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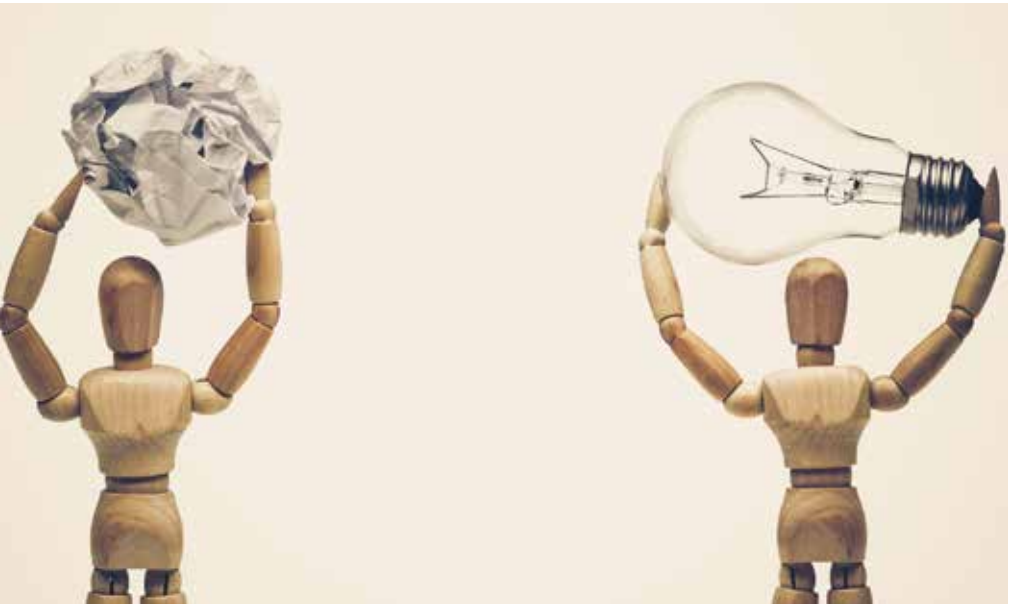

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J&J Immunology President On The Art Of Contract Negotiations

JESSICA MERRILL jessica.merrill@informa.com

Biosimilars are not small molecule generic drugs and therefore generic-like commercial dynamics should not be expected in the biosimilar market: that's the crux of **Johnson & Johnson**'s justification for tough contract negotiations with payers for *Remicade* (infliximab), which rival **Pfizer Inc.** says have unfairly blocked its biosimilar *Inflectra* (infliximab-dyyb).

J&J's Janssen Biotech immunology president Scott White talked with *Scrip* on Oct. 11 about the commercial dynamics in the infliximab market following the launch of the first biosimilar last year. He also pushed back against allegations by Pfizer in a lawsuit filed in September that its contracting arrangements are anti-competitive.

"First and foremost, we don't believe that the Pfizer lawsuit has any merit," White said. "The way we contract in the marketplace today is essentially no different than the way we were contracting prior to biosimilar launches."

The approach is largely the same, "but the level of discounts we provide is deeper because the overall market is more competitive, which includes biosimilars and goes beyond biosimilars," White said. "We are competing against all of these products and so we provide our competitive lens looking into the marketplace in its entirety."

Pfizer's Inflectra, developed with partner **Celltrion Inc.**, is the first biosimilar monoclonal antibody to reach the US market, and the launch is being closely watched as a measure of how the US biosimilar market might unfold. However, lackluster sales of Inflectra in the first year of its launch might be making biosimilar manufacturers anxious about the challenges ahead. J&J has largely been able to maintain Remicade's share of the infliximab market. Remicade accounted for 98% of the infliximab market as of the second quarter, according to J&J. The drug is J&J's top-seller, generating $6.97bn in sales in 2016.

Steep discounts and aggressive contracting with payers has been one of the keys to J&J's success in holding onto market share, but Pfizer, in the high-profile lawsuit it filed, says J&J crossed a line by coercing payers to block Inflectra from their formularies entirely in order to receive those discounts. *(Also see "Pfizer Sets The Stage For A Biosimilar Showdown Over Exclusive Contracts" Scrip, 20 Sep, 2017.)* Because Remicade is already so widely used and entrenched in the market, J&J's discounts would top anything Pfizer could offer on Inflectra when the volume of prescriptions is taken into account.

Exclusive contracts, as they are known, exist in the brand-to-brand market but at the heart of Pfizer's case are questions about what exclusive contracts could mean for the burgeoning biosimilar market in the long-term, if innovator companies compete on price and payers accept the arrangement.

White didn't dispute the allegations in Pfizer's lawsuit when it comes to J&J's contracting strategy, but argued that the contracts are lawful and that the company hasn't changed its market access strategy for Remicade in any significant way since the launch of Inflectra.

"I believe that the intent [of the Biologics Price Competition and Innovation Act] was to create a pathway for biosimilars to

CONTINUED ON PAGE 9

from the editor

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With the final quarter of the year now well under way, you may be wondering what 2017 still holds for our industry. In contrast to the general business slow-down over the summer months, many companies apply their turbochargers in the fourth quarter, accelerating projects, winning new trade and closing deals to meet targets set many months before. Similarly, we often see a flurry of extra activity by the regulators, with the US FDA often approving several new drugs in the final days of the year.

A number of interesting drugs are likely to receive approval decisions in the coming weeks, including AstraZeneca's IL-5 receptor-targeting MAb benralizumab for severe, uncontrolled asthma, which could shake up a market already occupied by GlaxoSmithKline with Nucala and Teva with Cinqair, and Kite Pharma's axicabtagene ciloleucel for leukemia, which promises to become the second CAR-T therapy to win FDA approval (and validate Gilead Sciences' announced acquisition of Kite).

For a round-up of other important approvals expected before year-end, see p10. You can also visit our website to read our online only coverage of key clinical trial results due to read out (see details in our exclusive online content section on p3).

In the near term, watch this space for our coverage of companies' third-quarter results. The season begins in earnest next week and will run into November. Next week the weekly issue will include our updates from Johnson & Johnson and Roche among others (you can read them online now); we will also be publishing regular Q3 preview articles to keep you ahead of the curve.

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exclusive online content

Seven Clinical Trial Read-Outs Due In Q4
http://bit.ly/2xPckg8
The last three months of the year should see data reporting from a number of key studies for novel products including Roche's emicizumab. *Scrip* takes a look at some of the more interesting studies expected by year end, with the help of analysts from Informa's Biomedtracker.

Tech Transfer Roundup: Neon Licenses NKI IP To Advance Cell Therapy Into Clinic
http://bit.ly/2yPslTp
Continuing a partnership between Neon co-founder and two Netherlands Cancer Institute researchers, agreement will help autologous T-cell candidate move into Phase I. Plus *Scrip*'s monthly roundup of tech transfer deals.

Biotech Aclaris Ready For Premium Pricing For Skin Drug A-101
http://bit.ly/2kTA9O0
Treating lesions on the face is a very significant opportunity for Aclaris, which is focusing on younger clientele.

Finance Watch: J&J Notes JLabs Incubators' Success Stories To Date
http://bit.ly/2ysQ5vZ
Private Company Edition: Life science firms in J&J's JLabs incubators have raised $9.4bn to date from deals and financings, including five IPOs. Also, October brings a wide range of new equity and VC financings.

Deal Watch: AbbVie Bets On Turnstone's Cancer Immunotherapy Technology
http://bit.ly/2zgYrDT
AbbVie takes options on three oncolytic virus immunotherapies under development at Turnstone. Amgen and CytomX swap IP in cancer immunotherapy collaboration, while Nicox and pSivida will team to fight glaucoma and other eye diseases.

