist of a T cell, one might be a checkpoint. So this multiplicity, this combination [strategy] is the theme in immuno-oncology, and to be able to target that is going to require more and more molecules. We at least can divide that by two, if not three, if we have the ability to robustly make bispecific and multi-specific antibodies easily and readily.

So our deals look like: we'll give you [the] rights to use this Fc domain for five of your internal programs. You have to make all the binding domains – we're not going to do any work for you – and you have to pay us for the right to use it. We've been doing deals like that for other aspects of what Fc biology can do for about 10 years now and we're getting triple the value, both in terms of royalties – we're going mid-to-high single digits – and you're getting multiple hundreds of millions in milestones. We have $45m up front from Amgen Inc. for doing nothing for them except handing them our intellectual property for a very limited set of things, because the demand is so phenomenally high for tools to be able to multi-target antibody molecules in a way that nature doesn't usually let you.

But it's for drug candidates, not curiosities in the lab, so moving fast is critical. I think we've seen the lessons that some of the pharmas have learned by being a couple of years slow in immuno-oncology. Novartis AG is number two in oncology right now in sales, but they will not be in three years. Who'd have thought that [*Keytruda* (pembrolizumab) developer Merck & Co. Inc.] would be a leading oncology company? They got lucky; they hit it with a PD-1 and Novartis was three years late. So, that speed is what everybody wants. People are terrified right now of missing the boat and we've got leverage as small companies.

SCRIP: *You all have pretty differentiated and different technologies. Do you feel like the deal-making environment in this area is getting easier or harder? I ask that because you're all working in immuno-oncology, which is a hot area, but it also is becoming a crowded space. At least, from my perspective, it seems like the market's getting flooded, because all kinds of companies that weren't really immuno-oncology companies before now say that they are.*

STIERNHOLM: That doesn't fool anyone.

HUMPHREY: But the billions of dollars in returns continues to escalate to such great levels that we're watching companies create deals for staggering amounts of money for individual assets. We're watching individual companies grab up multiple things over the course of a very short period of time, specifically so they have multiple choices and they can move quickly.

And the other thing that I'm observing is that the regulatory hurdles – I don't know if others are feeling that way too – but the regulatory hurdles for good immunotherapies, even with some toxicity, is dropping. You don't need the head-to-head trials. [Richard Pazdur, director of the US FDA's Oncology Center of Excellence,] doesn't want the non-inferiority designs – he has said as much – so under those circumstances you can drive value in an enormous market simply by being part of the story.

BOYLE: Are you referring to response rate studies as a pathway to approval?

HUMPHREY: Let's take the [Phase II IMvigor bladder cancer study for Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab)]. That's a single-arm study where they got approval in bladder cancer on the basis of showing not a dose effect – this is really clever – but on the basis of an effect where you got better response proportional to the expression of PD-L1. They could show that if the expression went up, the efficacy went up, and that's evidenced with a reasonable safety profile. That was evidence enough for the FDA in a really small study.

DAHIYAT: As an accelerated or as a full approval?

HUMPHREY: That's accelerated, because it was a single-arm study. But what's interesting about it is that AstraZeneca PLC had a Phase I study with multiple cancer types, [including] a small bladder cancer setup that must have seen something similar [to Tecentriq], but they just filed on Dec. 9. That filing was accepted and there's lot of good reason to believe that the FDA will approve it.

The difference is that the bladder cancer program for Merck was number four or five on their list of approvals, so that was a supplemental [biologic license application (BLA)], but this is AstraZeneca's first. And while they've treated enough patients to satisfy the safety criteria, being able to get in with a [PD-1 monotherapy] in a cancer type where others are filing like mad suggests there's real opportunity there, if you can show efficacy with good safety or a sufficient risk-benefit.

DAHIYAT: I don't think any of the big companies are fooled [by technology that's not really an immuno-oncology program], like Nic was saying. Just because there are more IO companies doesn't mean there are more deals. I think that for the companies that actually have the real stuff, I would say the partnering environment in IO is the best partnering environment I've ever experienced for a small company in my career. I think that there's a lot of noise, but pharma companies have whole armies of people designed to say "no," so they're really good at saying "no."

SCRIP: *Do you find it difficult to even get in the door, because there's so much noise?*

DAHIYAT: I wouldn't say so, because with the amount of hunger for information by these pharmas, they're trying to hoover up information from everybody, right?

HUMPHREY: I agree. [They're] rabid, I would say.

DAHIYAT: It doesn't mean they're going to buy everything, but I think the classic case here is what Novartis has done. They're behind the 8-ball, so they've literally bought or licensed one of every kind of pathway you can imagine and they're still buying them. Even if they're not getting the best in class, they want one because they figure, "Well, if we have the best-in-class of this one, the third in class of this one, combined [we] have the winner." They're all doing some version of that.

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Click here to read the five companies' profiles: **http://bit.ly/2IwcAdU**

UK's Crackdown On Anti-Competitive Deals Continues

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The UK's competition authority is keen to expose supposed pay-for-delay deals made by pharmaceutical firms, and is warning drug suppliers to think twice before attempting agreements that slow the entry of generic products onto the UK market.

The UK's Competition and Markets Authority (CMA) is once again cracking down on Actavis UK, this time alleging that the company signed illegal agreements with Concordia International Corp. that enabled Actavis's price hikes for generic hydrocortisone tablets to be prolonged in the UK. Over the last year, the CMA has fined Actavis once for its part in an anti-competitive deal with GlaxoSmithKline PLC and launched two investigations into its conduct in the UK.

In a March 3 statement, the CMA says a pay-for-delay agreement between Actavis and Concordia, which has spanned several years, has deprived the National Health Service of "the significant price falls that would be expected to result from true competition." Concordia was the first potential competitor to Actavis UK to obtain a marketing authorization for 10mg hydrocortisone tablets.

"We allege these agreements were intended to keep Actavis UK as the sole supplier of a drug relied on by thousands of patients – and in a position which could allow it to dictate and prolong high prices," Andrew Groves, CMA senior responsible officer, said in a statement.

The competition authority has released a Statement of Objections provisionally finding that both companies broke competition law. The CMA has also suggested that Auden McKenzie Ltd., which was acquired by Actavis in 2015, abused its dominant position by inducing Amdipharm (now owned by Concordia) to delay its independent entry into the market with a generic hydrocortisone product. The CMA's statement says that Actavis UK supplied Concordia with a fixed supply of its own 10 mg off-brand hydrocortisone at a "very low price" for Concordia to resell in the UK. "Actavis UK remained the sole supplier of the tablets in the UK during most of this period [January 2013 to June 2016], when the cost of the drug to the NHS rose from £49 to £88 per pack," the CMA said.

Big Generic Players In UK

- Actavis UK (Teva Company)
- Bristol Laboratories
- Concordia
- Dr. Reddy's
- Lupin
- Mylan
- Sandoz (Novartis Company)
- Wockhardt
- Zentiva (Sanofi Company)

In a separate case, announced in December 2016, the CMA provisionally found that Actavis UK had been imposing "excessive" price rises on its generic version of hydrocortisone. This action was possible because the product is now off patent and therefore not subjected to NHS price regulation the same way branded drugs are. The CMA said Actavis had raised the price of hydrocortisone 10 mg tablets by 12,000% compared with the price of the branded version sold by another company before April 2008. The amount the NHS was charged for packs of the product soared from £0.70 ($0.90) in that month to £88 by March 2016.

