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Novo Nordisk Will Eat Itself In Obesity

ALEX SHIMMINGS alex.shimmings@informa.com

Novo Nordisk AS's highly promising Phase II trial data for its new GLP-1 agonist semaglutide and the resultant full-steam ahead progression into Phase III could open up a large new market for the investigational antidiabetic, but it seems most of it will come at the expense of the company's older GLP-1 agonist *Saxenda* (liraglutide). Moreover, a change in attitudes will be needed for the product to reap its full rewards in this difficult market.

Last week Novo Nordisk reported weight loss of up to 13.8% in a 957-patient study after a year of treatment with semaglutide in combination with diet and exercise, compared with 2.3% weight loss with diet and exercise alone – results the company described as very exciting. By contrast, Saxenda resulted in placebo-adjusted weight loss of around 5%. *(Also see "Novo Nordisk's Great Hope Semaglutide Shines In Ph II Obesity Study" Scrip, 26 Jun, 2017.)*

Analysts were impressed too.

"The drug was associated with significantly more weight loss than we've previously seen with other weight loss drugs," commented Kevin Shannon an analyst from Datamonitor Healthcare. "This is also the first drug associated with more than 10 kg of weight loss, which is significant as more than 70% of physicians in Datamonitor Healthcare's 2016 Obesity Survey said they would like to see >10kg of weight loss before they would consider prescribing a weight loss drug."

But, he added, resistance to weight loss drugs among prescribers - and a reluctance among patients to seek therapy – could prove difficult challenges to Novo Nordisk.

"Efficacy is only a small piece of the puzzle for weight loss drugs. Only a very small percentage of patients meeting treatment guidelines for weight loss drugs actually receive them, due to physicians' and patients' hesitations over side effect/safety profiles and the necessity of these drugs. Many obese patients avoid seeking treatment for obesity due to stigma surrounding the disease and the embarrassment they often feel when visiting the doctor's office," Shannon said.

"On top of this, for the patients who do seek treatment, many physicians believe that lifestyle changes are the only effective way to combat obesity and are very hesitant to prescribe drug therapies."

While a product as effective as semaglutide is hinting that it might be may be able to shift these perceptions, Shannon believes doctors and patients are looking for more than just kg losses – adverse events matter too, especially following the phen-fen issues in the 1990s and the later withdrawal of **Sanofi**'s *Acomplia* (rimonabant) from the EU market on psychiatric adverse event concerns (this product never reached the US).

The GLP-1 agonist products are associated with significantly higher rates of nausea and vomiting, which could hamper their take-up, and they have the added disadvantage of being delivered by subcutaneous injection (N.B. an oral version of semaglutide is in Phase III development for diabetes). As such, analysts are keen to see how the side-effect profile for semaglutide breaks down by dose when the full Phase II obesity study data are reported.

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BROUGHT TO YOU BY THE EDITORS OF **PHARMASIA NEWS**, **START-UP** AND **SCRIP INTELLIGENCE**

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Could shame be wielded against pharma today? (p14)

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from the editor

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Clinical trials are more likely to fail than succeed, and many biopharma stocks surf on waves of hype and hope, only to be dragged out to sea by negative study results. It is therefore noteworthy that June saw not one but two major Phase III successes for which expectations had been low.

First Novartis announced that in its three-year CANTOS study, canakinumab (which is already marketed for auto-inflammatory disorders including a form of juvenile arthritis) reduced the risk of major cardiovascular events. The hypothesis that targeting inflammation with canakinumab could treat atherosclerosis was untested in Phase II, so the CANTOS trial was quite a leap of faith. Then Merck & Co announced that its CETP inhibitor had met its Phase III primary endpoint of reducing the risk of major cardiovascular events (see p8). As one of the last relics of a class that has seen many major casualties over the years, anacetrapib had been widely expected to fail.

Novartis was confident enough to tell us that it intends to discuss a filing after analyzing the data, while Merck was more reticent, saying only that it would consider whether to file after reviewing its data. Some interpreted Merck's coy manner as a sign that there are hidden drawbacks not yet revealed, and others flagged up the challenges Novartis may face in working out a path for its medicine to be prescribed. But with 40,000 patients having participated in the two studies, it is to be hoped that they will eventually lead to advances in treatment.

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Internally derived Pentarins offer the targeting advantages of antibody-drug conjugates in cancer, but with better affinity, pharmacokinetics and deeper tumor penetration.

Podcast: Scaling Up Your Business
http://bit.ly/2sDURQC
BIO International 2017. Informa's global content editor Mike Ward discusses how to scale up your SME and access international markets with experts in the field. This content was produced by Scrip alongside a sponsored project with MSP, a provider of specialized science campuses in Manchester and Cheshire, UK.

ConSynance Differentiates NASH Asset To Charm China
http://bit.ly/2thZmSK
Dr. Shuang Liu, president and co-founder of ConSynance Therapeutics, talks with Scrip's Brian Yang about the US-based startup's plans to develop and commercialize in China its assets for indications including NASH.

Biological E Taps Takeda Tech For Affordable Combo Vaccines
http://bit.ly/2uBYFTU
Takeda is to transfer selected vaccine technologies to an Indian manufacturer to enable the production of affordable combination vaccines for lower income countries, although likely volumes and prices remain unclear for now.

Heptares' GPCR Discovery Pact With PeptiDream Focused On Inflammation
http://bit.ly/2uFs1k3
An undisclosed G-protein coupled receptor playing a role in inflammatory disease will be the focus of a drug pact between Heptares and PeptiDream.

Otsuka Ties Up With Mylan To Advance MDR-TB Drug In India?
http://bit.ly/2uFD3pK
Otsuka, which has been under fire over delayed access to delamanid in India, appears to have allied with Mylan, which has now secured a key clearance for the novel multidrug-resistant TB therapy in the country.

inside:

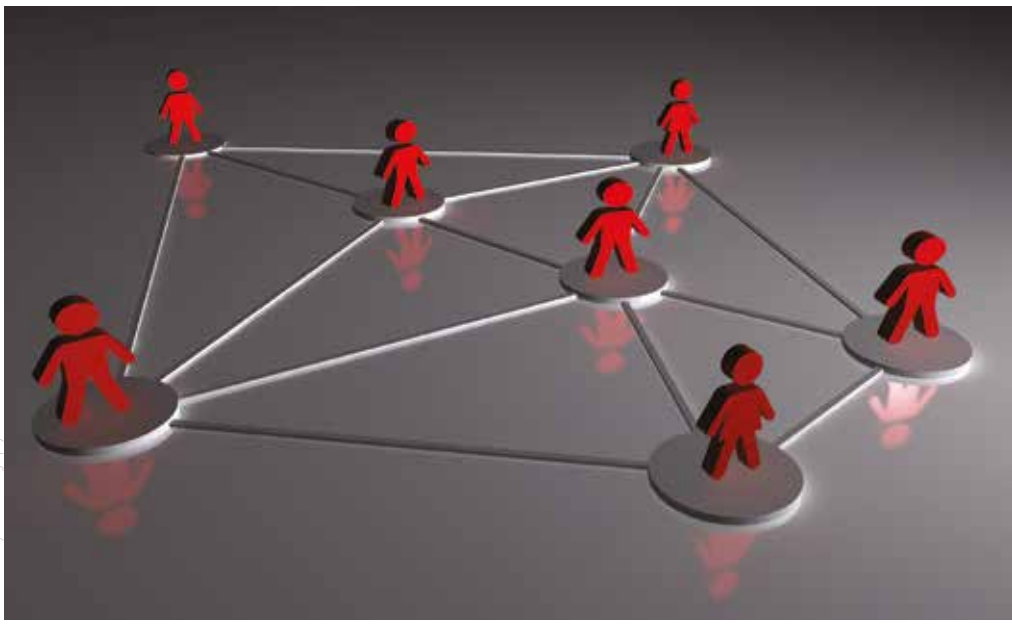
Red Teaming: What Pharma Can Learn From The US Military

LUCIE ELLIS lucie.ellis@informa.com

Bryce Hoffman, a former journalist turned commercial consultant and business author, is the first civilian to complete the US Army's Red Team Leaders Program – a military system designed post-9/11 to help organizations make better decisions under extreme circumstances. He believes this system can be used commercially to help companies implement critical thinking and make smarter decisions under pressure.

Hoffman spent several months participating in the US Army's Red Team Leader course to learn what he calls a "game changing" system used by the armed forces to stress test their strategies. Now, Hoffman is translating these military tools into a commercial business environment through his new book, *Red Teaming: How Contrarian Thinking Is Revolutionizing the Military – And How It Can Transform Your Business*.

In an exclusive interview with *Scrip*, Hoffman explains Red Teaming, how the process could be beneficial in business and why the pharmaceutical industry particularly should be paying attention to this military technique.



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> 'We have entered this era of incredible disruption and complexity in the market place. The tools leaders have used for years to set their strategies and make important decisions are ill-equipped for this new world'

WHAT IS RED TEAMING?

Red Teaming as a process was developed by the US military and intelligence community after the terrorist attacks in the US on September 11, 2001. Hoffman said the tools were developed to combat "a catastrophic failure of imagination" by the US security agencies that made possible terrorist attacks on 9/11 and led to poor decisions, by the military's own admission, in the invasions of Afghanistan and Iraq.

"Determined not to make those mistakes again they created a system that pulls together an array of critical thinking, contrarian analysis and group mitigation techniques to help organizations plan better, think more clearly about the choices they are making and evaluate alternative ideas or perspectives," Hoffman said.

He added that to date Red Teaming has been "incredibly effective" in the military and a lot of America's allies, including the UK, Canada and New Zealand, have adopted their own Red Team programs.

BUSINESS BENEFITS

Hoffman believes the military process could benefit business in the US and further afield. "We have entered this era of incredible disruption and complexity in the market place," he said. "The business tools leaders have used for years to set their strategies and make important decisions are ill-equipped for this new world."

While a lot of companies use similar approaches either informally or organically, Red Teaming is a set of tools and techniques for the management of critical decision making in varied situations. Hoffman noted that some newer businesses that have managed to seriously disrupt market places, such as online retail giant Amazon, are already known for their self-critical and contrarian cultures. But more established businesses, even very successful ones, could benefit from the introduction of novel strategies such as Red Teaming as the market place continues to rapidly evolve, he believes.

Red Teaming as a commercial tool is not commonly used yet, according to Hoffman, mainly because it is new to the sector. "Red Teaming was developed by the CIA and the US army: these are not organizations that typically share their work with the world," he highlighted, adding that while some of the individual Red Team ideas are older, the system itself has only been developed over the past 10 to 15 years. *Scrip* asked various pharma consulting groups about their familiarity with Red Teaming as a com-

mercial tool and none of those asked is using it yet. One consultant said: "There are many individuals and consultants with methodologies and books that promise much on the basis of some experiences and successes. Whether they work in a company facing different strategic challenges depends heavily on the context and individuals that apply the methods."

PHARMA RELEVANCE

While researching for his book Hoffman interviewed Marine Corps Red Team Lieutenant General Paul Van Riper, who described dealing with complex issues in combat as being like playing chess on a board where all the pieces are connected to each other by rubber bands; moving one piece pulls all the other pieces in another direction from where they were before and the board rearranges itself. "If you think about the challenges people are facing in the life science industry or the pharmaceutical industry, that description probably sounds very familiar," Hoffman said.

The traditional way to manage change in the industry is systems analysis, which involves breaking problems down to deal with each issue individually; but when developments or problems are interconnected this method can be flawed. "You might come up with a plan that works for one area of your business strategy but that could screw everything else up," Hoffman said. "Red Teaming was created to evaluate things like the war on terrorism – that's a very complex problem."

Making organizations more agile is also a big part of Red Teaming. "When I talk about Red Teaming, some people assume it will be a lengthy process. Sure, there are tools that take weeks to use but there are also tools you can use in as little as 15-30 minutes," Hoffman noted.

He outlined one example of a simple Red Teaming technique called pre-mortem analysis. This tool is for use before a strategy or plan gets final sign off or approval for action. "You gather your team together and say 'If this goes wrong, not kind of wrong but turns into an unmitigated disaster for our company, how could that happen?'," Hoffman said. Using pre-mortem analysis, management teams should think through what catastrophic failure looks like and work backwards to identify what would lead to failure happening. "You pull the lens back and look at where you are sitting today and how you might get to that catastrophic failure; the point is not to be negative but to simply look at the ways your plan could unravel so that you can strengthen it and account for those problems," Hoffman highlighted.