What Korean Pharma Wants To Build On Innovation Momentum
http://bit.ly/2yrG01W
A recent policy forum in Seoul discussed why the South Korean government and the pharma industry should work in tandem to take forward thriving innovation in the country and how faster approval timelines can aid this process.

inside:

Spark's Gene Therapy Is On The Cusp Of Approval; Now It Gets Interesting

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Payers want to reimburse life-altering medicines along the lines of Luxturna

Shutterstock: vchal

Spark Therapeutics Inc. put together a convincing lineup of patients and advocates to provide testimony urging the FDA's Cellular, Tissue and Gene Therapies Advisory Committee to support the US FDA approval of *Luxturna* (voretigene neparvovec) for a rare inherited blindness.

The testimony at the panel's Oct. 12 meeting, largely showcasing Luxturna as a life-altering therapy that gives patients a chance to live an independent life, highlights the challenge awaiting payers, who may not have much leverage when it comes to reimbursing what is expected to be a very expensive product.

The panel recommended 16-0 that the FDA approve Luxturna for the treatment of vision loss due to confirmed biallelic RPE65-mutation-associated retinal dystrophy. The positive recommendation is momentous because it represents an enormous step forward in the industry's decades-long quest to bring a gene therapy to market, and because Luxturna is the first treatment option for patients with an inherited form of blindness for which there are no other treatments, pharmaceutical or medical.

The FDA usually accepts its panels' recommendations. The BLA is under a priority review at the FDA with a Jan. 12 user fee date. Luxturna is poised to be the first gene therapy approved by the FDA in the minds of many in the drug industry, although the FDA did characterize **Novartis AG**'s CAR-T therapy *Kymriah* as a gene therapy. *(Also see "Cornering The Market On Innovation? The First CAR-T And The First Gene Therapy" Scrip, 31 Aug, 2017.)*

Spark's stock was halted on the stock exchange on Oct. 12, but closed on Oct. 11 at $86.20, up 54% since Spark announced the completion of the rolling BLA submission on May 18.

While there have been some questions about the clinical meaningfulness of the novel clinical endpoint Spark used in the Phase III clinical trial – change in score on the multi-luminance mobility testing (MLMT) – notable improvements in a disease like blindness have gotten Luxturna lots of attention. The MLMT measure was designed to assess functional vision by requiring patients to navigate through a course accurately and at a reasonable pace at different light levels. The outcome measure has never been used as an efficacy endpoint and its use as an endpoint was one of the questions the FDA asked committee members to consider.

Payers want to reimburse breakthrough, life-altering medicines along the lines of Luxturna, but they are also bracing for an onslaught of expensive new treatments like gene therapy and CAR-T therapy that can run many hundreds of thousands of dollars or even approach $1m. They aren't sure how to pay the bill, even though many of the initial treatments target niche patient populations, as is the case with Luxturna. Spark estimates that RPE65-mutation-associated blindness affects only 1,000 to 2,000 patients in the US.

The Institute for Clinical and Economic Review (ICER) is working on an assessment of the comparative clinical effectiveness and value of Luxturna, with a report anticipated in January that could help inform payers.

Some payers have already pointed out that Spark's treatment doesn't restore full vision in patients. During the Biotechnology Industry Organization's annual meeting in June, **Express Scripts Holding Co.** chief medical officer Steve Miller talked about the challenges with reimbursing high-cost gene therapies that could cost as much as $1m. While he acknowledged that treatments like Luxturna that improve health need to be reimbursed, he pointed out, "these kids can see better, but they still can't see newsprint."

POWERFUL PATIENT TESTIMONY

But it was the patients who made the case for Luxturna at the advisory committee meeting, and their stories were powerful. "I would do it over and over again," said Katelyn Corey, a young woman who participated in the Phase III clinical trial. She talked about seeing vibrant colors following the surgical procedure, going out for dinner and seeing utensils by candlelight and walking confidently in the dark. "I was independent and mobile, which I had not been for some time," she said. "I may not have gained normal vision but I gained all of my independence."

Ashley Carper, the mother of two young children who participated in the Phase III trial, talked about the improvements her children experienced following treatment. "Our highest expectation for the surgery was just that it would stop progression of loss of vision," she said. "Their vision is better than we could have ever imagined." While improvements are notable on her children's vision exams, she said "the true results are played out every day in our house in everything that they do."

Spark showed the panel a video of patients in the clinical trials navigating through the course before and after treatment and in different lights. Although some panelists had technical questions around the endpoint, most agreed it was a reasonable measure in an area that had not previously had one.

The FDA advisory committee members also appeared to take the patient testimony to heart, as well as a patient questionnaire on activities of daily living included as part of the trial but not as a primary or secondary endpoint.

"We've heard what I would consider very compelling first-hand discussion of functional benefits," said Barry Byrne, professor of pediatric and molecular genetics and microbiology at the University of Florida College of Medicine's Powell Gene Therapy Center. Those accounts along with the questionnaire appear to corroborate the results of the MLMT endpoint, he said.

LIMITED DISTRIBUTION

The advisory panel also felt comfortable with the safety profile of the therapy given the potential benefits, despite some serious adverse events seen in the clinical trials. Spark's safety analysis was based on a total of 41 subjects enrolled in Phase I and Phase III studies. Thirty subjects had ocular adverse events with the most common being conjunctival hyperemia, increased intraocular pressure and cataract development. Two serious adverse events involved permanent vision loss.

Spark is proposing a risk management plan that would limit distribution of the gene therapy to approximately five to eight centers of excellence in the US associated with an active ophthalmology practice, pharmacovigilance Head Deborah Kelley said.

"For the surgical staff, there will be a training program on sub-retinal delivery of the product, including an in-person workshop with the principal investigators running the program, with multi-media presentation and hands-on training," she said.

Spark is already following patients from the two Phase I trials and one Phase III trial out to 15 years post-administration for both safety and efficacy. The company said it will open a safety registry to collect long-term safety data from all patients in the first five years.

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Pfizer Déjà Vu: Is It Time To Sell The Consumer Health Business?

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Drug industry analysts and other observers couldn't be faulted for asking, "Haven't we heard this before?" after **Pfizer Inc.** on Oct. 10 said it is considering selling is consumer health business.

Even so, the announcement sparked discussion of the pros and cons. On one hand, the consumer unit –which includes the *Advil* and *Nexium 24HR* OTC drug and the *Centrum* multivitamin lines – is a dependable source of revenue; on the other hand prospects for growth aren't strong, even with some potential Rx-to-OTC switches in the pipeline. The company indicated a decision isn't expected until sometime next year.

"This is not a new development," noted BMO Capital Markets analysts in a report posted soon after the announcement. BMO and other analysts expect Pfizer would attract suitors for all or parts of its consumer health business, with $15bn to $17bn a likely price, but also say the New York-based firm might be better off continuing to compete in the sector that accounted for revenues of around $3.4bn in 2016.

Morningstar analyst Damian Conover stated in a same-day note that even the best outcome of a consumer health sale or split-off likely would add little value to Pfizer shares.

"If Pfizer were to pursue a sale of the consumer group, the tax implications would likely erase any valuation creation from the deal," said Conover. In a separate post titled "Pfizer's Divestiture Plan No Big Deal," he said a spin-off or split-off "would likely create a minor level of value-creation for shareholders at best."