Hydrocortisone tablets are used as the primary replacement therapy for people whose adrenal glands do not produce sufficient amounts of natural steroid hormones (adrenal insufficiency), as for example with Addison's disease.

OTHER CASES PENDING

The CMA has recently been chasing numerous cases of supposed pay-for-delay deals in the UK between pharmaceutical companies and it has already fined Actavis in the past for its involvement in an anti-competitive agreement with GSK. In February 2016, the CMA fined GSK, Generics UK and Actavis a total of £45m for anti-competitive agreements in relation to the supply of the anti-depressant drug paroxetine. The bulk of that fine was charged to GSK, despite the UK big pharma continuing to claim it did nothing wrong. GSK has since appealed this fine.

Meanwhile, in December 2016, the authority fined Pfizer Inc. and Flynn Pharma Ltd. nearly £90m for charging excessive prices for the anti-epilepsy drug phenytoin sodium, after that drug was also debranded – the case is similar to the one being brought against Actavis UK and highlights the high penalty Concordia and Actavis could be facing. The CMA also has two other investigations ongoing into the pharmaceutical sector.

In a March 3 response to the CMA's Statement of Objectives, Concordia emphasized that the case raised by the competition authority is provisional and no wrongdoing has been confirmed. The company said it would cooperate fully with the CMA. "We believe that the conduct of Amdipharm was not in breach of competition law. We will review the CMA's provisional position as set out in its Statement of Objections and then intend to respond in detail to it," Concordia said.

FREE MARKET PRICING

In the UK, generic manufacturers and suppliers have freedom of pricing, with Government only intervening if pricing competition fails to keep drug prices low – such as in he current case against Actavis UK. This is different to a lot of European countries that use centralized tendering or other grouped mechanisms.

The British Generic Manufacturers Association has continually lobbied for the UK to retain freedom of pricing in the UK for generic products – arguing against centralized tendering in primary care. It also says on its website that it believes a cost increase is needed in the UK "to create an economically sustainable market for manufacturers and to ensure that they can sustain the investment needed to produce new more complex generics and more costly biosimilar medicines."

The BGMA would not comment on the current cases against Actavis, but Warwick Smith, director general of the BGMA, said: "We have consistently made very clear that we would never support any activity which artificially raises the prices of medicines without good cause or clear benefit to patients."

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China's New Curbs On Rep Sales Activities

First came a warning, but few expected an outright ban to come so soon. Since January, when CCTV, China's state-run broadcaster, shocked the nation by broadcasting scenes of droves of medical sales reps strolling through large hospitals distributing envelopes stuffed with kickback cash to physicians in exchange for their drug prescriptions, industry observers have been anxiously waiting for a clampdown from regulators on such activity. The last time comparable irregularities in pharma companies' commercial activities came to light, the government handed out the largest ever corporate fine in China of CNY3bn ($436m) to UK-based multinational GlaxoSmithKline PLC. This time the government has issued a tough new rule that effectively bars company medical sales reps from selling drugs. The new apparent ban has raised questions over whether drug manufacturers should be taking more action to reign in their medical sales reps (MRs), commented Sidley & Austin lawyers Lei Li and Chen Yang. The overall government message, however, seems clear - pharmaceutical reps will be subject to more scrutiny, analysts say.

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Janssen's Drug Pricing Report Emphasizes Value Of Rebates

Janssen Pharmaceutical Cos.'s report on 2016 price increases shows that the company has kept average list price (wholesale acquisition cost) hikes below 10% for the past five years, while the average net price change (WAC minus rebates, discounts and returns) has ranged from 2.5% to 5.2%. The Johnson & Johnson unit's first annual US Transparency Report, released Feb. 27, also includes information about clinical data transparency and programs that support access to medicines. J&J CEO Alex Gorsky announced in a Jan. 24 earnings call that the company would be issuing an annual report on pricing transparency for its drugs. The report comes as the industry has continued to face fierce criticism over the high cost of drugs and sought to portray pricing in the context of other healthcare expenses. The day after the report was issued several members of Congress once again introduced bills in the House and Senate to allow Americans to import low-cost medicines from Canada. In its report, Janssen emphasizes the value of its discounts and notes that it sets prices below that of its competitors. The company notes that discounts and rebates to insurers, pharmacy benefit managers and others totaled approximately $11bn in the US, or a discount rate of 35.2%.

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Intercept Boosts NASH Commercial Potential

NICE, the HTA body for England and Wales, has made a final appraisal determination recommending Intercept Pharmaceuticals Inc.'s FXR agonist *Ocaliva* (obeticholic acid) for routine use on the National Health Service (NHS) for the treatment of primary biliary cholangitis (PBC). However, the company's key commercial success lays in securing approval for the product in non-alcoholic steatohepatitis (NASH), a much larger market with no approved therapies. In December 2016, Ocaliva was conditionally approved in the EU for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. US approval by the FDA was secured in May last year. "Ocaliva's approval in PBC will likely strengthen its commercial potential in NASH by allowing the drug to develop physician familiarity," Datamonitor Healthcare analyst Jack Allen told *Scrip*. Intercept is already testing Ocaliva in Phase III for NASH in the REGENERATE study, but there have been concerns over the speed of patient recruitment and the company also recently made some protocol changes.

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Novartis Under A Cloud

Novartis AG finds itself in a spot in India after a whistle-blower alleged that the Swiss multinational and its licensees for *Galvus* (vildagliptin) have colluded to set prices of the product in the country. The whistle-blower, who sent a letter to India's National Pharmaceutical Pricing Authority (NPPA), has claimed that while the business agreement may not be suggestive of the control exercised by Novartis over its co-marketing partners in terms of pricing, "in reality" the firms have formed a price cartel in both the trade and institutional businesses. "This is clearly anti-competitive and a clear case of blatant cartelization," the whistle-blower said in the letter as per a report in the local media. Novartis has been selling vildagliptin and vildagliptin in combination with metformin hydrochloride in India since 2008. The product is sold under different brand names by its partners Abbott (branded as Zomelis), USV Ltd. (Jalra) and Emcure Pharmaceuticals Ltd. (Vysov). Novartis told *Scrip* that it is committed to high standards of ethical business conduct and regulatory compliance in all aspects of its work. "Novartis has received no communication from the NPPA or the Competition Commission of India about any complaint against vildagliptin. Nonetheless, we wish to reiterate that vildagliptin is a patented compound and we are in full compliance with the law," it said.

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Hemophilia: How To Please Payers And Secure Market Share

Pharma companies are bringing forward innovative products that are set to shake up the hemophilia market – but convincing payers that they have substantial benefits over the current standards of care will be a challenge. Real-world data and early conversations with payers will be key, new research has found.