Hoffman has consulted with several companies and introduced Red Teaming as a strategy for critical thinking and for assessment of business plans. He said one key use for the tool is as a stress test for potential acquisition targets.

Whilst working with a Japanese company that was looking at acquiring an automobile supplier, Hoffman suggested the target was assessed using techniques from the Red Teaming tool kit. "We discovered that this

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ANALYSIS FROM THE FRONT LINE

Richard Veal, Global Director of Informa Pharma Consulting, describes types of simulation strategies that are similar to Red Teaming and explains how these methods are used by drug manufacturers. He shares examples from his experiences as a pharma consultant.

War gaming or as I call it "competitive simulation" is often used in the pharma world; Red Teaming is associated with this idea but is more of a military term.

Competitive simulation is not a new technique but it is being utilized more and more because it enables companies to generate, analyze and test a lot of scenarios in a short period time and in very dynamic ways. It is an excellent way for leaders to efficiently and effectively evaluate future market variables and mitigate risks. For pharma, these workshops are valuable because they can produce an incredible wealth of information across a broad array of stakeholders, and often lead to newly uncovered perspectives on how to anticipate and address market dynamics. The pharma industry is navigating so many moving targets right now, and pharma companies are constantly exploring broad scenarios when bringing a product to market. For example, the lack of clarity around the future of healthcare reform in the US had, and is still having, an impact on pharma's corporate strategies for both pipeline drugs and approved products.

Manufacturers use simulation techniques to create competitive environments that can get their internal teams to think differently, to extend the team's vision on how the market might react, and to put themselves in the role of how competitors might respond. These techniques can push teams to consider alternatives and different scenarios that they typically wouldn't think about. Often competitive simulations are whole day events.

One example: You are a dominant player in the rheumatoid arthritis space and a new product is about to reach the market from a competitor that could challenge your product or portfolio. You want your internal team to consider multiple variables and scenarios, and test how the events might unfold. Over the course of the simulation, you include different exercises so that at the end of the day you have created what you believe to be the battle plan of the competition and your own strategy and scenarios for winning against the new threat.

These workshops and exercises can take a lot of different forms and sometimes they are on more of a microscale. For example, how can one company win in the digital space as access to customers is becoming more and more limited. Or the simulation can be a head-to-head comparison between an internal brand and a single competitor. Alternatively, a session could focus on a specific drug portfolio and how its commercial strategy might have to change based on anticipated or unexpected market events.

Simulations are also good opportunities to bring together members from different business functions. Often management will want members from medical, marketing, access, as well as field representatives, to work together to leverage all their expertise in one moment. Along these lines, simulation exercises allow for employees from different disciplines to collectively participate regardless of bureaucracy or hierarchy.

CONTINUED FROM PAGE 5

target company had recently built several factories in Mexico to supply US automobile companies, which doesn't look like the best decision in the world now," Hoffman said. "What looked like a very attractive deal turned out to have a serious Achilles' heel; the company reevaluated that deal."

M&A is one area Hoffman always recommends Red Teaming because he thinks many companies "fall in love with a deal" and that can leave them blind to downsides. "Red Teaming is focused on identifying blind spots in decision making. No matter how smart we are, we all fall victim to an array of biases when we make decisions. The only way to overcome those biases is to have someone else look at our decisions with us with a critical eye," he said.

Red Teaming takes a plan or decision and breaks it down to focus on the assumptions the plan is based on, to make sure those assumptions are true (and likely to remain true) in all circumstances. "It's this deliberate challenging that makes Red Teaming different from other management systems and makes it so effective in M&A," Hoffman said.

NOT WHEN ENEMY IS IN THE WIRE

Hoffman said one thing the US Army course taught him was not to Red Team "when the enemy is in the wire." In other words, if the situation is urgent and calls for quick decision making, don't stop and Red Team the choice.

"You could use these techniques on any decision you make but in some cases that would be like using a sledge hammer to drive a nail into a wall," Hoffman said.

For example, if a company is looking to buy real estate for a new office in a new territory, management could Red Team these plans or they could simply use a real estate agent. "The answers are out there," Hoffman noted. "On the other hand, if you are thinking about expanding your small molecule research into a line of pathogens you haven't previously worked on before, that could be something that merits taking the time to Red Team. Is it worth the risk to open that new line of research?" he said.

Bryce Hoffman's latest book, Red Teaming: How Contrarian Thinking Is Revolutionizing the Military – And How It Can Transform Your Business, is available online and in stores.

Published online 30 June 2017

Setting The Course For Takeda's R&D Future

In the first of this two-part interview, conducted at **Takeda Pharmaceutical Co. Ltd.**'s headquarters in Tokyo during one of his regular visits to Japan, Dr. Andrew Plump, the Japanese company's chief medical and scientific officer, outlines the strategic thinking behind Takeda's recent R&D reorganization and its decision to focus on selected therapeutic areas.

IAN HAYDOCK: *What attracted you to Takeda in the first instance?*

ANDREW PLUMP: I was not sure about leaving Sanofi [where he was SVP, Research & Translational Medicine and deputy to the president of R&D] at first because I had not completed what I wanted to do there. When I first received a call from the [Takeda] recruiter, I said no as I wasn't sure I'd be qualified for the job. Eventually I acquiesced.

The first conversation Christophe [Weber, Takeda CEO] and I had, we just clicked, it was a shared vision of what it means to work in a global environment, and secondly and how you effectively advance innovation in R&D in our industry today. We were very much aligned. He's honest, he's direct, he's transparent.

IH: *What did you see as your biggest single challenge when you joined Takeda?*

AP: There's a lot that we've done, but I thrive at looking at an environment, understanding what the challenges are, developing the rationale and case for change and then enacting that change. I love that, if I believe that it's the right thing to do, I can rally people around that. The basic challenge always remains the same though: as the innovation bar gets higher, how do you deliver innovation to patients and at the same time, to the company?

IH: *Did you find the corporate culture different (from Sanofi) when you came to Takeda?*

AP: Yes absolutely. Every company has its own ethos, value system and culture, with some similarities. I don't think Christophe would have hired me if I hadn't had that experience at Sanofi. I have a sense for the people around me, and an experience of working in a truly international setting. Some people said you should be careful working for Japanese company, "everything's going to come back to Tokyo, it's going to be really bureaucratic and complex".

There are issues around process that we are trying to sort out, but relative to where I sit, this [Takeda] has the simplest governance structure, and I have not seen another company as decentralized as much as Christophe has made this organization. So ironically a lot of stereotypes [of a Japanese company] don't exist.

IH: *And has that situation changed quite a lot since you joined?*

AP: You could see it heading in that direction, in terms of Christophe decentralizing his business heads. He's deeply experienced in working in an international setting, and if you try to such decision-making back to a central point, you'll fail. You need to instill a common value system,

including focus around patients. But you need to operate very locally.

IH: *Last year, there was a major R&D reorganization. What were some of the major factors behind that from your perspective?*

AP: The driver for the transformation was a change in strategic direction. The world is changing, the level of innovation that is required, the explosion of science that you can now leverage, and the regional dynamics were completely different than a decade ago. That and the fact that the past 10-15 years have not been that productive - not only at Takeda – and we had a clear case for change.

We decided on three main therapeutic areas. Takeda was a platform company agnostic to disease area, but around 60% is non-small molecule, an area like oncology more like 75%, so we agreed to focus and go extremely deep, understand clinical regulatory and market/payer and we decided to go by therapeutic area was the way to go.

The decision played on where we had strengths, where the science was most advanced, and what we had in the pipeline. For GI, we didn't have much of a pipeline besides foundational product *Enyvio* [vedolizumab], and that it is incredibly innovative. It's so rare to be the only-in-class. In oncology, we had the Millenium acquisition and *Velcade* [bortezomib] and *Adcetris* [brentuximab vedotin] and there is so much opportunity [in oncology], and CNS was perhaps the one that raised most eyebrows given the challenges in CNS, but I look at that in a couple of ways.

I love the idea of being in an area where we weren't just following but leading, but we had made investments over the past five years and innovative early stage projects, so it looked like a great opportunity to match unmet medical need with science at the leading edge and a very early pipeline.

IH: *Will that therapeutic focus change in the future?*

AP: No change. We are committed to staying the course. In 10 years it might change but the next three to five years we are fully committed, and it's been incredibly effective. There are a few areas where the focus has driven our decision-making. There is no way we'd have been able to sign these 50-plus deals over the past 18 months without this focus. Quality of science and partner are key, but decision-making is so easy.

When I first got here, things were coming from all angles and there was no way to compare them, but it has made decisions and agility much better. And I don't know if we would have made the **Ariad** acquisition without this focus or so quickly. *(Also see "Major Takeda Boost To Japan's iPSC Ambitions" - Scrip, 20 Apr, 2015.)*

IH: *Do you find that it also affects the companies coming to see you?*

AP: Absolutely. So, one of the areas that cuts across is regenerative medicine, and we said we want that to be part of our future. We have the novel [induced pluripotent stem cell] partnership with Professor Yamanaka [at Kyoto University]. For the recent **GammaDelta** partnership [for gamma delta T-cells] they approached us. *(Also see "Takeda Picks Next Big Thing In Immunotherapy: Gamma Delta T Cells" - Scrip, 15 May, 2017.)*

IH: *What are some of the main challenges and benefits of pursuing this R&D externalization strategy?*

AP: If you look historically, there's no company that's not done it. They invest in internal labs and are then forced into M&A or major in-licensing, or take the decision to spend less and do it better. I can't think of any company that's not had to go out and buy innovation. All big pharma companies have gone through this sequence of hyper-investing internally and then that doesn't work so they in-license, which has typically not returned investment because you are filling gaps, so you end up doing a merger or acquisition, which is incredibly disruptive.

You go back around a decade ago, most of the medicines came from pharma companies. Today, the majority emerge from biotech labs. If you look at where innovation is greatest, in biotech it's in technology, which is very hard to do in a pharma company, which don't like to let things die. If you're in an entrepreneurial setting, if something's not going to work, you'll just go away.

Gamma Delta was blue sky thinking using tissue-resident T-cells. It would have been really tough for us to do internally. If you don't do it this way, eventually you're going to pay more to bring in innovation.

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The second part of this interview will appear shortly in Scrip.

From the editors of *PharmAsia News*.

Biological E Taps Takeda Tech For Combo Vaccines

Takeda Pharmaceutical Co. Ltd. has signed two licensing agreements with major Indian vaccines manufacturer **Biological E Ltd. (BE)** for the transfer of technology the partners say will enable the development, manufacture and delivery of affordable combination vaccines to lower income countries.

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Takeda will allow BE to access its technology for the bulk production of measles and acellular pertussis vaccines, and will also provide related technical services such as infrastructure review support, production and quality control training, process development and preclinical study design, needed for clinical and initial commercial batches.

As part of the new arrangement, BE will have rights to use the transferred Takeda measles vaccine technology in a combination measles-rubella product, and to use the acellular pertussis technology in any combination vaccines containing pertussis, such as a diphtheria, tetanus and pertussis (DTaP) product.

Privately held BE will then be responsible for manufacturing scale-up and conducting and funding other development activities, and will hold commercialization rights to the combination products in India, China and other defined markets in low- and middle-income countries with major unmet health needs for vaccines.

Anju Ghangurde & Ian Haydock
Published online 28 June 2017

View manufacturing plans here: **http://bit.ly/2uBYFTU**

Big REVEAL: Merck's Anacetrapib Surprises With Success, But What Next?

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Years after **Pfizer Inc.** dramatically discontinued the first CETP inhibitor torcetrapib – blowing a hole into a mechanism once hailed as the natural successor to the statins – **Merck & Co. Inc.** has breathed new life into the hypothesis by proving a cardiovascular outcomes advantage for its anacetrapib in the 30,000-patient REVEAL trial.

Merck announced on June 27 that the CVOT study had met its primary endpoint, significantly reducing major coronary events (a composite of coronary death, myocardial infarction, and coronary revascularization) compared with placebo in patients at high risk for cardiac events who were already receiving atorvastatin.

No further details were released except to say that so far, the drug's safety profile was generally consistent with that seen in its previous studies, including an accumulation of anacetrapib in adipose tissue. The full results of the four-year study will be presented at the European Society of Cardiology meeting on Aug. 29.