Pfizer CEO Ian Read's statement about a potential sale tracks with his comments in 2015 after an unsuccessful OTC Lipitor actual-use trial. An OTC drug and nutritional product business is worth keeping but also something to consider selling, Read said then, and now. *(Also see "Lipitor Switch Decision Could Portend Pfizer's Consumer Product Future" Pink Sheet, 31 Jul, 2015.)* But unlike the 2015 go-round, there's no obvious event triggering a sale review. "Although there is a strong connection between Consumer Healthcare and elements of our core biopharmaceutical businesses, it is also distinct enough from our core business that there is potential for its value to be more fully realized outside the company. By exploring strategic options, we can evaluate how best to fuel the future success and expansion of Consumer Healthcare while simultaneously unlocking potential value for our shareholders," the CEO said in the firm's latest release.

PERIODIC REVIEW

While the OTC Lipitor actual-use trial precipitated speculation of Pfizer selling all or part of its consumer health business a couple of years ago, the firm has periodically weighed the move since it re-entered the space through its 2009 acquisition of **Wyeth** – which brought consumer health brands as well as Rx properties. It already has sold the nutritional formula brands that came with Wyeth. *(Also see "Light Still On For Switches After Pfizer Pulls Plug On OTC Lipitor" Pink Sheet, 3 Aug, 2015.)*

Its 2016 decision against splitting into two separate companies, one offering innovative products and the other essential health products, included keeping its consumer health business, which is in the innovative silo. *(Also see "Stronger Together: Pfizer Decides Against A Split" Pink Sheet, 26 Sep, 2016.)*

"Pfizer has a history of ambivalence toward the OTC business. With all the pressure from activist investors, it likely has lost patience," said pharma industry consultant Susan Lavine Coleman, president of NCI Consulting Inc.

In Europe, **Merck KGAA** currently is seeking a purchaser or partner for its consumer unit, saying "increasing internal constraints" make it harder to fully support that business. *(Also see "Big Pharma Set To Compete For German Merck's Consumer Health Unit" Scrip, 5 Sep, 2017.)*

Pfizer said its options include that it "may ultimately determine to retain the business" now operating in more than 90 countries.

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Albert Bourla, president of Pfizer's division that includes consumer health, Innovative Health, noted in the release that with the role of OTC drugs and nutritional supplements in health care growing, the business operates in a promising market.

"Consumers are taking more ownership of their health and wellness through OTC products, preventive treatments and alternative health paths. Pfizer Consumer Healthcare is playing an important role in changing the world's well-being," Bourla said.

Despite that, making a consumer health business comparably valuable in a large pharma's overall business doesn't come easy, say Barclays analysts.

"Despite the high valuations attributed to consumer staples companies in recent years, it has proven somewhat challenging for diversified biopharmas such as Pfizer and [J&J] to garner a similar premium for their respective businesses," according a same-day Barclays note.

The analysts consider Pfizer's potential move "mostly … a positive step for a non-core business that has not contributed meaningfully to re-rating shares."

That's because consumer health sales growth won't drive earnings growth. "While additional branded-to-OTC conversions could put modest upward pressure on sales forecasts, the generally steady cash flows remain the primary appeal along with brand equity," Barclay's analysts say.

Morningstar's Conover suggested that leaving the consumer health sector would shrink a revenue stream Pfizer can rely on consistently. With the business accounting for 6% of its overall revenues, "the loss of branding power is not material for the company," he said.

BMO's Alex Arfaei considers a potential sale "incrementally positive" for Pfizer shares and expects that because it is a reliable revenue stream, business is worth five to six times its 2016 revenue total. Like the animal drug business **Zoetis Inc.** Pfizer spun out in 2013, "the consumer business will likely garner a greater valuation outside of Pfizer because of its durability," Arfaei said.

Although Arfaei like others pointed out Pfizer's announcement isn't its first about a potential consumer health business sale, the BMO analysts "believe a sale/divestiture seems likely."

SWITCH OUTLOOK NOT KEY

Pfizer's decision likely will be influenced by its outlook for potential OTC switch candidates among its Rx products, prospects on which pharma industry consultants offer different views.

"I wouldn't think that Pfizer's consideration on divesting their OTC business is due to prospects on switch candidates. The switch environment looks strong to us – FDA and industry both seem very invested in switches," Jim DiBiasi, founder and president of 3D Communications LLC, said in an email.

Pfizer's most likely OTC switch candidates are the cholesterol-lowering drug *Lipitor* (atorvastatin) and *Viagra* (sildenafil) for erectile dysfunction.

In contrast, NCI's Coleman believes the potential nonprescription futures of Lipitor and Viagra likely influence Pfizer's potential decision.

"I assume Pfizer has concluded that the FDA is unlikely to approve a Viagra switch," Coleman said, adding that the September interim decision by Australia's drug regulator against nonprescription sales of sildenafil could also be influencing the firm.

Lipitor and other currently Rx Pfizer products might not be switch candidates that would be particularly profitable or have a good chance of approval, Coleman said.

"I think Pfizer abandoned the switch of Lipitor several years ago. And other drugs with switch potential in the Pfizer portfolio either have questionable commercial potential or high hurdles to approval," she said in an email.

Pfizer has conducted an actual use trial for nonprescription Lipitor, though it ended the project in 2015 without filing a new drug application for a switch of 10 mg (atorvastatin). The trial not meet its primary objectives of demonstrating patient compliance with the direction to check their LDL cholesterol level and, after checking, to take appropriate action based on test results.

The results of Pfizer's trial were similar to the FDA's reasons for rejecting three previous NDAs that other firms have submitted to the agency for statin switches – concerns about whether consumers could accurately self-select and safely use a statin.

Additionally, Pfizer in 2008 withdrew an application in Europe to switch 50 mg sildenafil from Rx to nonprescription after the European Medicines Agency's Committee for Medicinal Products for Human Use noted concerns including unsupervised use could delay the diagnosis of underlying diseases, such as coronary artery disease, for which ED can be an indicator.

Still, in 2016 the firm seemed to indicate some confidence in a potential Viagra switch when it posted on the professional networking online platform LinkedIn an advertisement for a sexual health brand manager with responsibilities including "support vision and strategies that drive probability of success for the Rx-to-OTC Switch program."

Conover doesn't share the confidence Pfizer could have been showing then. While Lipitor and Viagra "hold potential for a Rx-to-OTC switch, we are skeptical the major regulatory agencies will approve the label change," he said.

And the entire OTC switch outlook probably isn't pointing Pfizer to stay in the consumer health business, Conover said. "With no major … switches likely over the near term, we view the synergy of holding the consumer health business with Pfizer's prescription business as less important." Additionally, with the firm focusing more on critical-care areas such as oncology, "future Rx-to-OTC switches seem less likely."

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From the editors of the Tan Sheet

What Was On Hold Is New Again As Impact Raises $22.5m For Fedratinib

MANDY JACKSON mandy.jackson@informausa.com

It's a straightforward, roundabout story: **Impact Biomedicines** acquired fedratinib from **Sanofi** for a minority stake in the start-up, convinced the US FDA to remove a clinical hold on the JAK2 inhibitor that's completed a Phase III clinical trial in myelofibrosis, and raised $22.5m to seek approval.

The roundabout part of the straightforward story is that Impact's CEO John Hood was the chief executive at **TargeGen Inc.**, which Sanofi purchased in 2010 to acquire fedratinib. The French big pharma gave up on the drug after the FDA initiated a clinical hold in 2013, but doctors and patients involved in the pivotal Phase III JAKARTA-1 trial began seeking access to the drug after experiencing relapses. Those stories and the available fedratinib data convinced Hood that it was an asset worth pursuing.

"I didn't really have much of a choice in that physicians had patients who had responded and – when it was on hold and they couldn't access it – they started relapsing and dying," Hood told *Scrip*.

One patient in particular had a five-year durable response to fedratinib and relapsed after a year off treatment.