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The hemophilia market is expecting an influx of new products currently at the later stages of clinical development, including gene therapies, that will pile pressure on payers looking to contain costs. To secure market access, it will be critical for companies with entirely novel hemophilia therapies, as well as those providing incremental treatment benefits, to start conversations with payers as soon as possible. Care should also be taken over the design of clinical trials in order to maximize a new product's attractiveness.

New research published by Datamonitor Healthcare shows that payers are likely to favor therapies that substantially reduce the frequency of dosing for prophylaxis, eliminate bleeds and have new mechanisms of action that do not trigger inhibitor development, coupled with subcutaneous delivery.

Payers view frequency and mode of administration as important as they have the potential to improve patients' treatment adherence, result in better health outcomes and reduce overall treatment costs. While the goal of prophylaxis may be to prevent bleeds, this is not viewed as cost-effective at the moment, leading to suboptimal dosing regimens and undertreatment of patients.

"Payers are looking to contract for preferred products in the future, so differentiating the products (with features like new formulation, longer half-life), conducting the proper trials with the proper arms and endpoints (for example, including patient-reported outcomes as well), are all things manufacturers can do to optimize their products' commercial potential," noted Datamonitor Healthcare analyst, Maha Elsayed, author of a new report, Hemophilia Pricing, Reimbursement and Access.

The report highlights that payers have named Roche's emicizumab and Alnylam Pharmaceuticals Inc./Sanofi's fitusiran as the most anticipated pipeline agents for a variety of reasons.

PREFERRED PIPELINE AGENTS

Compared with long-acting recombinant agents, both emicizumab and fitusiran offer significant improvement in dosing frequency for hemophiliacs both with and without inhibitors. Emicizumab is an anti-Factor IXa/X bispecific antibody with a unique mechanism of action and longer half-life of four to five weeks. It is currently in clinical trials with a treatment protocol of weekly up to monthly injections. Datamonitor Healthcare forecasts the launch of emicizumab in 2018/2019 following the submission of Phase III data in hemophilia A patients with inhibitors (Haven 1) sometime in 2017. Roche, in partnership with Chugai Pharmaceutical Co. Ltd., also plans to submit the Phase III data in hemophilia patients without inhibitors in 2018.

Fitusiran, on the other hand, is a short interfering RNA antithrombin inhibitor in Phase II development that can be given to both hemophilia A or B patients, with and without inhibitors. Also, in line with payers' preference, fitusiran requires infrequent dosing and may be administered monthly.

According to one French payer, reducing treatment frequency to once a month or even less could improve treatment adherence significantly, and result in enhanced quality of life and learning abilities for children, thus attracting superior reimbursement prospects:

"I would be much more optimistic about long-acting technologies, not just extending the half-life a bit, because today for example Elocta [Sobi/Biogen's recombinant factor VIII Fc fusion protein to be administered every 3-5 days as a prophylactic injection] got ASMR V [an assessment of no clinical added value over existing therapies], and I was not surprised at all, I was very much anticipating this kind of outcome. Now, if you have a technology that would be once a month instead of every other day, then I would suppose that the manufacturer would [be rewarded with an assessment of] at least the slightest additional medical benefit because the transparency commission committee is likely to recognize the burden of the infusion for toddlers, at least in pediatrics that would be acceptable. I think there might also be a grade on the medical benefit for improved adherence or compliance reasons, and if not the economic committee is also likely to most probably recognize the benefit, and recognize that some kind of risk sharing agreement, some kind of patient access scheme may be acceptable because there is something that is genuinely new."

FORMULATION

Unlike the current therapies for hemophilia, which are administered intravenously, both emicizumab and fitusiran have a subcutaneous formulation. Subcutaneous delivery has been highlighted by payers as a preferred feature because it is easier to use and allows treatment to be administered by patients at home, thereby enabling improved patient adherence and thus offering the prospect of better health outcomes and reduced costs.

A US payer cited in the report said: "I think emicizumab is an exciting product because it is probably the first foray into treating hemophilia that is not a factor replacement, it actually helps work downstream in the clotting cascade... It is exciting because maybe you are going to have something there that you can give relatively infrequently, and really prevent bleeding."

INHIBITOR SEGMENT

In addition, these products address the needs of an underserved patient segment. Both agents could offer new options to severe hemophiliacs with inhibitors, where there is a gap in the market. While only one third of hemophiliacs develop inhibitors against clotting Factor VIII or IX therapies, these patients are the most difficult and expensive to treat, and have limited therapy options.

"Obviously, the inhibitor patients are very expensive, they often have to be

treated with things like Novo Nordisk's bypassing agent NovoSeven and other quantities of factors, and they can sometimes spend in excess of a million dollars per patient per year," said one US payer.

PAYERS' DATA DEMANDS

To maximize reimbursement success, pharmaceutical companies should look to demonstrate their products' value by establishing benefit in relation to standard of care treatment. "For new pipeline products, they need to design their trials better, have the right comparator in an adequately powered trial," Elsayed said. At the moment, not all trials compare the pipeline product with standard care of therapy. Rather, the majority compare mode of therapy such as on-demand (the clotting factor is given when there is a bleed) versus prophylaxis.

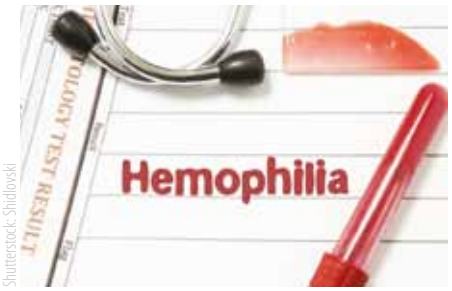
In the report, payers also mention that studies are under scrutiny and should meet certain requirements if developers want their drug to gain an added benefit or price advantage. They stressed the need for head-to-head comparative trials to prove whether a product provides any real benefit or not. A minimum of a one-year trial is preferred, with the most important endpoint being annual bleeding rate (ABR). A detailed analysis of severe bleeding rates or bleeds leading to hospitalization are also desired by payers and can support a product's value proposition. Further analysis of the impact on healthcare resource use can also support reimbursement submissions or price negotiations.

For example, one Spanish payer said: "I think that the most important endpoint is a highly clinical relevant endpoint, for example, the number of bleeds or bleeding, or reduction in number of bleeds over time or reduction in number of joint bleeds over time. We prefer a clinical endpoint; a clinically relevant parameter."

Meanwhile, a payer from Germany said: "Not for the G-BA, but during the pricing negotiation the health economic endpoints are appreciated. Let us say economic endpoints would be appreciated, we do not need health economic models in the long run or whatever, but any evidence that can show us that we can save direct costs compared to older interventions would be beneficial."

COMMERCIAL POTENTIAL

Elsayed predicts that emicizumab will take a large chunk of market share in hemophilia A patients with or without inhibitors. However, those already in this market can do various things to optimize their commercial potential and help offset the emerging competitive threat. For example, manufacturers can develop pharmacokinetic services – along the lines of PKFit, which Baxalta/Shire provides for Advate – to individualize therapy and limit excessive factor use. While payers are not willing to pay significantly more for these value-added services, they can help boost market share. Another value-added service that companies can leverage to stay on top of competition is offering specialist healthcare delivery services to patients treated at home, which would be especially valuable in some countries where availability of support services is limited.