REVEAL makes anacetrapib the first inhibitor of the cholesteryl ester transfer protein to show an effect on CV outcomes after others in this class failed, raising huge doubts over the mechanism. Pfizer's pioneering product torcetrapib was dropped back in 2006 after an increase in CV death despite an increase in the "protective" HDL-cholesterol with the product, but it was hoped that the problem lay with the molecule itself rather than with the mechanism more broadly. Subsequent outcomes trial failures have also raised questions about the value of raising HDL.

Development of other CETP inhibitor candidates continued, only for them to fall along the way – **Eli Lilly & Co.** ended the Phase III program for its evacetrapib in late 2015 after the 13,000-patient ACCELERATE CVOT study was stopped for futility. *(Also see "Who Suffers From Lilly's Evacetrapib Failure?" Scrip, 12 Oct, 2015.)* And **Roche**'s dalcetrapib failed in the dal-OUTCOMES trial in 2012, although this product has since been acquired by **DalCor Pharmaceuticals**, which is hoping to find a genetic marker to keep it alive. *(Also see "DalCor To Develop Failed Roche CETP Inhibitor In Genetic Subgroup" Scrip, 22 Apr, 2016.)* Also still in development is **Amgen Inc.**'s AMG-899 at the Phase II stage.

'Overall, we get a sense that the magnitude of benefit is likely modest'

COLD FEET?

The string of failures has left Merck pretty much in command of the field, but the company seems uncertain of its next steps. It has said merely that it planned to review the REVEAL results of the trial with external experts, and would "consider whether to file new drug applications" with the FDA and other regulatory agencies.

This reticence was pounced upon by analysts. "The cryptic language in the press release suggests a less than definitive risk/reward profile of the drug," Leerink Swann's Seamus Fernandez said in a June 27 note.

Tim Anderson at Bernstein said that their best guess as to the potential issues related to two things: anacetrapib's very long half-life, which means it accumulates in tissues, such as adipose tissue; and the size of its effect on heart attack rates, which they suggest may not be clinically meaningful.

"If anacetrapib ends only up looking like a weak LDL-lowerer (without any clear clinical benefit coming from the HDL raising it also causes), because of the tissue accumulation issue and the presence of generic cholesterol drugs (statins, and even Merck's own *Zetia*), then the company might reason that the commercial case to file for approval is a weak one," Anderson said.

Fernandez was also worried at the mention of accumulation in adipose tissue. "We believe the mention of this highlights a potential long-term regulatory concern – one that we believe would require a very robust impact on key CV events – like death – for [Merck] to file anacetrapib," he commented.

OPPORTUNITY

The size of the trial means both that it's enough to provide a definitive answer on anacetrapib, but also that even a small effect could be statistically significant, Fernandez pointed out. "We estimate this could be a relative risk reduction well below 10%, which we would argue is not clinically significant unless the benefit was driven almost entirely by CV death," he said. "We remain skeptical of the opportunity for anacetrapib and believe the risk of launching this drug given potential safety uncertainty around accumulation in adipose tissue may substantially outweigh the product's value."

But Umer Raffat from Evercore ISI believes Merck should take a punt anyway. "In fact, I would argue: why not? (especially after spending hundreds of millions on this trial and meeting primary endpoint). Ultimately, there is a need for added control beyond statins … if you need modestly more benefit, you could consider Vytorin and now anacetrapib … if you need MUCH more LDL benefit, you could consider PCSK9s," he said.

MUCH REMAINS TO BE SEEN

A lot will rest on the size of the benefit seen when the full data are released, and by extension the commercial upside for Merck, given that most observers had expected the trial to fail.

In this, its comparison with *Vytorin*'s effect in IMPROVE-IT will be illustrative. While the CETP inhibitors were moving through the clinic (mostly to oblivion), Merck had success with the major CVOT trial for its older combination dyslipidemia product *Vytorin* (ezetimibe plus simvastatin) – showing a more than 6% benefit and hitting statistical significance in the 18,000-patient study. However, the data did not convince the FDA to add the CV risk reduction claim to its label. *(Also see "Merck Fails To Win Zetia/Vytorin CV Risk Reduction Claim" Scrip, 17 Feb, 2016.)* Although sales for the Zetia/Vytorin franchise have slackened recently, revenues for 2016 still hit $3.7bn.

Raffat points out that while REVEAL was powered to show a 15% relative risk reduction, the fact that it has met its primary endpoint does not mean that it was as effective as this. "REVEAL is an even bigger trial [than IMPROVE-IT] … so perhaps it could have hit [statistical significance] at as low as about 5% potentially," Raffat said. "Overall, we get a sense that the magnitude of benefit is likely modest … perhaps in single digits."

Credit Suisse analysts are maintaining their current estimates for anaceptrapib, including peak sales of $851m in 2026, until they see the full data at the ESC meeting. But the Bernstein analysts are more positive about anacetrapib's potential, estimating 2025 revenues of $1.65bn as compared with consensus of $670m.

"We have long maintained that the market was overly negative on the odds of anacetrapib working. This is because the first two failed CETP inhibitors had no LDL effect (they only raised HDL) – by contrast, Lilly and Merck's drugs both raised HDL and lowered LDL," Anderson said. "And Lilly's drug was studied in a much smaller, shorter trial than Merck's, and also in a slightly different patient population – this was Lilly's attempt to yield results more quickly than Merck, but the strategy backfired."

A version of this article has also been published in the Pink Sheet.

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What Now For Lonely Stada? Bain & Cinven Takeover Bid Collapses

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Bain and Cinven's strong €5.3bn ($5.6bn) takeover bid for German generics company **Stada Arzneimittel AG** has collapsed because not enough shareholders got onboard for a public takeover.

Stada's share price (XETRA) dropped to €56.51 on June 27, the lowest price since April, after news broke that the acquisition had fallen apart, but the target company's stock stabilized by the morning of the following day to reach €60.38.

The bid for Stada from the private equity groups had been viewed as a "great deal" by analysts at Jefferies, who said in a June 27 note that they were surprised by the takeover miss. "We are perplexed as to why investors didn't take the deal," Jefferies analysts said, adding that previously they had valued a best-case offer at €65 per share.

The takeover offer did not win enough shareholder support after just 65.52% of Stada's equity capital signed up for the deal, falling short of the 67.5% acceptance threshold.

Missing out on Bain and Cinven's offer is a major setback for Bad Vilbel, Germany-based Stada. Analysts at Natixis said the fact the offer did not win enough shareholder support is "staggering."

"We fail to see what shareholders who did not tender their shares hope to gain, since we see the valuation of €66 [per share] as perfectly generous for the group in its current state," Natixis analysts said in a June 27 note.

The best-case scenario now for Stada investors is a counter-offer but none seems to be on the table and Bain and Cinven's takeover bid was already the best of three put forward earlier this year.

Natixis suggested Stada shareholders could be gambling on an improved offer from Bain and Cinven, but they called this option a "risky" move.

In the wake of the takeover failure, Stada's management has unsurprisingly confirmed the company's growth targets for 2017, with sales expected to come in between €2.28bn and €2.35bn (Jefferies' forecast is slightly lower that the company's own at €2.27bn). Stada also highlighted that termination of the takeover offer will have no effect on its medium-term growth targets for 2019, which include sales forecasts of €2.65bn to €2.70bn, EBITDA of €570m to €590m and net income expectations of €250m to €270m.

However, Jefferies analysts are not optimistic the group can meet these goals. "Organic growth in the business has historically missed our expectations," they said.

M&A DRAMA

Bidding started for Stada in February this year, with Cinven putting in an original offer of €56 per share for the company. Advent also entered a bid for the German drug maker, but details of this offer were not disclosed. A third unknown rival bidder was also in the running at that time.

The M&A drama follows a long campaign by activist fund Active Ownership Capital to remove Stada's former chair and members of its supervisory board and replace them with management more open to takeover. *(Also see "Stada Braces For Battle With Activist Investors" Scrip, 5 Jul, 2016.)*

Stada is a leading generics company in Europe, comprising two main segments: a non-branded generics business focused on low pricing and active ingredient marketing, and a branded products business. Germany is its biggest market, but Stada has expanded and diversified its geographical revenue base by building an international sales infrastructure in Eastern Europe and CIS countries.

Generics make up 58% of sales for the German group, which generated total sales of €2.1bn in 2015 and has some 10,500 employees worldwide.

Bain and Cinven were expected to use Stada's products and infrastructure as a nucleus around which to add smaller acquisitions, mostly in Europe, leading to an eventual exit. *(Also see "Acquired Stada To Act As 'Core' For Future Bain and Cinven Bolt-Ons" Scrip, 10 Apr, 2017.)*

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CONTINUED FROM COVER

Still, the arrival of Novo's Saxenda onto the US obesity market was the catalyst for an expected near-doubling of its size by 2016, Datamonitor Healthcare recently forecast. It

A Frog Eat Frog World

Shutterstock/By Brute Vielklene

'I would expect semaglutide to cannibalize most of Saxenda's revenue'

presumed growth of other current obesity products, *Qsymia* (**Vivus Inc.**'s phentermine/topiramate) and **Orexigen Therapeutics Inc.**'s *Contrave* (bupropion/naltrexone), will also contribute, but use of **Eisai Co. Ltd.**'s *Belviq* (lorcaserin) and **Roche**'s *Xenical* (orlistat) meanwhile was expected to reduce.

Datamonitor Healthcare had forecast Saxenda to reach $784m in revenue in the US in 2026 and the entire US market to be valued at $1.2bn in the same year.

But semaglutide could change all that. "Considering the balance between semaglutide's superior efficacy compared to current therapies and the many factors dissuading use of weight loss drugs, I would expect semaglutide to cannibalize most of Saxenda's revenue, as well as taking some market share from the oral therapies and expanding the weight loss market, to a small extent," Shannon said.

However, he admitted that this model reflected current prescribing trends in which less than 1% of overweight and obese patients receive drug treatment. "Current treatments are only forecast to be used in a small percent of obese patients, and while I would expect Saxenda improve in this, there are many other factors that would have to change in order to significantly increase the percent of patients receiving pharmacological therapies," he said.

There are a number of other products in mid-stage development for obesity. Sanofi is developing a GLP-1 product in Phase II, SAR439977 (langlenatide), while other candidates include **Johnson & Johnson**'s SGLT2 inhibitor *Invokana* (canagliflozin) and **Novartis AG**'s SGLT-2 inhibitor LIK066.

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Alkermes' ENLIGHTEN Hints At Benefit

The first of two Phase III ENLIGHTEN studies for **Alkermes PLC**'s combination product for schizophrenia, ALKS 3831, show it has at least equivalent efficacy to olanzapine alone, but the study was too short to tell whether the combination can lessen the weight gain problem that plagues the older product.

The broad-spectrum antipsychotic product contains the novel drug samidorphan co-formulated with the established antipsychotic agent, olanzapine, in a single bilayer tablet. The idea is that it would provide the same efficacy as the mainstay antipsychotic but with more favorable weight and metabolic properties.

Overall, ENLIGHTEN-1 gave a hint of improved efficacy for ALKS 3831 over olanzapine and no real signal for a weight-gain benefit, although more data are needed to see if either finding will hold true.

The study compared ALKS 3831 with placebo over four weeks in 403 patients experiencing an acute exacerbation of schizophrenia. Patients were randomized to receive once-daily, oral tablets of ALKS 3831 (10 mg samidorphan co-formulated with either 10 or 20 mg of olanzapine), olanzapine (10 or 20 mg) or placebo for four weeks.

The trial met the pre-specified primary endpoint, with ALKS 3831 demonstrating statistically significant reductions from baseline in Positive and Negative Syndrome Scale (PANSS) scores compared with placebo at week four ($p<0.001$). Olanzapine achieved similar improvements from baseline PANSS scores, compared with placebo, but with a p value of 0.004.

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Read full story here:
http://bit.ly/2uFLIZd

Alnylam's Overshadowed Givosiran Comes Into The Phase III Light

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Alnylam Pharmaceuticals Inc. is to start a Phase III trial program for its antisense product givosiran (formerly known as ALN-AS1), by the end of the year on the back of new Phase I data suggesting it gives consistent reductions in attacks of acute hepatic porphyria (AHP), an ultra-rare condition.