"There was a pretty clear and compelling need for it in the community, because for these patients this drug worked for them," Hood said.

FDA DISCUSSIONS ONGOING

San Diego-based Impact will discuss the path forward with the FDA, but the options may include submitting a new drug application (NDA) based on results from 18 completed trials that enrolled 877 patients, including JAKARTA-1, or completion of an additional study prior to an NDA filing.

Medicxi, which announced its new $300m venture capital fund to support later-stage drug developers in June, was the sole investor in Impact's $22.5m Series A round. The money will finance the regulatory process for fedratinib and manufacturing preparations for commercialization – and initiation of an additional study, if the FDA decides it's necessary to prove the drug's safety and efficacy.

Sanofi bought TargeGen in 2010 for $75m up front and up to $485m in milestone fees tied to the development of fedratinib, although Hood left TargeGen in 2008 after the company had a verbal agreement to be acquired by Sanofi, the Impact CEO said. He then co-founded and served as chief scientific officer at **Samumed**, which is developing drugs that modulate the Wnt pathway across a variety of degenerative diseases – lead indications are hair loss and osteoarthritis – and cancer.

Meanwhile, fedratinib development was discontinued three years after Sanofi closed the TargeGen acquisition, despite positive Phase III results in JAKARTA-1. The drug was put on clinical hold due to cases of brain swelling, specifically incidences of Wernicke's encephalopathy (WE), an acute neurological condition associated with a vitamin B deficiency.

It was three years later when physicians and patients who had participated in fedratinib clinical trials started calling Hood looking for a way to remove the clinical hold on the drug.

In fact, Impact co-founder and interim chief medical officer Catriona Jamieson was the principal investigator for several fedratinib trials. Jamieson is a professor, chief of regenerative medicine and deputy director of the Sanford Stem Cell Clinical Center at the **University of California, San Diego** (UCSD). She's also co-leader of the hematologic malignancies program and director of stem cell research at UCSD's **Moores Cancer Center**, where she specializes in myeloproliferative neoplasms and leukemia.

NEW ANALYSES JUSTIFIED MOVING FORWARD

Impact submitted new analyses of prior clinical trials for fedratinib to the FDA noting that a deficiency of vitamin B1 (thiamine) is not unusual for cancer patients undergoing treatments that cause nausea, vomiting and other side effects that can lead to malnutrition. In fact, patients who experienced WE in trials for the drug had severe weight loss. Hood said the brain-swelling side effect wasn't diagnosed based on early symptoms experienced by trial participants, because it's not unusual for myelofibrosis patients to be tired, have memory loss and feel depressed.

"It wasn't until patients started reaching out to me that I realized how many people can't use the standard of care [**Incyte Corp.**'s *Jakafi* (ruxolitinib)] and yet they can't get fedratinib, because of a vitamin B deficiency that's treatable and reversible," he said. "When you start looking at it, it's pretty clear this drug should be out there."

Fedratinib met the primary and secondary endpoints in JAKARTA-1 by reducing spleen size in 47% of myelofibrosis patients by more than 35% at 24 weeks ($p<0.0001$) and improving symptom scores in 36% of patients by greater than 50% at 24 weeks ($p<0.0001$), according to data published in peer-reviewed journals. This was "the highest response rate of any trial in these patients," Hood said.

Biomedtracker analysts gave the top-line results in 2013 high marks, but noted at that time that overall survival (OS) results would be needed to differentiate fedratinib from Jakafi, since Incyte's drug "demonstrated an OS advantage over both placebo and best available therapy in its pivotal COMFORT studies."

Impact noted that in a Phase II follow-on study known as JAKARTA-2, which enrolled myelofibrosis patients who were unresponsive to all other available therapies, fedratinib performed slightly better than in JAKARTA-1. In the mid-stage study, 55% of fedratinib-treated patients who were resistant to or couldn't tolerate Jakafi had a spleen-size reduction of greater than 35%.

The most common adverse events across both studies were anemia, nausea, diarrhea and vomiting.

Impact plans to pursue development and approval of fedratinib across myeloproliferative neoplasms, a related group of blood cancers characterized by mutations of JAK2, MPL or CALR, including myelofibrosis and polycythemia vera. Jakafi is the only FDA-approved drug for both indications.

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'Game-Changer' For Ardelyx As Tenapanor Phase III Is A Hit In IBS-C

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Strong data in a second Phase III study of **Ardelyx Inc.**'s investigational treatment for constipation-predominant irritable bowel syndrome (IBS-C), tenapanor, have put the product back on track, and could prove to be transformational for the company. Shares in the firm were up by more than 48% on NASDAQ on the data, restoring some of the value lost back in May when the first Phase III study T3MPO-1 results underwhelmed investors.

Ardelyx's next steps are to seal a licensing deal for the product ahead of a planned NDA filing in the second half of 2018.

"These results are a game-changer for patients with IBS-C, their treating physicians and for Ardelyx as a company," said president and CEO Mike Raab. "They demonstrate the significant benefit tenapanor can have for patients with IBS-C, importantly, leading to a normalization of bowel movements for many patients." Raab added that the results showed that tenapanor had significant potential in the market and "bolsters our commitment to identify the ideal collaboration partner".

The first-in-class product is a small molecule that inhibits the sodium-proton exchanger NHE3 in the gastrointestinal tract, increasing the amount of sodium and fluid in the gut, thereby loosening stool. The company notes that it seems to have an effect on pain too.

The previous study results had suggested that tenapanor was slightly less effective than its competitors and therefore would be dependent upon its novel mechanism of action to differentiate itself in this heterogeneous condition. But the new data suggest that, once on the market, tenapanor should be able to hold its own against its rivals, the guanylyl cyclase C receptor agonists, **Allergan Inc./Ironwood Pharmaceuticals Inc.**'s *Linzess* (linaclotide), and **Synergy Pharmaceuticals Inc.**'s *Trulance* (plecanatide).

"In sum, Ardelyx needed to hit a home run (and did) with its T3MPO-2 trial, after the weaker-than-expected results shown in the T3MPO-1 trial back in May," commented analysts at BTIG.

ALL ENDPOINTS HIT

The topline data show T3MPO-2 hit statistical significance for the primary endpoint and all secondary endpoints evaluated. The 26-week trial randomized 593 patients meeting the ROME III criteria for the diagnosis of IBS-C to either 50 mg of tenapanor or placebo twice-daily following a two-week screening period.

For the primary endpoint of combined responder rate for six of 12 weeks, more tenapanor-treated than placebo-treated patients (36.5% vs. 23.7%, $p<0.001$) had at least a 30% reduction in abdominal pain and an increase of one or more complete spontaneous bowel movements (CSBM) in the same week for at least six of the 12 weeks of the treatment period.

In addition, tenapanor achieved significance for the CSBM and abdominal pain responder rates in the six of 12 and nine of 12-treatment weeks, with a consistent response across the 26 weeks of the study. The drug was also well tolerated, with the most common adverse event being diarrhea (16.0% vs. 3.7%), flatulence (3.1% vs. 1.0%), nasopharyngitis (4.4% vs. 3.7%) and abdominal distension (3.4% vs. 0.3%). The placebo adjusted discontinuation rate due to diarrhea was 5.8%.

In a conference call to discuss the results on Oct. 11, the company noted that, based on historical data, tenapanor compared well to Linzess and Trulance on the six of 12-week combined responder rate and to Linzess on the nine of 12-week combined responder rate. In both comparisons, tenapanor performed better in T3MPO-2 than in T3MPO-1.

The conference call also included 13 of 26-week responder results for combined responder, CSBM responder and abdominal pain responder, which were similar to the 6 of 12-week rates, indicating strong and consistent efficacy over 26 weeks. The company stressed the importance of the nine of 12-week data as a measure of the normalization of bowel function.