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In countries like France, Roche for example has the option of seeking a Temporary Authorization for Use scheme (ATU) for emicizumab, giving it the opportunity to provide patients with the drug earlier. It will be funded and until it receives market authorization, Roche can collect real world data to support pricing and reimbursement negotiations.

GENE THERAPIES

Gene therapy is pegged to have the potential to transform the treatment of hemophilia patients with its approach of correcting and replacing a defective gene, potentially once and for all. Nevertheless, gene therapy developers have hurdles to overcome, funding to secure and physicians to convince before they gain market access. Pharma companies will need to engage with various stakeholders within different healthcare systems to make this transition smooth as possible.

There are various gene therapies in the pipeline, with the majority in Phase I/II or Phase II development, including BioMarin Pharmaceutical Inc.'s BMN-270, Spark Therapeutics Inc.'s SPK-8011 and uniQure NV's AMT-060.

Payers, however, are not yet keen on this form of therapy for two reasons: firstly, current healthcare systems are organized in such a way that they do not support one-off payments, something gene therapy would entail. A single one-off treatment necessitates a different pricing model from that in place for long-term, ongoing therapies. In addition, payers are not likely to be willing to pay a high figure without evidence of long-term efficacy.

Elsayed says that companies need to discuss with payers how to approach these payments and the shape of the new financial arrangements so that they can be prepared to contribute the data required. Potential options discussed by payers included annuity-based payments linked to an outcome-based agreement, meaning payment will be made as long as the treatment is effective. They also mentioned an alternative, partial upfront payment that is based on duration of response provided in trials, with the remaining paid on an annual basis.

Legal changes will also be required within health insurance frameworks. Considering how rare the disease is and the high upfront costs, there is potential for difficulties to arise around which insurance funds pay for and which one benefits financially from the gene therapy. As a result, gene therapy developers will need to communicate with stakeholders in healthcare systems to move along the process of introducing new legal and financial frameworks that will make funding gene therapies possible.

Companies will also need to liaise with regulators, the EMA and various HTA bodies about clinical trials and how they should be designed and the comparator arms to include.

Financial, regulatory and legal barriers are not the only hurdles developers will need to think about: there are also trust barriers that will require attention, particularly when it comes to patients and patient advocacy groups.

Analysis from *Datamonitor Healthcare*
Published online 3 March 2017

View Table Summarising Pipeline Product Features Desired By Payers In Different Markets here: http://bit.ly/2ISSfeY

Roche's APHINITY Trial Boosts Outlook On Its Oncology Business

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Roche released positive headlines from its APHINITY trial examining use of Herceptin and Perjeta together in the adjuvant treatment of breast cancer, offering promise that its aging oncology franchise can be protected.

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A huge sigh of relief accompanied Roche's announcement Mar. 2 that the keenly-awaited Phase III APHINITY trial showed that *Perjeta* (pertuzumab), combined with *Herceptin* (trastuzumab) and chemotherapy, extended disease-free survival in patients with HER2-positive early breast cancer when compared with Herceptin and chemo alone, and that no new safety signals were seen.

APHINITY's aim was to show that adding Perjeta would significantly improve invasive disease-free survival rates in women with early HER2-positive breast cancer. By meeting the primary endpoint, Roche's combo has boosted prospects the world's biggest maker of cancer drugs can off-set biosimilar threats to its oncology business with new therapies. Some 40% of group revenues are set to face biosimilar competition over the next five years.

APHINITY DETAILS

But analysts and investors must await full details from APHINITY. Analysts think that will occur at this June's American Society of Clinical Oncology (ASCO) meeting in Chicago, Illinois. "Without full details of the data, some degree of hand-wringing will likely continue, in terms of just how big the clinical benefit is likely to be," Bernstein analyst Richard Wagner said in a reaction note.

That's because observers are closely watching Roche's succession plans for its HER2 franchise, which has already revolutionized the treatment of breast cancer. Of particular interest are new drugs *Perjeta* and *Kadcyla* (ado-trastuzumab emtansine), the antibody-drug conjugate version of Herceptin. Roche hopes therapies like those will replace revenues lost when its three top-selling drugs *Herceptin*, *Rituxan/MabThera* (rituximab) and *Avastin* (bevacizumab) – which account for some $20bn in yearly sales – begin to lose patent protection in the next three years.

Perjeta has already been approved in the US in combination with Herceptin in metastatic disease, and received accelerated approval in the pre-surgical, or neoadjuvant, setting, where it has been shown to reduce the size of tumors.

APHINITY is evaluating Perjeta's ability to stop the recurrence of the disease for women who have undergone surgery, or "adjuvant" treatment, which if successful would greatly boost the number of patients eligible for the combination of HER2-blocking agents.

"These APHINITY results serve as confirmation for the conditional approval and will also assure the label-expansion approval of Perjeta for adjuvant treatment. This label expansion will help Roche increase its revenues even as it faces competition from Herceptin biosimilars," said BioMedTracker analyst David Dahan.

REGULATORY APPROACH

Roche said it would now discuss the APHINITY results with the FDA and European Medicines Agency (EMA) as well as HTA authorities for potential approval of the drug mixture for treating people with HER2-positive early breast cancer.

"We cannot speculate on the timing of potential regulatory decisions. We hope to bring this treatment option to patients as soon as possible," a Roche spokesperson said.

Analysts at Berenberg took heart at the regulatory approach Roche indicated it would use for the combo in the early HER2-postive breast cancer setting. "Roche intends to file on a global basis, which we think is encouraging, because this indicates it believes the data will be strong enough to secure adoption on a wide basis," they said.

The significance of the trial reflects the fact that treating breast cancer effectively and early, before it has spread, may improve the chance of preventing the disease from returning and potentially reaching an incurable stage.

Herceptin is Roche's second-biggest earner after Avastin. Some 70% of Roche's $6.8bn Herceptin sales came last year from patients who might benefit from the combination being tested in the APHINITY trial.

> 'These results serve as confirmation for the conditional approval and will assure label-expansion approval'

But while positive for Roche, Datamonitor Healthcare analyst Zachary McLellan says the APHINITY trial's results "are a significant blow" to Puma Biotechnology Inc. and its pan-HER inhibitor, neratinib. Puma is trying to position its lead asset for the extended adjuvant setting after treatment with Herceptin in breast cancer patients.

"Neratinib has not been studied in patients that received both Perjeta and Herceptin treatment and will not be indicated for use in these patients. So, if approved, neratinib will likely see little to no uptake in its targeted indication," McLellan told *Scrip*.

BioMedTracker's Dahan agreed, adding: "detailed results will be key - and it will be interesting to see how Perjeta performed in patients with hormone-receptor positive disease, a subgroup which did very well on neratinib."

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Juno Ends JCAR015 Development In ALL

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Juno and partner Celgene closed the ROCKET study for JCAR015, which has been on clinical hold since November, and ended development in ALL in favor of its new and improved CD19-targeting CAR-T therapies.