Though from a small number of patients, analysts are encouraged by the data for the product which has been overshadowed by Alnylam's more obvious pipeline assets, patisiran and fitusiran; the company is busy building its economic case for the porphyria therapy.

Most eyes are awaiting the Phase III data for patisiran in familial amyloid polyneuropathy (FAP), due in September, especially given the recent safety setback for rival **Ionis Pharmaceuticals Inc.**'s inotersen, and a filing is hoped for by year end. *(Also see "Ionis Touts Inotersen's Convenience As Phase III Safety Data Disappoints" Scrip, 15 May, 2017.)* Observers are also eager for details of the regulatory pathway for its hemophilia therapy fitusiran. *(Also see "Alnylam's Fitusiran Could Provide Comprehensive Hemophilia Therapy Option" Scrip, 29 Aug, 2016.)*

AHP represents a very significant unmet need, and as a once-monthly subcutaneous investigational RNAi therapeutic with a potential to prevent debilitating porphyria attacks, the company believes givosiran "could be a transformative therapy for patients ", the company's EVP of Research & Development, Akshay Vaishnaw, told a conference call.

Analysts at Credit Suisse were intrigued: "We think the porphyria program is an interesting fast-to-market program in a high unmet need area." They are forecasting unadjusted peak sales of $475m.

Jefferies analysts concurred: "We believe givosiran is an underappreciated asset for Alnylam, and the Phase I results … showed positive efficacy signals, supportive of the therapeutic potential in an indication with high unmet need." They think the product could command a price of about $300,000 with an estimated market entry of 2021.

Givosiran is an RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) and already has both Breakthrough Therapy and PRIME designations from the FDA and EMA. Alnylam has also retained exclusive global rights to the product and intends to develop and commercialize givosiran on a global basis, after **Sanofi** decided not to take up an option for the program last November. The French company decided instead to co-develop and co-commercialize Alnylam's fitusiran for hemophilia and rare bleeding disorders.

The only available treatment for acute hepatic porphyria attacks is hemin, a preparation of heme administered via central intravenous line, and there are no approved prophylactic treatments, although glucose and hemin are sometimes used in this manner in patients who experience recurrent attacks.

However, chronic administration of hemin may result in renal insufficiency; iron overload, which can in turn lead to liver cancer; systemic infection, secondary to central venous access; and in some instances, tachyphylaxis, Vaishnaw added.

ALAS1 is an enzyme that acts upstream of the genetic defects in acute hepatic porphyrias and the enzyme responsible for overproduction of aminolevulinic acid (ALA) and porphobilinogen (PBG), the toxic heme intermediates that mediate acute attacks and chronic porphyria symptoms. The hypothesis is that silencing ALAS1 with givosiran will lower levels of ALA and PBG, thereby reducing the number and frequency of porphyria attacks in patients.

DATA

New data presented at the the International Congress on Porphyrins and Porphyrias (ICPP), in Bordeaux, France, from the first three unblinded treatment cohorts from Part C of Alnylam's ongoing double-blind, randomized, placebo-controlled Phase I study, showed that givosiran-treated patients (N=9) experienced a mean 63% reduction in the annualized number of all porphyria attacks relative to the run-in period attack rate, with consistent effects observed across a wide range of baseline attack rates.

Evaluating only attacks that were treated at a healthcare facility or with hemin, givosiran administration was associated with a mean 73% reduction in annualized attack rate relative to placebo during the treatment period. In addition, a 73% mean decrease in annualized hemin doses relative to the run-in period was reported.

Another new analysis showed that the observed reduction in annualized attack rate was associated with the degree of ALA and PBG lowering, the company said. The product was generally well tolerated.

In addition, initial results from an ongoing open label extension study show consistent reductions in porphyria attacks with continued givosiran therapy.

ECONOMIC IMPACT

Alnylam is also arming itself with economic data to support the value of the product and reported natural history data from its EXPLORE study of 112 AHP patients in 13 countries which evaluated health care utilization and costs associated with AHP in recurrent attacks.

This found the mean attack rate was approximately five attacks per person per year, with a mean attack duration of seven days, translating into, on average, five weeks spent per annum in the hospital. An analysis of costs associated with acute hepatic porphyrias and recurrent attacks reveal the average estimated annual expenditure per patient ranges from $400,000 to $650,000.

"These analyses only incorporate direct costs, such as hemin use, office time, ER visits and overall hospital visits, et cetera, and do not reflect indirect costs, such as the costs associated with lost productivity or workdays for both patients and their caregivers," Vaishnaw said.

The planned randomized Phase III trial is expected to include 50-100 patients with recurrent attacks of acute intermittent porphyria (AIP) and have endpoints of change in annualized attack rate compared to baseline, ALA, PBG and ALAS1 levels, hemin usage, hospitalization, quality of life, safety and tolerability.

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Full Circle: David Hung Looks Forward To Axovant's Alzheimer's Data, Reflects On Medivation

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Now that David Hung is heading up **Axovant Sciences Ltd.**, the high-profile CEO's drug development career seems to be coming full circle, since **Medivation Inc.** got its start by developing dimebon in partnership with **Pfizer Inc.** for Alzheimer's disease.

Axovant's future hinges on the Phase III results for its Alzheimer's disease therapy intepirdine, due in September. Hung's ambitions for Axovant involve building the firm into a premier neurology company – much in the same way Medivation had become a leading prostate cancer company before being sold to Pfizer for $14bn last year. After dimebon's failure in 2010, Medivation's focus shifted to other programs, including *Xtandi* (enzalutamide) for prostate cancer.

Scrip spoke with Hung during the recent BIO International Convention about Axovant's prospects if lead drug candidate intepirdine succeeds – and what will happen if it joins the ranks of Alzheimer's disease failures. He also discussed Medivation, a company he didn't plan to sell.

Hung took some time to consider multiple job offers after Pfizer closed its purchase of Medivation in September 2016, just a month after beating out **Sanofi** for the deal. *(Also see "Pfizer's $14bn Medivation Buyout Shows How Far Pharma Will Go In Oncology" Pink Sheet, 22 Aug, 2016.)* He landed at Axovant only about two months ago, but hit the ground running. *(Also see "Appointments: Sanofi, Recipharm, Axovant, e-Therapeutics & Diplomat" Scrip, 14 Apr, 2017.)*

Axovant's active pipeline didn't leave Hung with much time to get up to speed, since results from the Phase III MINDSET clinical trial in mild-to-moderate Alzheimer's disease are expected for the 5-HT6 receptor antagonist intepirdine (RVT-101) in September. The drug hails from the same class as idalopirdine from **H. Lundbeck AS** and **Otsuka Pharmaceutical Co. Ltd.**, which failed in two Phase III trials. *(Also see "Can Axovant's RVT-1 Redeem 5HT6 Class After Lundbeck's Idalopirdine Failure?" Scrip, 8 Feb, 2017.)* However, Axovant believes that it has given intepirdine the best chance for a different outcome than idalopirdine, chief development officer Lawrence Friedhoff told *Scrip* in December.

HUNG: 'PASSIONATE' ABOUT ALZHEIMER'S

"I started Medivation around an Alzheimer's drug," Hung pointed out at BIO. "It's something I've always been passionate about and I think it's one of the most important diseases in the world." He thinks that intepirdine offers "one of the best shots at hitting its endpoints in Alzheimer's of any drug in 15 years," but "even though it's still a risky space, I think that some risks are just worth taking."

Intepirdine also is being studied in the Phase II HEADWAY trial in dementia with Lewy bodies (DLB), a disease with about 1.1m patients in the US alone and no approved drugs in the US or Europe. The HEADWAY study, expected to report out in the second half of 2017, could serve as a pivotal trial for US FDA approval if MINDSET also has positive data. Axovant's pipeline also includes the 5-HT2A receptor agonist nelotanserin (RVT-102), which is in Phase II for REM sleep behavior disorder in DLB and visual hallucinations in DLB, and the combination of RVT-103 and RVT-104 – a pair of glycopyrrolate and cholinesterase inhibitors – in Phase I for Alzheimer's disease and DLB.

"We're looking at lots of different things [to potentially license or acquire], but we're trying to really focus on what we have on our plate right now. We raised another $140m when I joined, so we have a pretty full war chest now," Hung said. The exec noted that he's personally interested in therapies that may be able to treat spinal cord injuries, blindness and neurosensory hearing loss.

"If MINDSET hits, we're probably going to do a lot more business development, but probably even more upstream, earlier-stage, more risky, new MOA – some really swing-for-the-fence approaches," Hung said. "If MINSDET isn't positive, we're probably going to use our cash to get through our other trials, to get nelotanserin developed, intepirdine in DLB, but also potentially license in later-stage programs where we can get a sooner readout, just because investors at that point will be more nervous and less patient."

Axovant just started talking to payers about pricing and reimbursement for intepirdine, in case the drug is successful in Phase III.

"I think this is going to be a major issue, because this is a huge patient population, but it's also a really important one," Hung said. "If you look at the cost of nursing home care, as an example, every month that you can delay nursing home placement is a tremendous cost savings to the system. We have to make sure we'll make a compelling case as to why this drug is so beneficial to patients and families."

XTANDI'S VALUE STANDS, DESPITE ZYTIGA CHALLENGE

Medivation's commercial product Xtandi has enjoyed favorable prescriber opinions in the post- and pre-chemotherapy setting for metastatic castrate-resistant prostate cancer, ostensibly driving Sanofi's and Pfizer's interest in the company, and Hung expects the drug to continue to do well. *(Also see "New Xtandi data bolster case for pre-chemo use" Scrip, 23 Jan, 2015.)* However, Pfizer reported disappointing first quarter 2017 sales for the drug due to higher demand that was offset by greater interest in patient assistance programs for the androgen receptor inhibitor. *(Also see "Xtandi Sales Disappoint Pfizer, Returning Focus To The High-Priced Deal" Scrip, 2 May, 2017.)*

Johnson & Johnson's competing prostate cancer drug *Zytiga* (abiraterone), a CYP17 inhibitor, recently delivered positive results in an earlier treatment setting. *(Also see "Janssen's Zytiga Shines At ASCO But Prostate Cancer Pipeline Progress May Dampen Impact" Scrip, 4 Jun, 2017.)* However, Pfizer and partner **Astellas Pharma Inc.** revealed plans to amend the protocol for the ongoing PROSPER study, which – if positive – could help Xtandi compete. *(Also see "Pfizer/Astellas Amend Trial To Position Xtandi In Early Prostate Cancer" Scrip, 12 Jun, 2017.)*

"I still feel that Xtandi has very significant advantages in not requiring steroids, which is a huge issue for patients, and I think

the mechanisms are different between Xtandi and Zytiga," Hung said. "I think [J&J] has done a very good job developing their drug, but I do continue to believe that there are some mechanistic advantages of Xtandi's approach to the disease. Pfizer has its work cut out for it and needs to move aggressively. It's competitive out there, so they need to really lean in and match Zytiga's data. They do have the PROSPER study reading out, so hopefully that will be a positive. At some point, it's just trench warfare that I'm sure Pfizer knows how to do."

Hung lamented Medivation's sale to Pfizer in a "fireside chat" during the BIO meeting on June 20, expressing some frustration that Sanofi's unsolicited bid forced the company to consider a sale when its executives didn't have plans seek a buyer for the firm. *(Also see "Medivation Rejects Sanofi's Latest Bid, But Enters Confidential Negotiations" Scrip, 6 Jul, 2016.)*

"We weren't looking to sell. We were able to create tremendous value in a relatively short time – a 21,000% return in 13 years," Hung told *Scrip*. "I don't think it was a fluke; I think we could've continued to do that. I think that there are things that a smaller, more nimble company can do that a larger company can't do. That said, it wasn't my decision. It never is as a public company, it's the decision of the shareholders. That's what they voted on and our job at that point was to get them the best price and that's what we did."

Asked about similarities and differences between Medivation and Axovant, he noted that the objectives for both companies are the same.

"Our goal is to make our company the best company in the world in our indication. We strove to make Medivation the best prostate cancer company in the world and I think we did," Hung said. "Now, my goal is to make Axovant the best neurology company in the world and I think if this [MINDSET] trial hits, then we will be, just by virtue of the fact that we're the only one with [a new] Alzheimer's drug for probably for the next 10 years."