Furthermore, Ardelyx outlined the unmet medical need for its product. Its own market research has revealed that only 21% of prescription-treated IBS-C patients were satisfied or very satisfied with their current treatment and that two-thirds of IBS-C patients were willing to try a different prescription drug. "If approved, there will likely be significant demand for tenapanor with its novel mechanism of action."

The BTIG analysts said: "We believe tenapanor's commercial value is increased, with study results showing a solid efficacy profile that is competitive to that of Allergan/Ironwood's Linzess. With the solid pivotal results shown from this Phase III study, we think tenapanor's efficacy/side effect profile will be competitive in a sizeable market where there are more than 30 million patients with IBS-C."

'COMPELLING'

The analysts believe tenapanor has the potential to become a significant new treatment for IBS-C, with peak sales potential of at least $500m by 2025, given an approval decision in the second half of 2019. The compound has patent protection in the US and Japan out until 2029.

Analysts at JPM were similarly impressed. "We believe tenapanor is a compelling compound that possesses a unique mechanism of action with a potentially differentiated profile that addresses large market opportunities."

Furthermore, the company is also in a good position cash-wise and with its pipeline, having a "differentiated technology platform capable of churning out multiple clinical development candidates".

Tenapanor is also in development for hyperphosphatemia and has another program poised to enter Phase III, RDX022 for hyperkalemia.

Earlier this year, Ardelyx announced positive top-line results from its Phase III trial with tenapanor in patients suffering from hyperphosphatemia and end-stage renal disease. *(Also see "Ardelyx's Tenapanor Data Challenge Phosphate Binders In Hyperphosphatemia" Scrip, 17 Feb, 2017.)*

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CONTINUED FROM COVER

increase the level of competition," White said. "The more competitive the marketplace, the better price and value is going to payers who buy a portion of the portfolio or the entire portfolio. The big challenge for new medicines, whether new brands or biosimilars, he said, is going up against a trusted entrenched medicine like Remicade. The early adoption rates for Inflectra are not that different from the adoption rates of new branded biologics, he insisted. And new patient starts – the patients most likely to try a new product like Inflectra – are limited to about 20% to 25% of the market.

J&J offering steeper discounts on Remicade

Shutterstock: popovic

"It takes time to drive adoption in the market," he added. "The lawsuit was generated well before biosimilars have had a year in the market, so I would say it's unclear how the market is going to evolve. I wonder if the effort was premature."

Indeed, the market will surely be evolving as more biosimilars reach the market and as outstanding legal issues are taken up in court. **Merck & Co. Inc.** already launched a second biosimilar version of Remicade in July, *Renflexis* (infliximab-abda). Merck hasn't provided much in the way of commentary yet about how Renflexis is being received by payers, but another competitor will surely only intensify the pricing pressure in the category.

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to be demonstrated in the marketplace." The intent of the law, he maintained, wasn't to guarantee generic-like activity in the market for biosimilars, referring to the swift price erosion and coinciding market share erosion for brand drugs that typically occurs when a small molecule generic drug enters the market.

J&J is offering steeper discounts on Remicade, though White declined to quantify the level of the discount.

"When we provide a contract with a payer, we provide a bid, and the bid looks at different contracting or pricing terms for a preferred position, a parity position, a step-through position in terms of a variety of discounts we provide," White said. "We submit the grid. We find out where we stand at the end."

J&J, like many drug manufacturers, also ties some discounts to other portfolio products, a tactic known as bundling. White said each of the company's product contracts stand independently but acknowledged the company does offer an "incremental" discount

Interfering Virus: A New Treatment Strategy For Flu

A new UK biotech has been set up to move forward research indicating that specifically engineered influenza virus particles can have a broad-spectrum therapeutic effect on respiratory viral infections.

The company, **VirionHealth Ltd.**, has been founded on the research of Nigel Dimmock and Andrew Easton, professors in the school of life sciences at the UK's University of Warwick. It is supported by the US/UK international venture capital firm Abingworth, which has just raised up to £13m in a Series A funding round for the company, and has recruited some well-known pharma figures to its executive team.

These include as CEO Nicola Thompson, previously the vice president and head of external drug discovery at Roche, and as chair, Jeffrey Almond, formerly the vice president of discovery and external R&D at Sanofi Pasteur. Laura Lane has been appointed chief operating officer.

Although other academic groups are active in this field, VirionHealth believes it is the first company to take this sort of approach forward commercially. "We are really thrilled to be working with Abingworth," said CEO Thompson in an interview. "The funding will be used to move the research into preclinical testing, and should be able to take us to the end of first-in-man studies," she told *Scrip*.

VirionHealth believes its non-infectious, defective interfering viral particles represent a new class of biological antivirals that could simplify and accelerate treatment by being effective without the need to isolate and identify the precise strain of the infection. They are believed to have two modes of action, Thompson noted. They can out-compete incoming pathogenic flu viruses, and they can also prime or stimulate the innate immune system, inducing a local interferon type 1 response that enables the body to fight off infection more efficiently.

john.davis@informa.com, 12th Oct 2017

Read here about Sanofi's New Flu Vaccine Facility: **http://bit.ly/2xIrrTJ**

Ten Approvals To Look Out For In Q4

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From AstraZeneca's benralizumab in asthma to Kite Pharma's CAR-T therapy, *Scrip* takes a look at some of the more interesting drug approvals expected by the end of the year, with the help of analysts from Informa's Biomedtracker.

KERYX BIOPHARMACEUTICALS' AURYXIA

Catalyst: PDUFA for sNDA – First Review
Target action date: Nov. 6
Biomedtracker's LOA Opinion*: Above
**Biomedtracker's proprietary rating of the likelihood of approval of a particular drug, in comparison to average approval rates for drugs in that class*

As it is already approved for hyperphosphatemia, the chances for approval of the sNDA for **Keryx Biopharmaceuticals Inc.**'s *Auryxia* (ferric citrate) in iron-deficiency anemia appear hopeful, BMT analysts believe. Current oral iron formulations are over-the-counter and efficacy can be limited by side effects or compliance due to multiple doses, so the company is hoping that Auryxia could fill a needed gap in treatment.

The oral, inorganic, iron-based compound has the capacity to bind to phosphorus in the gastrointestinal tract and form non-absorbable complexes. Its absorption into the body is lower in patients with normal iron stores and higher in those with iron deficiency. Auryxia was originally approved for hyperphosphatemia in the US in 2014 in dialysis patients and in the EU in 2015 for both dialysis and pre-dialysis patients.

Improvement in anemia was known to be another potential advantage for the drug early on, and because there were no oral iron agents approved in the US for iron deficiency in non-dialysis dependent (NDD) CKD patients – with use of just over-the-counter iron preparations or IV iron in some – Keryx decided to pursue this indication as well.

The sNDA was based on data from a 24-week placebo controlled Phase III trial in 234 adults with stage 3-5 NDD-CKD.

ASTRAZENECA'S BENRALIZUMAB IN ASTHMA

Catalyst: PDUFA for BLA – First Review
Target action date: Q4
Biomedtracker's LOA Opinion: Above

The PDUFA date for the BLA for **AstraZeneca PLC**'s benralizumab for the treatment of severe, uncontrolled asthma is set for the fourth quarter of 2017. The humanized monoclonal antibody targets the interleukin (IL-5) receptor, which is involved in regulating the differentiation, proliferation, and activation of eosinophils.