Juno Therapeutics Inc. has ended development of its CD19-targeting chimeric antigen receptor T-cell (CAR-T) therapy JCAR015 for the treatment of acute lymphoblastic leukemia (ALL) due to safety concerns, answering with certainty the question of whether the company could catch up to its competitors, which will be seeking approvals for their CAR-T therapies any day now.

Juno said on March 1 in its fourth quarter and year-end 2016 earnings report that the company and its partner Celgene Corp. ended the pivotal ROCKET clinical trial that had been placed on clinical hold multiple times due to severe neurological side effects and patient deaths. The company will focus its efforts in ALL on its defined cell technology instead, including the CD19-targeting JCAR017, which it has been promoting as better and safer than JCAR015 since the first ROCKET clinical hold.

Juno's stock price fell 7.9% after the stock market closed to $23.30 per share based on the JCAR015 update, keeping the stock toward the low end of its 52-week range of $17.52 to $49.72.

JCAR017 will move into a pivotal Phase II clinical trial in non-Hodgkin lymphoma (NHL) at some point in 2017, keeping Juno a year or more behind Kite Pharma Inc. and Novartis AG, which are expected to submit their CD19-targeting CAR-T therapies for US FDA approval during the first quarter of this year.

Kite is pursuing its first approval for axicabtagene ciloleucel (KTE-C19) in the treatment of aggressive relapsed or refractory NHL, including diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL), and reported durable response rates through six months of treatment from its ZUMA-1 study on Feb. 28. The first potential indication for Novartis's CTL019 will be relapsed or refractory pediatric ALL.

Juno insisted in its 2017 financial update that JCAR017 will keep the company in a competitive position in the CAR-T field, positioning its next-generation CD19-targeting product candidate as a potential best-in-class product. The overall response rate (ORR) for NHL patients treated with JCAR017 in the Phase I TRANSCEND clinical trial was 80% in data reported in December during the American Society of Hematology (ASH) annual meeting with a 60% complete response (CR) rate.

In Kite's Phase II ZUMA-1 study, at six months the ORR was 82% and the CR was 41%.

"We continue to experience encouraging signs of clinical benefit in our trial addressing NHL," Juno President and CEO Hans Bishop said in the company's March 1 statement, "but we also recognize the unfortunate and unexpected toxicity we saw in our trial addressing ALL with JCAR015. We have decided not to move forward with the ROCKET trial or JCAR015 at this time, even though it generated important learnings for us and the immunotherapy field. We remain committed to developing better treatments for patients battling ALL and believe an approach using our defined cell technology is the best platform to pursue. We intend to begin a trial with a defined cell product candidate in adult ALL next year."

Although the hold put on ROCKET in July was lifted within a matter of days, the FDA stopped the trial again in November based on an unexpectedly high incidence of severe neurotoxicity, including five deaths from cerebral edema among the patients treated with JCAR015. The study has remained on hold while Juno conducted an investigation.

"Through the investigation Juno identified multiple factors that may have contributed to this increased risk, including patient-specific factors, the conditioning chemotherapy patients received, and factors related to the product. Although Juno believes there are protocol modifications and process improvements that could enable Juno to proceed with JCAR015 in clinical testing in adult [relapsed or refractory (r/r)] ALL, Juno would first need to establish preliminary safety and dose in a Phase I trial," the company said in its earnings report.

"As a result of the timing delay that would entail and Juno's belief that it has other product candidates in its pipeline that are likely to provide improved efficacy and tolerability, Juno, in collaboration with partner Celgene, has made a strategic decision to cease development of JCAR015 at this time and to redirect associated resources to the development of a defined cell product candidate in the adult r/r ALL setting," Juno reported.

PATENT DISPUTES OFFER UPSIDE

Juno did remind investors about some upside in its earnings report, however, related to Kite's CAR-T development programs. The companies are engaged in two separate patent disputes, including an inter partes review that Kite sought with the US Patent and Trademark Office (USPTO) Patent Trial and Appeal Board (PTAB) in August 2015 related to a patent for CAR-T technology used in the treatment of B cell and other malignancies, which Juno licensed from the Sloan-Kettering Institute for Cancer Research, an affiliate Memorial Sloan Kettering Cancer Center. The PTAB upheld all of the patent's claims, but Kite has appealed the decision to the US Court of Appeals for the Federal Circuit.

Meanwhile, Juno has filed a lawsuit against Kite claiming axicabtagene ciloleucel infringes the patent upheld by the PTAB, which covers a CD19-targeting CAR-T construct that uses a certain CD28 co-stimulatory domain. If the court issues a declaratory judgment in Juno's favor or if the two companies reach a settlement, Kite could be on the hook for licensing fees, royalties or other payments.

A lawsuit settled in 2015 related to a separate patent resulted in Novartis agreeing to pay Juno $12.25m plus future milestone fees and royalties. The settlement ended a dispute between Novartis's partner the University of Pennsylvania and Juno's partner St. Jude Children's Research Hospital.

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WHO's List Of Pathogen Threats To Rouse Developers

The World Health Organisation has released a list of 12 bacteria it says pose the greatest threat to human health as a way of urging governments and the drug development industry to incentivize and launch an R&D response against the increasing global issue of antibiotic resistance.

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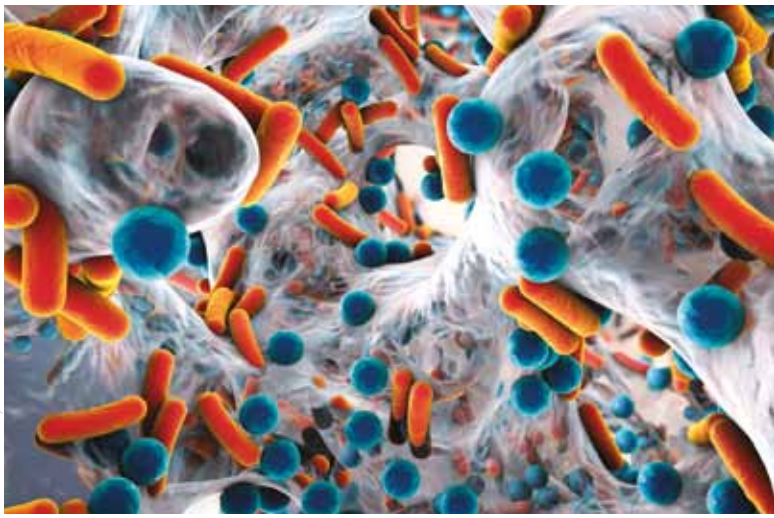
The World Health Organisation has highlighted 12 families of bacteria, the majority of which have become resistant to available antibiotic treatments, on a newly established watch list of critical threats – similar concerns as those raised by the US Centers for Disease Control and Prevention (CDC) in a 2013 report on the top 18 drug-resistant threats.

The WHO's list highlights in particular the threat of gram-negative bacteria that are resistant to multiple antibiotics. "This list is a new tool to ensure R&D responds to urgent public health needs," Dr Marie-Paule Kieny, the WHO's assistant director-general for health systems and innovation, said in statement. "Antibiotic resistance is growing and we are fast running out of treatment options. If we leave it to market forces alone, the new antibiotics we most urgently need are not going to be developed in time," she added.