He added: "One thing I do like about our situation at Axovant is that since we're 70% controlled by **Roivant Sciences GMBH**, which is a private company, hopefully we can maintain our independence longer and develop our company more fully, in the way that I wanted to do at Medivation, and become the world leader in neurology. You never want to kill the golden goose. When you have a high-performing team and they're doing good stuff, you want to keep them going."

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ImCheck Therapeutics Pursues IO Antibodies

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The emerging French biotech, **ImCheck Therapeutics SAS**, is developing a new generation of antibodies that act at novel sites in immune cell co-signaling pathways, and two of its compounds could enter clinical studies at the beginning of 2019.

"Checkpoint inhibitors block the interaction between immune cells and cancer cells, but we have targets and mechanisms of action that are different to PD-1 and CTLA4, and the expectation is our research could lead to antibodies with better efficacy than other checkpoint inhibitors," said recently appointed CEO Pierre d'Epenoux in an interview with *Scrip*.

One of the company's founders, Daniel Olive, professor of immunology at Aix-Marseille University (AMU) and Marseille's Paoli-Calmettes Cancer Institute, is a leading authority on immuno-oncology and adaptive and innate immunity including the role of gamma-delta T-cells, d'Epenoux noted.

ImCheck Therapeutics is not alone in looking at gamma-delta T-cells, with the aptly named UK biotech, **GammaDelta Therapeutics Ltd.** also active in the field.

The Dutch company, **Gadeta BV**, is also evaluating changing T-cell receptors to become more active against cancer cells.

ImCheck Therapeutics was spun out of the Paoli-Calmettes Institute in 2015, with intellectual property licensed from the French governmental technology transfer agency, Inserm Transfert, and the Southeast France technology transfer accelerator, SATT-SE. In early May, 2017 ImCheck Therapeutics raised €20m in a Series A financing round from corporate and institutional investors. "It was considered remarkable that a French biotech company could raise that amount of money at such an early stage in its development," d'Epenoux commented.

The company now has a great mix of investors, according to d'Epenoux. The investors were led by Boehringer Ingelheim Venture Fund (BIVF), Kurma Partners and Idinvest, and those were joined by Gimv and LSP (Life Science Partners).

ImCheck Therapeutics' product pipeline includes two potential first-in-class immunomodulatory antibodies and several discovery programs, for targets that have immune-modulating roles in both innate and adaptive immunity. Of the two antibodies expected to enter clinical studies in 2019, one is targeted at BTLA (B- and T-cell lymphocyte attenuator), and the other target has not been disclosed. "We will need further funding in the future to accelerate other research, and we are also attracting attention among the wider biotech/pharma sector with our science," noted d'Epenoux.

The ImCheck Therapeutics executive noted that monotherapy with marketed checkpoint inhibitors, and with different combinations, still leaves a significant proportion of patients who do not respond to such inhibitors, and are potential candidates for different therapies.

As for the company's location, d'Epenoux said Marseille and its surrounding region has a lot to offer in terms of research institutes, universities and hospitals, and is growing rapidly, and might be in a position to rival more established European biotech clusters, such as those in Munich, Cambridge and London, in the not too distant future.

D'Epenoux is an experienced biotech and pharmaceutical executive, having most recently been chief strategy officer at the Paris-based biotech Theravectys. Before that he was head of strategy and business development, Europe, at French big pharma **Sanofi**.

From the editors of Start-Up.

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Mehta Analysis: Shaming Biopharma Managers

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President Kennedy successfully persuaded US steel industry executives to manage their price increases responsibly for the collective good by shaming them from his pulpit. Would such a bully pulpit offer an effective answer to balancing the biopharma budgets?

Let us fast forward two generations from the early 1960s to assess what has changed.

First, self-interest has gained primacy today, at the same time as bipartisan decorum and the sense of common good have declined. The ability to publicly shame an individual or a company, let alone a whole industry, in this environment is open to debate.

Second, with the US healthcare industry accounting for 18% of domestic GDP (and a still considerable 10% of GDP in the rest of the world), multiple stakeholders have a lot to lose, making it challenging even for a president to target such a diverse group with conflicting self-interests. (In fact, as we write this, reports from Washington indicate that a president who had called for price controls and drug importation while accusing the biopharma industry of getting away with murder has now succumbed to the same lobbying that tied his predecessors' hand. It appears that the centerpiece of this administration's stick for the biopharma industry will be nothing more threatening than a mild reform in the form of value-based pricing.)

Third, drug costs account for less than 3% of the GDP in the US and most other major markets, even though biopharma is a more tractable target with a few dozen major players. So a bully pulpit is unlikely to make enough of a difference in solving the healthcare cost problem.

At the core of the matter, it is not so much a question of what percent price increases are appropriate. The real challenge for a healthy society is to ensure that all of its citizens have access to reasonable healthcare, including the benefits of ongoing innovations, and to do so without bankrupting the system, or starving other essential services, such as education and other infrastructure and cultural opportunities that add up to a healthy quality of life.

PATCHWORK OF BAND-AIDS

Whether this essential goal for any good society can be met by a particular form of healthcare system is a topic for another set of columns. It goes without saying that it is not possible to actually lower healthcare costs in an ageing society that is fortunate to benefit from an accelerating flow of innovative therapies. The perennial objective therefore is managing overall healthcare costs, and biopharma cost spikes within these costs for their growing share of healthcare cost inflation. To date, the complexity of healthcare systems globally has led to a patchwork of 'Band-aids'. A holistic solution remains even more elusive than a comprehensive tax system reform.

Time is rapidly approaching, however, when legislators, managers, academics, and in fact all stakeholders will be compelled to find such a solution as the only path to maintaining a healthy quality of life.

MODERN TECHNOLOGY'S POTENTIAL

In this approach, there are many more levers to apply to the challenge than just the bully pulpit; all anchored around both information technology (IT) and life science innovations that call for a clean slate approach to deploy the tools that modern technology has ushered in.

The contribution of IT in transforming our lives is experienced moment by moment by all of us; though its value in applying our vast data trove to drug discovery and development is only beginning to be realized. These tools promise even more dramatic benefits in healthcare delivery. Innovative online personal behavioral modification for a better health and a more fulfilling quality of life, for example, may well be the single most important opportunity for cost-effective healthcare. Beyond such IT innovations, the post-genomic life science transformation is gathering momentum. It is quite likely that the impact of life science breakthroughs on our society over the next two generations will be greater than that which IT has had over the previous two generations. We have seen early cures for more accessible targets, such as HCV and certain cancers, and many more have become manageable chronic diseases rather than a death sentence. The sum total of this progress is even greater demand for healthcare, and at a much higher unit cost – and the innovation cycle has only just begun.

Payer groups are responding with a variety of pricing pressures, which will only intensify if the US government limits its biopharma action to value-based pricing. EvaluatePharma revised its biopharma sales projections down by nearly $400bn over the next five years, primarily because of these pricing pressures, in what is likely to be the first of such tapers.

Value-focused price negotiations will expose one of the more difficult challenges facing biopharma, namely, its legacy structures with their entrenched costs – how the industry operates and carries out its discovery, development, sales and marketing functions. Perhaps that is where the blended impact of IT and life science innovation will provide disruptive answers, wiping the slate clean and creating a brand new way of delivering innovative and effective healthcare.

BREAKING WITH TRADITION, BUILDING NEW FRAMEWORK

The first steps, not surprisingly, are being taken by non-industry players – thanks to their freedom from entrenched costs, and their ambition to leverage their IT power to find completely different pathways for biopharma innovation will make up for their R&D inexperience. The changes being ushered in by the new US FDA commissioner Scott Gottlieb to reduce regulatory risk (per his testimony to the US Congress on June 20th) will benefit all companies, but those with a fresh perspective may benefit sooner. Such bold regulatory refinements are likely to win bipartisan support over time, changing cost calculi that may prove catalytic for system wide acceptance of IT and LS innovations that disruptively push out entrenched costs.

The ultimate shift will happen when such new initiatives add up to a fresh framework for delivering and procuring healthcare.

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Viren Mehta founded and is managing member of Mehta Partners, LLC, a globally integrated boutique providing strategic insights to senior management teams in the biopharmaceutical sector for nearly 30 years.

This Means War: Identical Labels Recommended For Gilead, AbbVie's HCV Drugs In Europe

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AbbVie Inc. and **Gilead Sciences Inc.** have secured positive recommendations for approval of their respective new hepatitis C drugs, *Maviret* and *Vosevi,* and now it is game on in Europe for the two companies to see who can secure the best reimbursement deals and convince physicians to prescribe their therapy.

Shutterstock: Tashatuvango

AbbVie's positive recommendation from the European Medicines Agency's scientific committee, the CHMP, was expected for the use of Maviret as an eight-week regimen in all treatment-naïve non-cirrhotic hepatitis C patients (the majority of patients going forward) regardless of genotype. But the CHMP's positive vote for Gilead's Vosevi as an eight-week regimen in the same all-round patient population came as a surprise because of previously reported mixed trial data for some patient subsets.

Datamonitor Healthcare lead analyst Michael Haydock told *Scrip*, "In the POLARIS-2 study, Vosevi failed to show overall non-inferiority to Gilead's *Epclusa* because of a higher rate of relapse in genotype-1a patients, so it was unexpected that this subgroup is also considered eligible for the eight-week regimen."

Haydock added that a recommendation for a 12-week regimen for this set of patients had been anticipated for Vosevi.

Market authorization applications for both products were recommended this month by the CHMP for approval in Europe and published by the committee on 23 June in a roundup of decisions.

BREAKING GILEAD'S RULE

The matching indications in Europe will further increase competition between AbbVie and Gilead in the HCV space. But importantly to Gilead, Vosevi's eight-week label allows the company to position its new treatment as a first-line successor to Epclusa (sofosbuvir/velpatasvir fixed dose combination), one of its marketed HCV therapies.

Haydock said, "The recommended label will allow Gilead to partially protect its patient share from Maviret."

However, he believes the success of each drug will be entirely determined by its price. "The launch of these drugs will lead to a further decline in both prescription volumes and the market value because payers are going to play Gilead and AbbVie off against each other," Haydock said. "Previously Gilead still had an edge in the negotiations because of its dominance of the genotype-2 and genotype-3 segments, but that will disappear once Maviret is approved," he said.

Leerink analysts also highlighted in a June 23 note that, "For the first time, two companies will each have once-daily, oral, ribavirin-free, pan-genotypic HCV regimens with eight-week treatment duration for all treatment-naïve HCV infected individuals."

Gilead has, until now, ruled the non-genotype-1 setting in the HCV market with *Sovaldi* (sofosbuvir) and more recently Epclusa; but the company will face tough competition from Maviret in this space once AbbVie's drug is approved by the European Commission. Leerink analysts noted that "by early 2018, Gilead is likely to face direct competition for the treatment of these patients, as well as for the current genotype-1 patients."

In the genotype-1 setting, Gilead currently has the only eight-week treatment option available via *Harvoni* (sofosbuvir plus ledipasvir fixed dose combination). However, AbbVie's regimen will match Gilead's best treatment option on treatment duration (eight weeks), dosing convenience (once daily) and even tolerability, Leerink analysts said.

> 'The launch of these drugs will lead to a further decline in both prescription volumes and the market value'

Furthermore, AbbVie's new HCV drug could be considered the better option. "At the margin (and the differences are small in our opinion), AbbVie's regimen could even be construed as better than Gilead's, given a higher SVR (sustained viral response) rate in their pivotal trials and the lack of any treatment restrictions for patients with impaired renal function (although Gilead has the offsetting advantage of existing approvals for patients with cirrhosis)," Leerink analysts said.

Leerink analysts have forecast that Gilead's hepatitis C revenue will decline by $2.1bn next year.

Meanwhile, Maviret has been dubbed a potential blockbuster for AbbVie with forecasts suggesting the drug will see cumulative sales of $7bn-$8bn between 2018 and 2022. Despite this ample income, Leerink said HCV revenue "is a short-term windfall, rather than a core strategic opportunity" for AbbVie. Analysts believe contribution from AbbVie's hepatitis C portfolio will be modest post-2022.

Both Maviret (glecaprevir/pibrentasvir) and Vosevi (sofosbuvir/velpatasvir/voxilaprevir) have NDAs pending with the US FDA.