Where benralizumab is differentiated from the already marketed products, **GlaxoSmithKline PLC**'s *Nucala* (mepolizumab) and **Teva Pharmaceutical Industries Ltd.**'s *Cinqair* (respizumab) (given every four weeks), as well as major competitors in the pipeline, is in its eight-week dosing regimen after the first three doses. This is also longer than that used for another promising AstraZeneca pipeline drug, tezepelumab, in Phase II (every two and four weeks), though the latter has an upstream target and so may have broader effects.

From a mechanism of action standpoint, benralizumab may also have higher clinical and commercial attractiveness than Nucala or Cinqair, partly due to it targeting the IL-5 receptor rather than IL-5 itself, which is expected to lead to a more rapid reduction of eosinophils in the airway and faster onset of action, the Biomedtracker analysts say, although after steady state the difference may be minimal.

The BLA is based on results from the Phase III SIROCCO and CALIMA pivotal studies, both part of the WINDWARD program in asthma (comprised of six Phase III trials in 3,068 patients).

The company also filed an EU Marketing Authorization Application (MAA) in January, with an expected CHMP opinion due in late 2017 through early 2018, and a final decision expected from December 2017 through the first half of 2018. A Japan approval decision is also expected in 2018.

JOHNSON & JOHNSON'S SIMPONI ARIA FOR TWO MORE INDICATIONS

Catalyst: PDUFA for sBLA - First Review for axial spondyloarthritis
Target action date: October
Biomedtracker's LOA Opinion: Above
Catalyst: PDUFA for sBLA - First Review for psoriatic arthritis
Target action date: October
Biomedtracker's LOA Opinion: Average

The PDUFA dates are looming this month for two more indications for **Johnson & Johnson's** *Simponi Aria* (golimumab) – for axial spondyloarthritis and psoriatic arthritis.

A subcutaneous formulation of the anti-TNF-alpha antibody is already approved for psoriatic arthritis, rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, ulcerative colitis, and axial spondyloarthritis (axSpA). An intravenous (IV) formulation is also approved for rheumatoid arthritis, and Janssen Biotech is seeking to expand that IV formulation to psoriatic arthritis and ankylosing spondylitis.

Data from two pivotal Phase III studies of IV Simponi Aria were used to support the sBLAs. First, the Phase III GO-ALIVE study enrolled subjects with active ankylosing spondylitis, and the similarly designed, Phase III GO-VIBRANT trial studied IV Simponi Aria in patients with active psoriatic arthritis. With Simponi Aria having met major primary and secondary endpoints, the drug has a strong chance of expanding its label into these two new indications.

SEATTLE GENETICS' ADCETRIS

Catalyst: PDUFA for sBLA - First Review
Target action date: December
Biomedtracker's LOA opinion: Above

Following the failure of **Seattle Genetics Inc.**'s vadastuximab talirine (SGN-CD33A) in a Phase III acute myeloid leukemia trial, the pressure has been piling on the company's expansion strategy for the currently marketed lymphoma drug *Adcetris* (brentuximab vedotin) to drive near-term growth.

Seattle is seeking to expand the drug label for the anti-CD30 ADC product to include the most common subtypes of cutaneous T-cell lymphoma (CTCL): CD30-expressing mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL) in patients who require systemic therapy and have received one prior systemic therapy.

Adcetris is currently approved in the US for the treatment of patients with Hodgkin's lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates, and for the treatment of patients with systemic ALCL after failure of at least one prior multi-agent chemotherapy regimen.

The supplemental BLA is supported by results from two Phase II investigator-sponsored trials and the pivotal Phase III ALCANZA study of Adcetris versus investigator's choice of methotrexate or bexarotene in patients with CD30-positive CTCL, including those with pcALCL or MF. *(Also see "Pivotal ALCANZA Trial Secures Adcetris' Position in Cutaneous Lymphoma" Scrip, 7 Dec, 2016.)*

Based on the Phase III data, Adcetris was granted breakthrough therapy designation and priority review which have expedited its development and review for CTCL. CD30-positive CTCL affects approximately 10,000 patients in the US making it a relatively small market. Furthermore, Adcetris already sees off-label use in this indication.

MERCK & CO'S LETERMOVIR FOR HUMAN CYTOMEGALOVIRUS

Catalyst: PDUFA for NDA - First Review
Target action date: Nov. 8
Biomedtracker's LOA opinion: Above

Merck & Co. Inc.'s first-in-class viral terminase complex inhibitor letermovir (licensed from **AiCuris GMBH & Co. KG**) is an oral, once-daily, highly active and specific inhibitor of human cytomegalovirus (HCMV) for preventing clinically serious cytomegalovirus (CMV) following bone marrow transplant.

With a PDUFA date set for Nov. 8, letermovir is well positioned to beat **Astellas Pharma Inc./Vical Inc.**'s ASP0113, **Shire PLC**'s maribavir and **Chimerix Inc.**'s brincidofovir to the market, all of which have yet to submit regulatory filings. This could allow letermovir to solidify a holding as the standard prophylactic treatment for CMV infections.

The application was based on a Phase III study of letermovir in preventing clinically serious CMV following bone marrow transplant in 495 adults which showed a significant decrease in CMV infections and mortality rates in the first six months post-transplant. Letermovir also showed a relatively mild safety profile compared with the current treatments which rely on nucleoside analogs with harsh side-effects making them unsuitable for prophylaxis.

Letermovir was previously granted orphan drug designation and fast track status.

KITE PHARMA'S AXICABTAGENE CILOLEUCEL

Catalyst: PDUFA for BLA - First Review
Target action date: Nov. 29
Biomedtracker's LOA opinion: Above

This cell therapy could be the first approved product from **Kite Pharma Inc.**'s portfolio and the second CAR-T therapy approved by the FDA, following the approval of **Novartis AG**'s tisagenlecleucel-t (*Kymriah*) for relapsed/refractory B cell acute lymphoblastic leukemia in August 2017.

Kite Pharma – which is set to be bought by **Gilead Sciences Inc.** – announced that the US FDA has accepted for priority review the BLA for axicabtagene ciloleucel based on data from the ZUMA-1 Phase II trial demonstrating remarkable efficacy of a single infusion of axicabtagene ciloleucel in patients with refractory aggressive non-Hodgkin lymphoma (NHL). *(Also see "Kite On Course For FDA Filing On Positive CAR-T Durability Data" Scrip, 1 Mar, 2017.)*

The FDA has set a PDUFA target action date of Nov. 29.

This FDA-designated breakthrough therapy consists of a patient's peripheral blood T lymphocytes that have been genetically engineered in vitro with chimeric antigen receptors (CAR), enabling them to recognize the tumor-expressed molecule CD19 after infusion back into the patients.

DYNAVAX'S HEPLISAV

Catalyst: PDUFA for BLA – Second Review
Target action date: Nov. 10
Biomedtracker's LOA opinion: Above

Over the summer, the FDA and **Dynavax Technologies Corp.** agreed on a plan that would extend the user fee goal date of hepatitis B vaccine *Heplisav* by three months to Nov. 10 so the company can submit more information on a postmarketing study into myocardial infarction in response to feedback from the agency's Vaccines and Related Biological Products Advisory Committee meeting on July 28.

The FDA's primary concern had been that the safety data from the DV2-HBV-23 study that showed an imbalance in deaths and serious adverse events of myocardial infarction, with the relative risk in the Heplisav group being 3.15 times that of the comparator GlaxoSmithKline's *Engerix-B* group. In response to the FDA's questions, Dynavax submitted a major adverse cardiovascular events analysis that found that the imbalance of cardiovascular events was due to a lower than expected number of events in the Engerix-B group, rather than an excess of events in the Heplisav group.