The WHO's list of bacteria families – developed in collaboration with the division of infectious diseases at the University of Tübingen, Germany – is split into three priority categories: critical, high and medium.



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PRIORITY 1: CRITICAL

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

PRIORITY 2: HIGH

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter spp.*, fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

PRIORITY 3: MEDIUM

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella spp.*, fluoroquinolone-resistant

Criteria for selecting the pathogens on this list included how many treatment options remain and whether new antibiotics to treat them are already in the pipeline; as well as measures like how deadly the infections caused are and whether hospitals stays are required for those infected.

Dr Sue Hill, director of the department of essential medicines and health products at the WHO, told *Scrip*, "Even though there has been a lot of investment in the last couple of years from both private and public funding aimed at stimulating R&D for antibiotics, what we still see is a relatively limited number of products in the pipeline."

Hill noted that one of the WHO's next steps this year is to carry out a thorough pipeline analysis for treatments targeting the pathogens highlighted on its watch list. The WHO is also considering a global stewardship framework for monitoring and guiding the best use of antibiotics worldwide, looking for at the development of new drugs and how to repurpose available anti-infectives. Futhermore, the organization has an ongoing partnership with the non-profit group Drugs for Neglected Diseases Initiative (DNDI), focused on stimulating new R&D methods for antibiotics.

"The purpose of this list was to define more precisely the bugs we need antibiotics for most, to direct research efforts to the areas with the most need," Hill said. She compared the list to some of the WHO's previous projects, such as the 2013 Priority Medicines for Europe and the World report and the R&D Blueprint for Action to Prevent Epidemics that was released in May last year.

The list has received more than 124,000 downloads since its release on the WHO's website on Monday Feb. 27. Hill noted that one query raised about the list so far is the fact tuberculosis was not included as a threat. She clarified that while new drugs for TB is a major priority for the WHO, it is an initiative that has been defined for some years. "The idea of this list was to go beyond the pathogens where we already have priority measures in place," she added. "We know TB, malaria and HIV, for example, need new drugs – these have been R&D priorities for some time."

INDUSTRY INCENTIVES

Hill highlighted that current antibiotic developers or those looking to expand into antibiotic research should not only focus on pathogens highlighted as critical risks. "Drugs targeting the pathogens in the medium threat category might be easier or cheaper to developer. One of the reasons the critical group has that heading is because we have more problems with resistance there and see fewer product coming through the pipeline." Hill realizes that the economic setup for developers of new anti-

biotics is still unfit for purpose. "It is clear the standard market models are not working and are inappropriate," she said, "the last thing we want are new antibiotics developed and sold to millions of people. We want a new drug developed and locked up for future use."

Hill noted that this requires different thinking around incentives because companies are asked to invest in developing products but at the same time told not to sell them. "We have to think about whether buying out patents is an option, offering prizes – for example, like the FDA's priority review voucher system. We are having these discussions now to see what will be the appropriate mechanisms for incentivizing companies," she said.

As well as industry's response to the list, Hill hopes to spur academic groups and basic science researchers to act on the call to arms against antimicrobial resistance.

WHAT'S IN THE PIPELINE?

Pipeline activity for the three pathogens highlighted by the WHO as critical threats – *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae*– is limited, concentrated mainly in the early-stages of development.

According to data held by Informa Pharma Intelligence's Biomedtracker, there are only three compounds in development targeting *Acinetobacter baumannii* gram-negative bacteria, of these only one has entered the clinic. Entasis Therapeutics has a Phase I program (active in Australia) for EXT2541, a broad and potent inhibitor of class A, C, and D beta-lactamases. The company is developing the combination of sulbactam and ETX2514 for the treatment of severe *Acinetobacter baumannii* infections. The Phase I study is slated for completion by June this year. Antibiotic treatments against *Pseudomonas aeruginosa* are more advanced than *A. baumannii*. Biomedtracker has two Phase II programs listed: MEDI3902 from AstraZeneca PLC and panobacumab from Aridis Pharmaceuticals LLC. AstraZeneca's drug has been granted Fast Track status in the US and topline data from the Phase II EVADE trial in mechanically ventilated patients for the prevention of nosocomial pneumonia caused by pseudomonas aeruginosa are expected in 2018.

Targeting *Enterobacteriaceae*, Achaogen Inc., in partnership with Ionis Pharmaceuticals Inc., has three Phase III trials ongoing for antibiotic candidate plazomicin. The drug is being tested as a treatment for urinary tract infections, septicemia and hospital acquired pneumonia.

COMPARISON TO CDC ANALYSIS

In 2013 the CDC published a report outlining the top 18 drug-resistant threats, also categorized by level of concern: urgent, serious and concerning.

The pathogens at the top of both these lists remain similar four years apart, highlighting the slow progress in uptake of antibiotic research programs. The WHO's number one concern, resistant *Acinetobacter baumannii*, also topped the CDC's serious threats list in 2013. However, *Neisseria gonorrhoeae* was labelled an urgent threat in the US in 2013, but this pathogen has only been categorized as a high priority in 2017 by the WHO.

Drug resistant Pseudomonas aeruginosa, a critical threat on the WHO's list, was also considered a serious threat by the CDC four years earlier.

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New Anti-CMV Therapies Post-Transplant

Infections caused by cytomegalovirus, particularly those that erupt during immunosuppression, have been a particular bugbear of transplant patients, but a new generation of anti-CMV agents are nearing the market, with Merck & Co. Inc.'s letermovir forging ahead in the latter stages of the race to market.Letermovir is described as a first-in-class viral terminase complex inhibitor that unlike marketed CMV therapies is not a nucleoside derivative but a quinazoline, and has no activity against other viruses. Worldwide rights to the product were bought by Merck in 2012 with an upfront payment of $143m and $433m in development, regulatory and commercial milestones from the Bayer AG spinout and Wuppertal, Germany-based company, AiCuris GMBH & Co. KG. Merck intends to submit letermovir for approval in the post-transplant setting in the US and EU during 2017, seemingly putting the company ahead of a small group of potential new anti-CMV agents in late-stage development that include small molecules, vaccines and cell-based approaches. Following a brief announcement on Oct. 19, 2016 that the results of a Phase III study of letermovir to prevent CMV infection in post-bone marrow transplant patients were positive, Merck released further top-line data from the study on Feb. 26, 2017, indicating that significantly fewer patients with undetectable plasma CMV DNA at the start of treatment developed clinically significant CMV infection in the 24 weeks post-transplant, compared with placebo-treated patients.

john.davis@informa.com, 2 March 2017

Perrigo 'Unlocks Value'