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Pfizer's Inlyta Fits Well In Combos For Kidney Cancer

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Immuno-oncology continues to transform treatment landscapes as checkpoint inhibitors move into new markets, earlier lines of therapy and combinations. Early data presented at the American Society of Clinical Oncology annual meeting suggest that as PD-1/L1 inhibitors move into first-line metastatic renal cell carcinoma, **Pfizer Inc.**'s targeted therapy *Inlyta* may be the partner of choice.

Inlyta (axitinib), the follow-on to Pfizer's *Sutent* (sunitinib), has been established for use after one prior line of systemic therapy in metastatic renal cell carcinoma (mRCC), following approval in August 2014. But FDA approval of three new drugs for mRCC in recent years has raised questions about positioning in the future – **Bristol-Myers Squibb Co.**'s PD-1 inhibitor *Opdivo* (nivolumab), **Eisai Co. Ltd.**'s multi-TKI *Lenvima* (lenvatinib) and **Exelixis Inc.**'s *Cometriq* (cabozantinib), also a multi-target TKI (*see box*). Unlike Inlyta, the three newcomers all demonstrated an overall survival benefit in trials supporting labeling. *(Also see "Exelixis' Strong Cabometyx Start Signals Changing Of Guard In Kidney Cancer Market" Scrip, 5 Aug, 2016.)*

Pfizer reported sales of $401m for Inlyta in 2016, down by 7% from the prior year, as the drug faced new competition.

PD-1/L1 inhibitors look set to play an important role in the market in RCC – just as they have in other indications – and the thinking has been that they could be used in combination with tyrosine kinase inhibitors to get better results in the first-line mRCC setting. However, there have been some disappointments in research with TKI/PD-1 combinations. In a study presented at the ASCO meeting in 2014, the combination of Opdivo with two different TKIs – Sutent and **GlaxoSmithKline PLC**'s *Votrient* (pazopanib) – had similar efficacy as monotherapy and 70%-80% of patients had severe toxicity. *(Also see "Cancer Trials & Tribulations: Combinations Are Easier Said Than Done" Scrip, 1 Aug, 2014.)* At the time, researchers wondered if unknown factors, like PD-L1 status, influenced results.

Data reported at the 2017 ASCO meeting, held in Chicago June 2-6, show more promising results for other immunotherapy/TKI combinations and also suggest a role for the combination of PD-1 with IDO1 inhibitors.

"There are plenty of other opportunities to intervene and potentially complement and synergize with PD-1 and PD-L1 inhibitors," commented Hans Hammers, University of Texas Southwestern Medical Center, discussing results from RCC combination studies at the ASCO meeting on June 5.

One trial (abstract #4504) tested Pfizer/**Merck KGAA**'s PD-L1 inhibitor *Bavencio* (avelumab) with Pfizer's TKI Inlyta for first-line treatment of 55 patients. In that single-arm study, the objective response rate (ORR) was 58.2%, including three (5.5%) complete responses. Disease control was achieved in 78.2% of patients, investigators reported.

Studies are small and cross-trial comparisons are far from ideal, but the 58.2% ORR compares well to monotherapy data as well as other early results for combinations (*see table below*). **Merck & Co. Inc.**'s PD-1 inhibitor *Keytruda* has also demonstrated high efficacy in combination with Inlyta.

The rate of Grade 3 adverse events was 49.1% and the rate of Grade 4 events was 9.1%. The most common side effects were diarrhea, hypertension, dysphonia and fatigue.

The rates of Grade 3 and Grade 4 immune-related AE's were 30.9% and 5.5%, with one death reported. The rate of hepatitis (increased ALT/AST) was 3.6% at all grades and 3.6% at Grade 3.

The Phase III JAVELIN Renal 100 trial of the Bavencio/Inlyta combination compared to Sutent monotherapy in first-line mRCC is ongoing.

Discussant Hammers commented that the efficacy looked encouraging and that safety looked manageable, though there was more toxicity, than what would be expected with single agents and there was still a liver toxicity signal.

Nevertheless, he concluded that axitinib looks more combinable with PD-1/L1 inhibitors than other VEGF inhibitors, he said. The clinician added that it would be useful if in the future sponsors report whether there is a need for immunosuppressive therapy, such as steroids, to manage toxicity, as this would provide a good gauge of tolerability.

In a June 6 note, Credit Suisse analyst Vamil Divan said that the positive RCC combination data "should ultimately help slow Inlyta's decline."

"The combo of Inlyta plus PFE's Bavencio showed encouraging data with a confirmed ORR of 58.2%, with 3 CRs, 29 PRs, 11 SDs and 10 PDs, with even stronger responses in PD-L1 positive patients. This bodes well for the ongoing Phase III trial of the combo as compared to Sutent in the 1L setting, potentially allowing PFE to better compete in that market in the coming years," Divan said.

Response Rates In Metastatic RCC Trials, Mono And Combo Therapy

DRUG/COMBINATION	OBJECTIVE RESPONSE RATE
Roche's Tecentriq	25%
Bristol's Opdivo	25%
Roche's Tecentriq/Avastin	32%
Incyte's epacadostat/Merck's Keytruda	33%
Bristol's Yervoy/Opdivo	40%
Pfizer's Inlyta/Bavencio	58%
Merck's Keytruda/Pfizer's Inlyta	67%

Source: Adapted from V. Gruenwald (Medical School of Hannover), review of recent data at ASCO 2017

VOTRIENT COMBO FAILS

Another study presented at ASCO (abstract #4506) alongside the Bavencio/Keytruda data tested Merck's Keytruda (pembrolizumab) with Novartis' TKI Votrient, which is indicated broadly for advanced RCC. In the first two dosing cohorts of this Phase I/II trial,

unacceptably high liver toxicity was reported for the combination.

Investigators changed the dosing regimen to start with a run-in period of Votrient followed by the combination, and adjusted the trial protocol to exclude patients at risk of hepatotoxicity events. However, while this minimized hepatotoxicity, researchers saw new and unexpected safety signals – e.g. severe cases of pneumonitis, bowel perforation and elevated lipase level.

"Although preliminary signs of efficacy were observed, the poor tolerability does not support the initiation of the Phase II part of this study and this will not proceed. Therefore, we conclude that pazopanib is not recommended in combination with pembrolizumab," Simon Chowdhury of the London Kidney Cancer Group reported at the meeting.

Hammers commented that there was "clearly a determination to get this combination to work" by investigators, in terms of changes to trial design, and yet the toxicity was prohibitive. The results are reminiscent of prior data combining PD-1 inhibition with Sutent, he said.

"A lesson from both studies now is really is we have to be cautious with some of these PD-1/PD-L1 TKI combinations. But the simple truth is not all VEGF inhibitors are the same and there is an argument to be made for more selective, potentially more combinable VEGF inhibitors as we are moving now into dual and triple combination therapy," Hammers said.

SELECTIVITY MATTERS

Hammers said that tivozanib tends to be the most selective out of all TKIs. Tivozanib, being developed by **Aveo Pharmaceuticals Inc.**, is being evaluated in the Phase III TIVO-3 study as a monotherapy against Sutent. On June 8, AVEO announced that a combination of tivozanib with Bristol's Opdivo was well-tolerated in a Phase I study of advanced RCC and has progressed to Phase II.

Aveo has faced some setbacks getting tivozanib to the market in the US and Europe as a monotherapy but on June 22 it was recommended for approval in first-line advanced RCC in the EU, where it will be marketed as *Fotivda*.

Hammers also noted that while cabozantinib is multi-targeted, it is combinable with PD-1 immunotherapy, though with some liver toxicity, and has progressed to Phase III. Bristol and Exelixis have a collaboration to test Cometriq with Opdivo and Yervoy in the CheckMate 9ER study. Exelixis is planning to submit a supplemental filing for cabozantinib as a monotherapy in first-line metastatic RCC in the third quarter, based on the Phase II CABOSUN study, in which the drug demonstrated a progression-free survival benefit compared to Sutent.

> Efficacy looked encouraging and safety looked manageable, though there was more toxicity than what would be expected with single agents

Roche is also making a bid for combining its TKI *Avastin* (bevacizumab) with its PD-L1 inhibitor *Tecentriq* (atezolizumab) in first-line advanced renal cell carcinoma, with a Phase III study ongoing. The randomized Phase II IMMotion150 study tested the combination in this setting against either Sutent or Tecentriq monotherapy. Data from the trial, which included 305 patients, were reviewed at the ASCO meeting. But as previously reported, the combination failed to demonstrate an improvement in progression-free survival compared to Sutent.

The response rate for the combination was 32% compared to 25% for Tecentriq alone and 29% for Sutent alone.

There was a large numerical increase in PFS for patients with at least 1% PD-L1 expression taking the combination compared to monotherapy. And tolerability for the combination was similar as for single agents.

Hammers noted that the ORR rates overall "pale to some degree in comparison to the more potent TKIs," which are in the 58% to 70% range. However, he also pointed out that the results for those with more than 1% PD-L1 expression are "quite promising."

IMMotion150 investigators also reported better results for the combination in a cohort of patients with T-cell infiltration and myeloid inflammation.

"Reduced clinical activity in this subgroup suggested a potential mechanism of innate resistance to atezo monotherapy which might be overcome by the addition of bevacizumab, possibly through its proposed ability to target myeloid inflammatory cells," reported investigator Michael Atkins, of the Georgetown-Lombardi Comprehensive Cancer Center. Hammers commented that the finding was interesting but questioned how independent this biomarker is of PD-L1 expression.

Roche is now testing the combination against Sutent in the Phase III IMMotion151 study of first-line mRCC with detectable levels of PD-L1. During a June 3 education session on RCC, the University of Utah's Neeraj Agawal said that the landscape of ongoing Phase III trials is "absolutely breathtaking" and that consequently enrollment in a clinical study is now a preferred treatment option in first-line metastatic disease.

POTENTIAL FOR ALL IO COMBOS

Meanwhile, a new PD-1/L1 combination partner is emerging in RCC, along with other indications – **Incyte Corp.**'s IDO inhibitor epacadostat. Incyte reported that the combination of epacadostat with Keytruda demonstrated a 33% ORR and 50% disease control rate in an RCC cohort of 30 patients in the Phase I/I ECHO-202 study (abstract #4515). The Grade 3/4 adverse event rate was 17% (eight patients), the most common being fatigue, rash and diarrhea. Merck and Incyte are planning to start a Phase III study of the combination in first-line mRCC in 2017.

Combinations are very interesting in RCC, but the toxicity with double immunotherapy and also immunotherapy/TKI approaches has been a problem, Viktor Gruenwald, Medical School of Hannover, commented during a poster discussion session on June 4.

Epacadostat in early trials seems to offer an increase in activity while maintaining the tolerability and safety of a single agent. "This is the major advantage that we may see with the addition of IDO1 to the PD-1 backbone," he said.

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View Phase III Combo Trials: PD-1/L1 With Targeted Drugs In Kidney Cancer here: **http://bit.ly/2sHOtbb**

Generic Drug Market Has Gaps, FDA Tells Firms In Solicitation For ANDAs

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Janssen Pharmaceutical Cos.'s *Elmiron* (pentosan polysulfate) needs generic competition, FDA says.

The orphan drug indicated for relief of bladder pain or discomfort associated with interstitial cystitis was approved in 1996 and contains no more blocking patents or exclusivity. In fact, the agency could "immediately accept an ANDA for the drug without prior discussion" with the sponsor.

But despite the glaring commercial opening, it and 266 other drugs are included on a list of products with no approved ANDAs that the agency published June 27 to try and spur the generic industry to enter the markets.

The FDA is hoping that spoon-feeding development targets to potential sponsors as well as offering to prioritize any applications will ultimately lead to lower drug prices. However, the PR push and review incentive may not be enough to generate interest among generic firms.

As drug pricing has become a prominent fixture of political debate, some of the most concrete steps the Trump administration has taken on the issue have come from the FDA, where Commissioner Scott Gottlieb has identified approving more generics as a key factor in reducing Rx costs.

Beyond the list of generic targets and the plans to prioritize applications, the FDA has promised that more policy changes could be made to help streamline generic approvals, all part of a Drug Competition Action Plan that could take firmer shape after a meeting next month.

In its most recent move, the agency changed an internal policy, called a Manual and Policies and Procedures, to prioritize ANDAs where there are less than three approved applications for the reference product and no blocking patents or exclusivities. The agency previously prioritized first-filers for a reference product, but not subsequent applications. *(Also see "Drug Pricing Panacea Or Just PR Victory? Expedited ANDAs May Have Limited Impact" Scrip, 21 Mar, 2016.)*

Many of the products the FDA identified already are well-known to the generic industry and a priority review alone is not going to move the needle. Often the markets remain open for other reasons.