"The VRBPAC committee voted 12-1-3 (Yes-No-Abstain) that this data supported the safety of Heplisav-B when administered to adults 18 years and older providing a positive outlook for the upcoming US approval decision," commented the Biomedtracker analysts.

Heplisav uses Dynavax's proprietary immunostimulatory sequence (ISS) to target Toll-Like Receptor 9 (TLR-9), stimulating an innate immune response. Heplisav's combination of ISS and HBV surface antigen aims to enhance the level, speed and longevity of protection.

ULTRAGENYX'S UX003

Catalyst: PDUFA for BLA - First Review
Target action date: Nov. 16
Biomedtracker's LOA opinion: Below

Ultragenyx Pharmaceutical Inc.'s investigational enzyme replacement therapy for the treatment of mucopolysaccharidosis VII (MPS VII, Sly syndrome), the recombinant human beta-glucuronidase UX003, is under priority review for its BLA, with a PDUFA goal date of Nov. 16. MPS VII is a rare lysosomal storage disorder that leads to a progressive accumulation of glycosaminoglycans (GAG) in many tissues and organs of the body.

The indication is difficult to study because it is quite rare. Hence, the Phase III study only involved 12 patients, and because of the impracticality of doing a parallel group controlled trial, used a placebo-controlled randomized start. How regulators view the results will depend to some extent how well they think this strategy helped weed out a placebo effect, said the Biomedtracker analysts.

In the Phase III trial, after 24 weeks of treatment, UX003 encouragingly reduced a

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biomarker, urinary GAG (dermatan sulfate) excretion, by 64.8% (p<0.0001). However, a functional measure, the multi-domain responder index (MDRI) score, just missed nominal statistical significance with a mean improvement of +0.5 domains (p=0.0527). There was also an improvement in the 6MWT of 20.8 meters, but it was based solely on the nine patients who achieved full data.

In November 2016, the company announced it had met the EMA and FDA, and each agency would be taking a different approach for evaluating the Phase III data. In Europe, the EMA accepted the urinary GAG excretion biomarker as a primary endpoint and indicated that some evidence or trend in improvement in clinical endpoints would also be necessary for approval. In the US, there is no primary endpoint declared; the FDA will consider the totality of data on a per-patient basis.

"As the primary endpoint for the EMA was met and there was a trend on the MDRI, approval in the EU appears likely. In the US, there is more uncertainty, but the fact that the FDA stated that it will review the data on a patient-by-patient basis suggests they may be lenient."

UX003 received orphan drug designation from the US and EU in 2012 and was granted Fast Track Designation in August 2015. An MAA is currently under review by the EMA with a CHMP opinion expected between February and August 2018.

AETERNA ZENTARIS' MACIRELINE

Catalyst: PDUFA for NDA - Second Review
Target action date: Dec. 30
Biomedtracker's LOA opinion: Above

AEterna Zentaris Inc.'s orally-active ghrelin agonist for diagnosis of adult growth hormone deficiency (AGHD), *Macireline* (macimorelin acetate) is getting its second chance at the FDA with a PDUFA date set for Dec. 30, after its first attempt met with a complete response letter in November 2014. *(Also see "Aeterna Zentaris tanks on FDA Macrilen rejection" Scrip, 7 Nov, 2014.)*

To address the concerns, the company began in 2015 a new pivotal, Phase III, open-label, randomized, two-way crossover trial designed to compare the product with the ITT (insulin tolerance test) in subjects suspected to have AGHD and a group of healthy control subjects. Following a meeting in March where the FDA stated that this Phase III trial addressed the prior deficiencies mentioned in the CRL, the company resubmitted its NDA for macimorelin.

Presently, there is an unmet medical need for a substitute for the ITT which can induce diabetic comas through its hypoglycemic effects. If approved, it would be the only FDA-approved drug for assessing AGHD. Given the recent NDA resubmission, a product launch is anticipated in the first quarter of 2018.

INDIVIOR'S RBP-6000

Catalyst: PDUFA for NDA – First Review
Target action date: Nov. 30
Biomedtracker's LOA opinion: Above

Indivior PLC is looking to RBP-6000 – its once-monthly injectable depot formulation of buprenorphine in the ATRIGEL delivery system – to buffer its fortunes after a US court ruling raised the prospect of earlier-than-expected generic competition to its flagship product *Suboxone Film* for drug addiction in September. *(Also see "Indivior To Appeal US Suboxone Setback, Flags Follow-On Drug RBP-6000" Scrip, 2 Sep, 2017.)*

RBP-6000 could offer a meaningful treatment option for adults with moderate-to-severe opioid use disorder (OUD) when compared with standard applications, Biomedtracker analysts say. It uses a delivery system that is intended to make abuse and diversion difficult and it also provides the potential for increased treatment adherence. If approved, RBP-6000 would represent the first once-monthly injectable buprenorphine treatment for OUD.

In July 2017, Indivior announced that the FDA had accepted the NDA for RBP-6000, with a Priority Review designation, for the treatment of adults with moderate-to-severe OUD, and set a PDUFA date of Nov. 30. The agency also notified Indivior that it would convene an advisory committee meeting to review the NDA for RBP-6000 since it meets the "new chemical entity/new combination product" criteria established by PDUFA IV. The committee meeting is expected in the fourth quarter of 2017.

The NDA was based on data from the pivotal Phase III RB-US-13-0001 study. *(Also see "Indivior Leaps On Phase III Data For Depot Opioid Addiction Treatment" Scrip, 18 Aug, 2016.)*

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Polyphor Pursues Inhaled Antibiotics

Polyphor Ltd. is looking at the potential of an inhaled version of its Phase III-ready antibiotic murepavadin as a new treatment option to reduce the number of lung infections.

The privately held Swiss company is one of two industry members (the other being Novartis AG) of iABC - a consortium of lung specialists in 18 hospitals and research institutions in eight countries dedicated to the development of inhaled antibiotics in bronchiectasis and cystic fibrosis (CF). It is getting up to €5m from the Innovative Medicines Initiative (IMI), the public-private partnership of the European Federation of Pharmaceutical Industries and Associations and the European Union (a sum which Polyphor will match) to develop treatments for chronic lung infections and one of them could be an inhaled formulation of murepavadin.

The drug is the first in a new class of outer membrane protein targeting antibiotics (OMPTA) and is being developed for the most severe Pseudomonas aeruginosa infection – nosocomial pneumonia – a disease with a death rate of 20-50%. Having received positive guidance from the US Food and Drug Administration and the European Medicines Agency, a Phase III trial of an intravenous formulation of murepavadin is expected to begin in the first quarter of 2018.

However Polyphor believes that an inhaled formulation of murepavadin could extend the therapy to the treatment of chronic infections by P. aeruginosa - affecting for example over 60% of adults with CF and many of those with non-CF bronchiectasis and other rare lung diseases.

The company quoted Stuart Elborn of the Royal Brompton Hospital in London as saying that just a few decades ago, most CF patients died in early childhood but "thanks to antibiotics, patients born today can expect to reach early middle age.

kevin.grogan@informa.com, 12th Oct 2017

Roche Goes Back To Nature With Warp Drive Antibiotic Pact

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With the threat of antimicrobial resistance once again making the headlines, **Roche** has unveiled a pact with **Warp Drive Bio Inc.** of the US to discover and develop multiple novel classes of natural antibiotics.

The Swiss major is getting access to Warp Drive's Genome Mining platform which the latter says enables access to natural product drugs "that have not been analyzed previously, owing to historical technology limitations." The Cambridge, Mass.-based group is evaluating over one hundred novel classes of potential antibiotics that were previously undiscovered and thus never analyzed for their impact on human health.