Perrigo Co. PLC is selling its royalty stream in multiple sclerosis drug *Tysabri* (natalizumab) to Royalty Pharma for up to $2.85bn, following pressure from hedge fund Starboard. The deal comprises $2.2bn in cash at closing and up to $650m in potential milestone payments. Starboard has highlighted the fact that Perrigo's share value has dropped since the firm convinced shareholders to reject a takeover offer from Mylan NV in 2015. It has been pushing for a sale of Perrigo's Tysabri stake and its prescription generic specialty topicals business to help turn around the firm's plummeting share price. However, while analysts are broadly positive about the Tysabri deal, they are not convinced Perrigo is solving its problems effectively. "Five new board members have recently joined, Tysabri has been sold, and management has found $130M in synergies," wrote Jefferies' David Steinberg in a research note dated Feb.28. The potential sale of the prescription business is still an unknown, but it's clear Perrigo's management is working hard to create more value. "However, has anything actually changed except reducing leverage and shrinking the earnings base? It's early but we'd say not really. The hope is that management can improve margins at BCH (branded consumer healthcare) and a floor on generic pricing can be reached."

sukaina.virji@informa.com, 28 Feb 2017

Astellas Builds Vaccine Portfolio

Astellas Pharma Inc. is paying $10m upfront to acquire exclusive worldwide rights to develop and commercialize a novel pneumococcal disease vaccine developed by Affinivax Inc. using the US venture's proprietary Multiple Antigen Presenting System (MAPS) technology. The candidate, used to prevent infections caused by the Streptococcus pneumoniae bacterium including pneumonia, meningitis, and sepsis, is Affinivax's lead pipeline project and is still at the preclinical stage, but has shown promising signs of activity. As part of the new agreement, Astellas will lead and fund in full a planned global clinical development program, with Affinivax eligible for further undisclosed milestone payments related to development, approvals in targeted indications, and commercial sales, plus tiered royalties. Astellas said there would be no financial impact from the deal on its existing guidance for the fiscal year ending March 31. The deal builds on existing links forged in September 2015 between Affinivax and Astellas's vaccines R&D partner ClearPath Development Company LLC to research prophylactic MAPS vaccines for the prevention of bacterial nosocomial infections. ClearPath, with support from Astellas, set up a dedicated venture, Nosocomial Vaccine Corp., in that year to develop products in this area. ClearPath and its parent RRD International have been helping Astellas identify and develop vaccine candidates, which led to the Japanese firm acquiring global rights in 2013 to Mymetics Corp.'s preclinical respiratory syncytical virus (RSV) vaccine. This product is being developed through RSV Corp, another company formed with ClearPath's support and an Astellas minority investment in the same year.

ian.haydock@informa.com, 28 Feb 2017

Sanofi/Lonza's JV: Flexible Biologics Manufacturing

Construction of a large-scale mammalian cell culture facility for monoclonal antibody production will start in Visp, Switzerland, this year under terms of a joint venture between Sanofi and Lonza Group Ltd. aimed at giving the duo commercial flexibility and scalability in response to demand for Sanofi's portfolio of late-stage biologic drugs, which currently comprise some 60% of its pipeline. The French drug maker and Swiss contract development and manufacturing group said Feb. 27 they were setting up their first ever JV, under which Lonza will design, construct, start up and operate a state-of-the-art large-scale mammalian cell culture facility. The two will split the €270m initial cost equally.

sten.stovall@informa.com, 27 Feb 2017

Shire's Wellhoefer On Genetic Disease R&D And Expanding Access To Medicines

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Scrip spoke with Shire's Head of Genetic Diseases, Medical Affairs, Hartmann Wellhoefer about upcoming milestones in the company's R&D pipeline and improving access to medicines for rare diseases after the Baxalta merger.

Hartmann Wellhoefer

Shire PLC vice president Hartmann Wellhoefer, head of genetic diseases, medical affairs, recently spoke with *Scrip* about the company's research and development pipeline in lysosomal disorders and hereditary angioedema (HAE), noting that more patients with those conditions will have access to Shire's medicines after its purchase of Baxalta Inc.

"The biggest advantage in genetic diseases from Baxalta was expanding our presence into more countries," Wellhoefer said in a Feb. 15 interview during the WORLD Symposium in San Diego.

The transaction gave Shire a presence in India, where it didn't sell its drugs before, expanding the company's presence from about 60 to almost 100 countries. "Demand is as big as in Europe or the US, but access is a challenge in these countries," he said.

Even with a presence, it still takes time and patience to bring relatively high cost medicines for rare and genetic diseases to patients who haven't had access to them before.

"In rare and genetic diseases, there's a lot of education for health authorities to not just look at large and communicable diseases," Wellhoefer said. "There are countries that struggle to realize that it's important to have equal access to rare disease drugs."

EARLY DIAGNOSIS CAN LIMIT DISEASE BURDEN

Among Shire's many collaborations in the rare disease space, the company is working with patient groups – sometimes just a small grouping of families whose children have a specific genetic disease – to help individuals find treatment or enroll in clinical trials. The company and the patient groups also work together to help governments understand how many people have HAE or lysosomal disorders and communicate the importance of providing treatment before irreversible effects of the diseases set in.

Early diagnosis has become a greater focus for Shire and for the lysosomal disorder research community, because new and available treatments can halt or slow progression of the disease before difficult symptoms take hold or before they become harder to manage. Early diagnosis was a frequent topic of discussion during the WORLD (We're Organizing Research On Lysosomal Diseases) Symposium. It's also an area in which Shire is actively pursuing partners.

Wellhoefer said delayed diagnosis is the biggest problem facing patients with lysosomal disorders, because it can take years to get to a final diagnosis and by then symptoms can't be reversed, including severe neurological effects. For instance, Fabry disease begins with nonspecific gastrointestinal and pain issues that don't immediately indicate the lysosomal disorder, but a diagnosis often isn't established until Fabry patients have progressed so far that they're on dialysis due to kidney failure.

"Uncertainty about diagnosis is a huge burden for families," Wellhoefer said.

The earlier a patient with Hunter syndrome is treated, however, the more likely that bone structure can be preserved and joint stiffness can be reduced, potentially maintaining patients' mobility and extending their lives.

Shire's partnerships focused on disease diagnosis include collaborations with diagnostic companies and academic laboratories in various countries to provide free testing for people who may have HAE.

PIPELINE PROGRESS IN HAE, HUNTER SYNDROME

One of the most advanced programs in Shire's genetic disease R&D pipeline is the HAE drug candidate SHP643, a monoclonal antibody that inhibits plasma kallikrein. The company acquired the potential blockbuster with its $5.9bn purchase of Dyax Corp. in late 2015. SHP643 offers a new prophylaxis option for HAE patients via a more convenient subcutaneous injection versus Shire's approved prophylactic treatment Cinryze (C1 esterase inhibitor [human]), a twice-weekly infusion.

Phase III data for SHP643 are expected around the second quarter of this year. If successful and the drug is approved, "we could be changing the treatment approach," Wellhoefer said.

> 'The biggest advantage in genetic diseases from Baxalta was expanding our presence into more countries'

Shire also expects Phase III data this year for SHP609, an intrathecal version of *Elaprase* (idursulfase), the company's enzyme replacement therapy (ERT) for Hunter syndrome (mucopolysaccharidosis type II or MPS II). The company has a second novel ERT for Hunter syndrome in development with partner ArmaGen Technologies Inc. known as AGT-182; Phase I data may be available this year. Both products are designed to cross the blood-brain barrier to treat neurological symptoms of the disease.