In the case of Elmiron, it has long been a target for generic firms. Consultant Charles DiLiberti, president of Montclair Bioequivalence Services, said in an interview with *Scrip* that they have struggled for years to develop an ANDA for the complicated product, but need more help from the FDA.

"There are those complicated ones that generics would love to have, but are at a loss for how to do them," DiLiberti said. While the label "complex generic" is usually given to injectables and combination products, even some solid dosage products are maddeningly difficult to manufacture. Elmiron, for example, comes in opaque, hard gelatin capsules in 100 mg doses, according to the label.

Several of the products with no competition do not present much of an opportunity for revenue, DiLierti noted, especially when considering the development costs and user fee payments associated with them. "You have a class of products that are really low volume and companies are not going after them because they are so small," DiLiberti said. "Why would you spend $1m or $2m to get a $5m product?"

REPURPOSING OPPORTUNITY

Christopher-Paul Milne, director of research and research associate professor at the Tufts Center for the Study of Drug Development, said in an interview that some companies may be encouraged to enter the untapped generic markets by the potential of a priority review.

Special circumstances may have to emerge for the incentive to work, however. In cases where a sole supplier dramatically increases its price, priority review may allow a company "to strike while the iron is hot," he said.

"With priority review they could be competing in a couple months," Milne said. Milne also said priority review could be particularly useful for existing drugs that are repurposed. "Sometimes these things come up as a treatment for a disease that they were not known as a treatment before," he said. "All the sudden getting on the market early, that's important."

Such a situation could arise in the search for a treatment for a pandemic virus like Zika or Ebola, making not only the market, but the potential for shaving two months off the review time valuable, Milne said.

Kurt Karst, director at Hyman, Phelps and McNamara, also said in an interview that the potential for priority review would be a component in a generic sponsor's regulatory approval strategy and that it may entice some companies to enter those markets.

"That will matter based on cost and revenue," he said.

"If it's a single-source generic with hardly any sales, even priority review may not be an incentive," Karst noted.

LIST A REMINDER, NOT A REVELATION

It does not appear that the FDA's decision to publish a list of drugs with no approved generics was a commercial revelation for many generic companies. Milne said most companies follow the generic opportunities as drug patents expire. Still, he said some companies may be enticed by the potential to gain a first-mover advantage.

"It certainly doesn't hurt to have everyone look at them again," he said.

Robert Pollock, senior advisory and outside director to the board of Lachman Consultants, said large companies will not develop generics when the market is less than $10m to $15m in sales. But he said the list could help draw small firms to markets if they can capture 40% to 60% of the sales.

Karst said the FDA has done the legwork in developing potential targets, but whether it will incentivize sponsors is "going to depend on the product and the company."

The FDA developed the list from data in the agency's Orange Book, a record of patent and exclusivity information for all approved drugs and generics, as of May 30. Part I of the list includes drugs where an application could be submitted immediately. Part II includes drugs with "potential legal, regulatory, or scientific issues which should be addressed with the agency prior to submission of an ANDA."

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Mixed Data For Bluebird's LentiGlobin, But Conditional Approval On The Cards

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Gene therapy specialist **bluebird bio Inc.** has reported early Phase III data for *LentiGlobin* (lentiviral beta-globin gene transfer) in patients with transfusion-dependent beta-thalassemia (TDT) that have split analysts' opinions.

Despite mixed figures from the first three patients treated in the Northstar-2 trial, the results have demonstrated that bluebird's improved manufacturing process can address patient-to-patient treatment variability issues.

The company is also on track to seek conditional approval of the gene therapy product in Europe this year for patients with non-β0/β0 genotype TDT based on data from the Northstar and Northstar-2 trials, as well as the ongoing HGB-205 study in patients with TDT and sickle cell disease.

In parallel with data updates, on June 26, bluebird announced a public offering of $350m of common stock. Goldman Sachs & Co, Bank of America Merrill Lynch and Cowen are acting as joint book-running managers for the proposed offering.

MIXED NORTHSTAR-2 DATA

Early data from three TDT patients included in the ongoing Northstar-2 Phase III trial (also known as HGB-207) were presented on June 25 at the European Hematology Association (EHA)'s annual meeting in Madrid, Spain.

Transfusion-dependent beta-thalassemia, also called beta-thalassemia major or Cooley's anemia, is an inherited blood disease that can be fatal if not treated. LentiGlobin, an orphan drug product, has been granted fast track and breakthrough statuses in Europe and the US, respectively, for TDT.

Biomedtracker analysts have given the drug a high likelihood of approval rating in this indication at 69% – 9% above the average for a similar product at the same stage of development. They noted in an EHA analysis, "The salient point from this presentation was that the new [manufacturing] processes introduced by the company appears to be substantially increasing vector copy number." To date, bluebird's product has been manufactured for six patients in Northstar-2. The median drug product vector copy number (VCN) for these patients was 3.0 (range: 2.4-4.0), compared to a median VCN of 0.7 (range: 0.3-1.5) in the first Northstar trial.

However, BMO Capital Markets analyst Matthew Luchini called mixed data presented for one of three LentiGlobin treated TDT patients in Northstar-2 "a bit of a disappointment" in a June 23 note.

In the Northstar-2 trial, patients one and three appear to have higher VCN in their peripheral blood but patient two had much lower levels similar to the previous Northstar study that was conducted before manufacturing improvements were put in place.

Bluebird management said during a June 23 conference call that the VCN produced in patient two still appear to be at levels that could lead to transfusion independence.

Luchini concurred that the patient could "ultimately see a clinically meaningful response based on historical trends."

Biomedtracker analysts also highlighted that on examination of the patient's phenotypic profile of cells in the gene therapy product, "the patient appeared to be an outlier with a much higher proportion of committed lymphoid progenitors compared to stem cells."

Overall Biomedtracker believes Northstar-2 is on track to reach its primary endpoint, but analysts noted that the data presented at EHA for patient two are "somewhat disconcerting" and require further investigation.

The ongoing, open-label, single-dose, international Northstar-2 study is designed to evaluate the safety and efficacy of LentiGlobin for the treatment of patients with TDT and non-β0/β0 genotypes. Data from the first three patients treated show that the safety profile of LentiGlobin appears consistent with autologous transplantation.

In total, as of June 2, 2017, 16 patients had consented for transfusion in trial. The primary endpoint of the study is the proportion of patients who achieve transfusion independence, which is defined as maintaining an average total hemoglobin of greater than or equal to 9g per deciliter without red blood cell transfusions for greater than or equal to 12 months. So far, one patient has reached the six month follow-up point in the Phase III trial with no transfusions for 140 days. Patient one was also able to discontinue transfusions after just one month post-LentiGlobin treatment and at six months had a total hemoglobin level of 13.3g/dL – well above 9g/dL level that translates to transfusion independence

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UPCOMING CATALYSTS

Northstar-2 is still enrolling adult patients and bluebird plans to subsequently expand the trial to include children; bluebird expects to file LentiGlobin, however, for conditional approval in Europe later this year.

Furthermore, bluebird is set to initiate the Northstar-3 study in 15 patients with β0/β0 beta-thalassemia later this year, which will be first study evaluating new LentiGlobin in patients with the most severe disease genotype.

In December, during the American Society of Hematology's annual meeting, the company will also report further updates from LentiGlobin studies in patients with TDT and sickle cell disease.

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'Affordable' Russian Rituximab Biosimilar On Course In India

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Russian biotechnology company **Biocad**'s rituximab biosimilar appears on course for an Indian debut, trailing a clutch of local firms onto the market.

Biocad, which has been keen to expand its presence in Asia, indicated earlier this year that it expected to substantially expand supplies of its biosimilar rituximab in Vietnam, amid other plans in the region including in markets like Sri Lanka.

A key expert panel, which advises the Indian drugs regulator on trial-related permissions, has now cleared Biocon's rituximab in India. At its meeting on June 20, a Subject Expert Committee (oncology and hematology) recommended Biocad's biosimilar for marketing authorization in India "for all approved indications" of rituximab.

The Subject Expert Committee (SEC) go-ahead for Biocad's rituximab is significant given that in early June, India stipulated pivotal tweaks to its existing three-tier review process for clinical trial-related clearances. Under the new approach, in general, once global clinical trial (GCT) proposals are accepted or rejected by the SEC, no further approval of the Technical Committee or Apex Committee will be required, though reviews are possible in certain circumstances. The existing three-layered system required recommendations of the SECs to be vetted by the Technical Review Committee and then cleared by the Apex Committee.

Biocad did not respond to specific queries on whether it would need any further regulatory clearances in India for its rituximab, but appears to be gearing for a launch.

"We want to launch our rituximab (*Acellbia*) at the end of August; it will be promoted by our own marketing team in India. Early September Acellbia should be available for all customers," the Russian company told *Scrip*. Biocad's biosimilar rituximab first received regulatory approval for sale in Russia in April 2014.

COMPETITION

Significant competition, though, awaits Biocad's rituximab in India, with domestic firms such as **Dr. Reddy's Laboratories Ltd.**, **Intas Pharmaceuticals Ltd.** and **Hetero Drugs Ltd.** already selling their biosimilar versions and more competition likely in store.

Data in India's clinical trials registry indicates that firms like **Zydus Cadila** are also developing rituximab, while India is among the trial sites for the biosimilar for others like Archigen Biotech (the joint venture between **Samsung BioLogics** and **AstraZeneca PLC**), **Celltrion Inc.** and **Pfizer Ltd.**. The latest position on these could not, however, be immediately ascertained.

Dr Reddy's launched its rituximab biosimilar (marketed as *Reditux*) in 2007, while Intas launched its product (*Mabtas*) in 2013. Hetero introduced its biosimilar version (marketed as *Maball*) of innovator Roche's *MabThera/Rituxan*, in India in 2015.

Roche, though, apparently does not actively promote the *MabThera* brand in India. Instead its rituximab products are branded as *Ristova* and a second brand *Ikgdar* (through the alliance with the Indian firm Emcure).

Last year, Dr Reddy's told *Scrip* that in India alone, the number of patients treated with rituximab had gone up by 10 times following the introduction of Reditux, making it the market leader. Reditux had earlier emerged as the 300th biggest brand on the Indian market, as per February 2016 data from AIOCD AWACS, the market research agency that tracks retail sales.

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AFFORDABILITY AND EXPERIENCE

Asked about how it expected to make an impact with rituximab in India, given that the market already has established players, Biocad maintained that the pharmaceutical market of India is currently one of the most attractive "from the commercial point of view" and hence the level of competitiveness is "very high" and this trend will increase.

The Russian company emphasized that its main advantage will be "premium quality (confirmed by GMP [good manufacturing practice] certificates of different countries)" for the "affordable price and the gained experience" on the global stage.

"We are prepared for the competition with other players. Moreover, in consequence of full cycle production we have the possibility to guarantee high quality of the product on every manufacturing stage and control the expenses for production and promotion. This advantage allows us to drive [a] flexible pricing policy," Biocad said. *(Also see "Another Rituximab Debuts In India But No Price Contest?" Scrip, 13 Aug, 2015.)*

Biocad shared no specifics around its pricing plans for rituximab but said that Acellbia would be "affordable even compared with other rituximab brands on the Indian market". India had earlier imposed price caps on rituximab.

Biocad also indicated that it is gearing for the long haul and sought to emphasize the strength of its pipeline.

"Biocad does not want to limit itself to rituximab only in India. In distinction from many competitors we are not a generic company – our pipeline is rich in original molecules that sooner or later will get to the Indian market. It means that Biocad will operate in India for a long time," the company declared.

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Open Innovation: The Fast-Track To Global Pharma Power For Korea?

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South Korea has many novel pipeline drugs and outstanding technology, but most of these assets are in the early stages of development and are usually licensed out to third parties rather than development being completed by originators.

"The reality is frustrating. How can we create blockbusters by going all the way? We only have a few pharma firms that exceed annual sales of KRW1tn [$879.8m]. We don't have capacity to conduct clinical trials or market drugs in global markets by ourselves," Hee-Mok Won, chair of the Korea Pharmaceutical and Bio-Pharma Manufacturers Association (KPBMA, formerly the KPMA), told a recent forum in Seoul.