Wellhoefer said as Shire continues to look at new ways of treating rare and genetic diseases, the company will pursue novel technologies on its own and via partnerships, such as its intrathecal R&D programs and gene therapies. He noted that Shire gained gene therapy technology and partners via the Baxalta transaction, but said the company was investigating gene therapies prior to the merger.

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

CLICK

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

Selected clinical trial developments for the week 24 February –2 March 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Suspended			
PTC Therapeutics Inc.	*Translarna* (ataluren)	nonsense mutation cystic fibrosis	ACT CF; did not achieve primary or secondary endpoints.
Updated Phase III Results			
Amgen Inc.	*Kyprolis* (carfilzomib)	multiple myeloma	ENDEAVOR; improved overall survival versus bortezomib.
Adamas Pharmaceuticals Inc.	*Nurelin* (amantadine)	levodopa-induced dyskinesia	EASE LID 2; reduced off symptoms.
AMAG Pharmaceuticals Inc./Palatin Technologies Inc.	*Rekynda* (bremelanotide)	hypoactive sexual desire disorder	RECONNECT; improved symptoms significantly.
Phase III Completed			
Kite Pharma Inc.	axicabtagene ciloleucel (KTE-C19)	diffuse large B-Cell lymphoma	ZUMA-1; met primary endpoint of objective response rate .
Phase III Interim/Top-line Results			
Merck & Co. Inc.	varicella zoster virus vaccine (V212)	chickenpox, shingles prophylaxis	001-AM2; shingles reduced in immunocompromised patients.
Merck & Co. Inc.	letermovir	CMV infection, after bone marrow transplant	Effective and lowered all-cause mortality.
Roche/Chugai Pharmaceutical Co. Ltd.	*Perjeta* (pertuzumab) plus *Herceptin* (trastuzumab) and chemotherapy	HER-positive breast cancer	APHINITY; met primary endpoint, reduced invasive disease and death.
Accera Inc.	AC-1204 (caprylic acetate)	mild-to-moderate Alzheimer's disease	NOURISH AD; missed endpoints, may be due to formulation change.
Sumitomo Dainippon Pharma Co. Ltd.	Latuda (lurasidone)	bipolar disorder in children and adolescents	ILLUMINATE; improved symptoms, well tolerated.
La Jolla Pharmaceutical Co.	LJPC-501 (angiotensin II)	hypotension/shock	ATHOS-3; met primary endpoint.
Cempra Inc.	*Solithera* (solithromycin)	urinary and reproductive tract infections	SOLITAIRE-U; missed endpoint but encouraging results.
Cempra Inc.	*Taksta* (fusidic acid)	skin infections	Study 301; achieved primary endpoint .
Phase III Initiated			
BeyondSpring Inc.	plinabulin	febrile neutropenia	Associated with docetaxel therapy.
AbbVie Inc.	rovalpituzumab tesirine (*Rova-T*)	small cell lung cancer	MERU; after platinum-based chemo, as maintenance therapy.
Myovant Sciences Ltd.	relugolix, oral once-daily	advanced prostate cancer	HERO; Current therapies are injected.
Phase III Announced			
Theravance Biopharma Inc.	revefenacin	chronic obstructive pulmonary disease	A peak inspiratory flow rate study.
Genentech Inc./AC Immune SA	crenezumab	Alzheimer's disease	CREAD2; in prodromal or mild disease.
Mundipharma International Corp. Ltd.	MR308	moderate to severe pain	STARDOM2.
Sanofi/Lexicon Pharmaceuticals Inc.	sotagliflozin	type 2 diabetes	Combined with metformin or a sulfonylurea.

Source: Biomedtracker

Sanofi's board of directors has proposed the appointments of ***Melanie Lee*** and ***Bernard Charlès*** as new independent directors. Lee is chief scientific officer at BTG Plc and previously spent 10 years at Glaxo/GlaxoWellcome. In 1998, she was executive director of research at Celltech plc, which was acquired by UCB, where she became executive vice president of R&D. Lee was also previously CEO at Syntaxin Ltd and in 2014 she founded NightstaRx Ltd. Since 2016, Charlès has been vice chair and CEO of Dassault Systèmes, he joined the company in 1983 and was appointed strategy director for R&D.

Richard L. Wang has been appointed CEO of **Fosun Kite Biotechnology Co., Ltd.**'s. Wang has previously held leadership roles at Procter & Gamble, Bristol-Myers Squibb, AstraZeneca plc and GlaxoSmithKline Plc. Most recently, he was chief operating officer of Cellular Biomedicine Group and before this Wang was senior site leader and head of operations for GlaxoSmithKline research and development in Shanghai.

Milestone Pharmaceuticals USA Inc. has appointed ***Joseph G. Oliveto*** president and CEO – effective immediately. Founder and former CEO, ***Philippe Douville***, will now assume the newly created position of chief scientific officer. Before Milestone, Oliveto was president and CEO of Chelsea Therapeutics and also served as CEO of Galleon Pharmaceuticals. He began his career at Hoffmann-La Roche Inc., where he held various senior positions for 18 years.

Mark Foletta has joined **Tocagen Inc.** as executive vice president and chief financial officer. He will be succeeding the company's co-founder, ***Tom Darcy***, who is retiring but will continue to serve on the company's board of directors. With more than 30 years of experience as a financial executive, Foletta was previously senior vice president and chief financial officer at Amylin Pharmaceuticals Inc. for over a decade. He is on the board for various biopharmaceutical companies, including AMN Healthcare Inc., Regulus Therapeutics Inc. and DexCom Inc.; and also chairs each of their audit committees.

Hookipa Biotech AG has named ***Igor Matushansky*** global head, research and development. He joins the company from Daiichi Sankyo, where he was the global head of translational development for oncology. Prior to this he was global head for clinical and scientific development at Novartis's gene & cell therapy unit as well as a global clinical program lead within the company's oncology translational medicine unit. Before entering the pharmaceutical industry, Matushansky was professor at the Columia University Medical Center.

GW Pharmaceuticals Plc. has named ***Scott Giacobello*** chief financial officer (CFO) to be based at the company's US headquarters in Carlsbad, California. GW's former CFO, Adam George, has been appointed to the newly created role of managing director, UK. Giacobello brings 25 years of finance and operational experience to the company and previously he was CFO for Chase Pharmaceuticals Corporation. Before Chase, he held senior level finance positions at Allergan Inc., most recently as vice president of finance for global R&D.

Dynacure, a new biotechnology company focused on rare disorders, has appointed ***Stephane van Rooijen*** CEO, ***Frédéric Legros*** chief operating officer and ***Leen Thielemans*** head of development. The company, which was founded in 2016 as a spin-off from the IGBMC (Institute of Genetic and Molecular and Cellular Biology) of Strasbourg, has also named the members of its board of directors, they include: ***Frederic Chereau***, ***Chris Mirabelli*** and ***Brett Monia***, who have been appointed as independent directors; ***Rémi Droller*** and ***Vanessa Malier***, who represent Kurma Partners; and new CEO van Rooijen.

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