Many agree that the South Korean pharma industry has outstanding infrastructure in clinical trials, good technology, and a strong workforce. The country is seen as a key location for global clinical trials, and of the 7,000 novel drugs in the pipeline worldwide, 1,000 are from South Korea. However, the country accounted for only 1.8% of the total global pharma market in 2015.

In terms of economies of scale, South Korea is still far behind. While multinational pharmas can invest 20-30% of their revenues in R&D, domestic firms are having a tough time allocating more than 10%. Of the country's 28 novel drugs developed so far, none of them can be viewed as blockbusters.

POLICY SUPPORT, ROLE MODELS

The KPBMA chair stressed the government's role in growing the pharma and biotech industry.

"[Newly elected] president Moon Jae-in has to declare that the pharma industry is the country's future growth engine industry. We need a 'bucket of water' that can become the primer," he said. "This is the right time as we have the infrastructure."

Many global big pharmas are exploring South Korea's novel drug pipelines for licensing-in opportunities, but the country needs to take control of the development and go to the finish line. In order to achieve this, Won proposed that South Korean companies take a two-way, open innovation approach.

In the first stage, domestic firms, academia, researchers, and government should collaborate to develop South Korea-oriented technology. Then, the country must attract foreign companies to jointly research and develop this technology in a global open innovation system.

He cited global blockbuster drug *Opdivo* (nivolumab) as an example. Development of the PD-1-targeting product involved various collaborations among parties including Japan's **Ono Pharmaceutical Co. Ltd.**, Kyoto University in Japan, and **Bristol-Myers Squibb Co.**

He also suggested that South Korea should benchmark Belgium, where the government has provided significant tax incentives and simplified administrative processes to attract multinationals.

As a result, 29 of the top 30 global pharma companies are conducting joint research or development in the country rather than just licensing in drug candidates from local partners.

"It will take too much time for South Korean companies to have the capacity to conduct global clinical trials and marketing by themselves. We need to create an environment that can induce global pharmas to come to Korea and work together. Rather than seeking out-licensing, we need a strategy that enables us to reach the stage of global marketing and maintain our rights, while learn know-hows of advanced countries," he proposed.

"Global open innovation. This is the fastest way for South Korea to become a strong pharma nation. We need to become a novel drug development hub in Asia as Belgium is in Europe."

FOCUSING R&D, STRATEGY

Samsung BioLogics vice president Hoyeol Yoon noted that South Korea has too many diverse and scattered drug pipelines given the scale of investment.

South Korea's R&D spending accounts for a tiny portion of that of global pharma firms, so the economy of scale is poor. As it is difficult to trim costs for the global development of a novel drug, the country needs to create such portfolios appropriately, but at present they seem to be scattered too much, Yoon told the forum.

The country also lacks synergies in capital, technology, and workforce, and while it talks a lot about open innovation, in reality, processes are still closed.

"Many are still reluctant to share [information and data] on fears of exposure in technology and revelation of disadvantages. Despite these concerns, other countries are actively pursuing this in the belief others can do it better than yourself," he said.

Another key point is that South Korea still has too much of a "supply-oriented mind," and the country needs a different concept, a "demand-based mind," Yoon suggested.

"Countries are fiercely competing in the race of novel drug development. What we have learned from the CMO [contract manufacturing organization] and biosimilar business is that you will lose if you are late, you can't sell if it is expensive, and there is no market value without a global market entry strategy. If we can't differentiate in this, there will be limitations in growth," he said.

STRONGER GROWTH AHEAD?

For South Korea, the year 2015 was an inflection point for its biotech and pharma industries. It has now entered a preparatory period for substantial growth as suggested by **Hanmi Pharmaceutical Co. Ltd.**'s massive licensing out deals, and the global advancement in biosimilars by **Celltrion Inc.** and **Samsung Bioepis Co. Ltd.**

Depending on how South Korea behaves, it could serve a new leading role in the global pharma industry in the coming years.

"How could Switzerland, Ireland, and Singapore become strong pharma and biotech players despite their small size? They are globalized, poured investment into this sector, and the government led these moves. We can learn from these three messages," Yoon said.

From the editors of PharmAsia News. Published online 29 June 2017

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Selected clinical trial developments for the week 23–29 June 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Suspended			
Boston Biomedical Inc./Sumitomo Dainippon Pharma Co. Ltd.	napabucasin plus paclitaxel	gastric cancer	BRIGHTER; stopped at interim analysis, unlikely to improve overall survival.
Phase III Results Published			
Roche	*Rituxan* (rituximab)	diffuse large B-cell lymphoma	DLCL04; *The Lancet Oncology* online, June 28, 2017
Teva Pharmaceutical Industries Ltd.	*Austedo* (deutetrabenazine)	tardive dyskinesia	AIM-TD; *The Lancet Psychiatry* online, June 28, 2017.
Novartis AG	*Rydapt* (midostaurin)	acute myeloid leukemia	RATIFY; the *NEJM* online, June 23, 2017.
Threshold Pharmaceuticals Inc.	evofosfamide	sarcoma	*The Lancet Oncology* online, June 23, 2017.
Updated Phase III Results			
Bristol-Myers Squibb Co.	*Empliciti* (elotuzumab)	advanced multiple myeloma	ELOQUENT; four-year follow-up data.
Amgen Inc./Novartis AG	erenumab	migraine	STRIVE; reduced frequency.
Roche	emicizumab, once-weekly subcutaneous	hemophilia A	HAVEN 1,2; reduced bleeds.
Amgen Inc.	*Xgeva* (denosumab)	bone complications, metastases	Clinical benefits shown in multiple myeloma.
AOP Orphan Pharmaceuticals AG/ PharmaEssentia Corp.	ropeginterferon alfa-2b	polycythemia vera	PROUD-PV; effective and well tolerated.
Amgen Inc.	*Kyprolis* (carfilzomib)	multiple myeloma	ENDEAVOR, ASPIRE; clinical benefits shown.
Amgen Inc.	*Blincyto* (blinatumomab)	acute lymphocytic leukemia	TOWER; clinical improvements seen.
Rigel Pharmaceuticals Inc.	*Tavalisse* (fostamatinib)	immune thrombocytopenic purpura	FIT; improved clinical symptoms.
Roche	*Gazyva* (obinutuzumab)	indolent non-Hodgkin's lymphoma	GALLIUM; improved PFS confirmed.
Phase III Interim/Top-line Results			
Alkermes PLC	ALKS 3831	schizophrenia	ENLIGHTEN-1; positive top-line results .
Merck & Co. Inc.	anacetrapib, oral	dyslipidemia	REVEAL; reduced major CV events, the positive primary endpoint, well tolerated.
Seattle Genetics Inc./ Takeda Pharmaceutical Co. Ltd.	*Adcetris* (brentuximab vedotin)	frontline advanced Hodgkin lymphoma	ECHELON-1; met primary endpoint of improved PFS.
bluebird bio Inc.	LentiGlobin gene therapy	transfusion dependent beta-thalassemia	NorthStar-2; signs of improved efficacy.
Alder BioPharmaceuticals Inc.	eptinezumab	episodic migraine prevention	PROMISE 1; met primary and secondary endpoints.
Cosmo Pharmaceuticals NV	remimazolam	procedural anesthesia	Met primary endpoint in bronchoscopy.
Clarus Therapeutics Inc.	*Jatenzo* (testosterone undecanoate), oral	hypogonadism	inTUne; positive results, US NDA resubmitted.

Source: Biomedtracker

Arix Pegs LogicBio's Technology As 'Occam's Razor' Of Gene Therapy

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LogicBio Therapeutics has raised $45m in a series B financing, led by Arix Biosciences, bringing to $50m the total the recently launched firm has raised to complete preclinical development of an innovative gene therapy platform for pediatric diseases and move lead programs into clinical studies.

Arix's CEO Joe Anderson told *Scrip* that Arix had "identified limitations with traditional gene therapy and the need for gene therapy that works in pediatric populations," which resulted in the company hunting for a 'novel approach' and ultimately finding LogicBio.

Arix is interested in LogicBio because unlike traditional gene therapy, which is usually complicated, LogicBio's technology "strips away all those unnecessary components and hijacks the hosts machinery," resulting in stable integrated transgenes. Its approach does not require the use of promoters or nucleases for transfer of genetic material.

According to Daniel O'Connell, Arix's investment manager, other challenges that arise with traditional gene therapies include low integration rates and dilution, which prevent them from working in pediatric diseases. For example, as the liver grows, dilution occurs and the effect of the gene therapy wears off. However, O'Connell said that stable integration, such as LogicBio promises, could get around that problem, giving way to life-long therapy for life-threatening diseases from one single administration.

LogicBio was founded on two main platform technologies in the Kay Lab at Stanford University by Mark Kay, Adi Barzel and Leszek Lisowski. Its first platform is GeneRide, which uses homologous recombination to allow precise, site specific transfer of therapeutic genetic material; the second is its library of synthetic nonpathogenic recombinant adeno-associated viral (rAAV) vectors.

LogicBio's lead compounds are still in preclinical development and the company has not yet disclosed indications. However, it has highlighted that the liver is the initial target organ. Some of the proceeds from the series B fundraising will be used by the company to expand its technology to work in other tissues. With fresh cash in hand, LogicBio plans to progress its platform technology, with an initial focus on the liver and infants with inborn errors of metabolism.

The company was previously based in California but has since relocated to Cambridge, Massachusetts. The group secured seed investment of $4m in 2016 from OrbiMed Israel Partners. In addition to Arix, other investors in the series B round include Edmond de Rothschild Investment Partners, Pontifax and SBI Japan-Israel Innovation Fund.

For Arix, O'Connell said there is no one area of interest and it gravitates anywhere where there is "high science, cutting edge technology and areas of unmet needs." However, there are three areas that it has identified as especially attractive: anti-infectives, gene therapy and oncology (excluding immuno-oncology). With the goal of building its portfolio to up to 15–20 companies, Arix raised £113m in an IPO February this year, following a private fundraising of £52m when it launched in 2016, and LogicBio is its ninth investment so far

O'Connell believes that LogicBio's technology is the 'Occam's Razor' of gene therapy. The long-term goal for the company is to cure patients with monogenic diseases.

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APPOINTMENTS

Eton Pharmaceuticals Inc. has appointed ***Sean Brynjelsen*** CEO. Brynjelsen brings more than 20 years of experience in the industry to the company and previously worked at pharma companies, including Sagent Pharmaceuticals, Akorn Pharmaceuticals, Hospira and Baxter. Most recently, he was executive vice president of business development Sagent and before this, he was senior vice president, global business development for Akorn Inc.

The **Biotechnology Innovation Organization (BIO)** has named Alnylam Pharmaceuticals Inc.'s CEO, ***John Maraganore***, chair of its board of directors. ***Julie Gerberding***, Merck's executive vice president for strategic communications, global public policy & population health & chief patient officer, has been elected BIO's board secretary. Cerevast Therapeutics Inc.'s CEO, ***Bradford Zakes***, has also been re-elected as board treasurer in addition to the election of 15 new board members.

Michael Raya, CEO of **Hikma Pharmaceuticals PLC**'s US business, will be retiring at the end of this year with ***Riad Mishlawi*** being appointed CEO, Injectables Division. ***Brian Hoffmann*** has been promoted to president of the US Generics Division.

Astellas Pharma Inc. has promoted ***Caroline Walkinshaw*** to executive director, market intelligence and analytics, marketing strategy, and ***Jacquelyn Bonnell*** to national vice president, oncology sales for the US commercial organization. Walkinshaw joined the company as director of US market intelligence in 2011, following a 13-year career at Pfizer Inc. Before this new role with Astellas, she was senior director of global market intelligence and commercial analysis. Bonnell has over 25 years' experience and previously led the key oncology accounts team in the Western US within the health systems. Before Astellas, she held oncology commercial roles at various pharmaceutical companies including NanoString Technologies Inc., Sanofi, Berlex Laboratories Inc. (now Bayer AG) and Roche.

Akili Interactive Labs Inc. has appointed Cubist Pharmaceuticals Inc.'s former CEO, ***Robert J. Perez***, executive chair, and DreamWorks Interactive's former CEO, ***Glenn Entis***, and Google's former chief game designer, ***Noah Falstein***, executive advisors. Before Cubist, Perez was vice president of Biogen Inc.'s CNS business unit.

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