Warp Drive will receive up to $87m through an upfront payment, option fees and preclinical milestones, giving Roche an option for an exclusive worldwide license to develop and commercialize certain antibiotic classes that emerge from the collaboration. Warp Drive is also eligible for up to $300m in clinical, regulatory and sales milestones on the products licensed to Roche, plus tiered royalties.

Warp Drive says it "operates on the core principle that nature is the world's most powerful inventor of new medicines, unconstrained by the mechanistic and synthetic limitations of traditional medicinal chemistry." The company claims that its approach represents a paradigm shift in antibiotics research because by searching its genomics database for previously unexplored biosynthetic gene clusters that contain embedded resistance genes, Warp Drive scientists "are able to readily identify candidate antibiotic classes." It then deploys a synthetic biology platform to engineer and express novel natural products that can be isolated and tested for biological impact.

The company quoted Karen Bush from Indiana University as saying that "with the innovative platform developed by Warp Drive, there is the potential to discover novel natural product antibiotics, historically hidden within microbes. These previously-untapped antibiotic classes may play a key role in the future strategy to combat antimicrobial resistance."

Warp Drive notes that there are currently 10 classes of natural antibiotics that have been approved for patient use as compared to five classes of synthetic antibiotics. The last antibiotic from a novel natural class approved by the US Food and Drug Administration was daptomycin, discovered more than 30 years ago.

The company was launched in 2012 with financing from Third Rock Ventures and Greylock Partners and a high-profile partnership with **Sanofi**. The French drug maker is still very much a partner as their collaboration was extended last year to focus on three oncology programs as well as the development of new antibiotics targeting Gram-negative bacteria using both the Genome Mining and SMART (Small Molecule Assisted Receptor Targeting) platforms developed by the US group.

Under that deal, Warp Drive is eligible to receive in excess of $750m from Sanofi across four collaboration programs, including an equity investment, research, clinical and regulatory milestones, plus R&D services. However, the revamped pact, which saw Sanofi drop an option to acquire Warp Drive, meant the latter could deploy its platforms against other targets, both alone and in collaboration with other companies, hence the Roche deal – in March, it inked a cancer deal with **GlaxoSmithKline PLC.**

Many big pharma players have of course abandoned the clinically and commercially challenging field of antibiotics. Roche, which discovered iclaprim, an antibiotic that could soon be filed by **Motif Bio PLC**, returned to the area to much fanfare in 2013 with a $560m pact with **Polyphor Ltd.** and its compound murepavadin but two years later pulled out because "a streamlined development path as originally planned is no longer an option."

Roche and Warp Drive Bio to dig deep for new natural antibiotics

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It does have other ongoing antibiotic collaborations however, and last September inked a pact with the Biomedical Advanced Research and Development Authority (BARDA) of the US Department of Health and Human Services, whereby Roche is to receive more than $35m over two years and potentially more than $150m over five years for its antibiotics portfolio.

News of the Roche link-up with Warp Drive comes days after England's chief medical officer Dame Sally Davies repeated her warning of a "post-antibiotic apocalypse" that would spell "the end of modern medicine". She told the Press Association: "This AMR is with us now, killing people. This is a serious issue that is with us now, causing deaths. If it was anything else, people would be up in arms about it. But because it is hidden they just let it pass.

Last week, the Global Burden of Disease AMR (GBD AMR) project was launched at the Wellcome Trust's Call to Action conference in Berlin, which will gather and publish data on the impact of superbugs globally, allowing scientists to, for the first time, map disease and death caused by drug-resistant infections.

Scientists from the Big Data Institute and the Centre for Tropical Medicine and Global Health, both at the University of Oxford, and researchers at the Institute for Health Metrics and Evaluation University of Washington, will work together on the initiative. Other key contributors include the Wellcome Trust, which is investing £2.4m into the project, and the Bill and Melinda Gates Foundation.

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Competition Piles Up: 100 Teneligliptin Brands Now In India

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Newcomer teneligliptin has set a record of sorts with an estimated 100 brands (including its combination with metformin) on the Indian market in just over two years since it was first introduced in June 2015.

Teneligliptin has also emerged tops in 2016-17 in terms of sales, edging past established gliptins like sitagliptin and vildagliptin, according to some industry experts.

Market data referred to by these experts suggests that sales of all gliptins and their combinations including teneligliptin for the 12-months to June 2017 touched INR20bn ($307m) for the first time. The 100th teneligliptin brand – from **Goldline Pharma** - made its debut in May this year. These experts, however, explain that some local firms have a dual brand approach for teneligliptin, which has contributed to the molecule's growing brand numbers.

Interestingly teneligliptin surpassed vildagliptin and sitagliptin in terms of sales value for 2016-17 and the trend appears to be sticking in 2017, at least going by recent numbers. IMS data suggests that overall teneligliptin sales stood at around INR2.21bn in 2016-17, squeaking past vildagliptin at roughly INR2.12bn and significantly ahead of sitagliptin at about INR1.85bn. The other gliptins – linagliptin, saxagliptin and gemigliptin – are quite a distance behind, although linagliptin appears to have gained some momentum.

However, the vildagliptin + metformin combination led the gliptin combinations pack with sales of around INR4.90bn in 2016-17 - ahead of both the sitagliptin + metformin combination (INR4.55bn) and the teneligliptin combination with metformin (INR1.35bn). The vildagliptin + metformin combination group reported a market share of 42%, followed by sitagliptin + metformin (39%) and then teneligliptin and metformin (11.66%),as per the IMS data referred to by the industry experts.

Novartis did not respond to specific queries on teneligliptin inching ahead of vildagliptin or how *Galvus* (vildagliptin) had fared in India. The Swiss multinational, however, said that the vildagliptin group has 35% value and 28% unit market share in the DPP4i [dipeptidyl peptidase-4 inhibitor] segment.

"Vildagliptin and vildagliptin + metformin belong to the same family of molecules. We do not segregate data for the two to track market share and leadership movement as the shift generally represents a preference of HCPs to use either a plain or a combination molecule therapy, more than preference towards a particular molecule," Novartis told *Scrip*.

MSD declined to comment on *Januvia* (sitagliptin) or its combination's position in the Indian market compared with teneligliptin or vildagliptin.

GAME CHANGER?

The rise of teneligliptin in India is significant given that both vildagliptin and sitagliptin have had a significant headstart in the country and have long ruled the DPP-4 inhibitor market. Following teneligliptin's launch at a sharp discount to the prices of vildagliptin and sitagliptin, its volume growth appears to be rather impressive. Last year *Scrip* reported how volumes of teneligliptin had apparently edged past the combined volumes of vildagliptin and sitagliptin.

Glenmark Pharmaceuticals Ltd. launched the first cut-price version of **Mitsubishi Tanabe Pharma Corp.'s** *Tenelia* (teneligliptin) in June 2015 at about INR19.90 ($0.31 at the time) per tablet across India. At the time, Glenmark said that it was expecting teneligliptin to be a "game changer" since it would pare the daily cost of diabetes treatment for a patient by around 60% as compared to other gliptins, then estimated to be priced at around INR45 for a day's therapy.

Mitsubishi Tanabe had previously moved the Delhi High Court against Indian patent authorities in a case concerning its patent application relating to certain salts of teneligliptin, but it's unclear if the ongoing case could have any bearing on the surging local generics market for the product.

Novartis, which has been selling vildagliptin and vildagliptin in combination with metformin hydrochloride in India since 2008, has partnerships with a number of firms including **USV Ltd.** for the product. MSD, as **Merck & Co. Inc.** is known outside the US and Canada, launched Januvia in India also in 2008. India's top ranked drug firm **Sun Pharmaceutical Industries Ltd.** co-markets sitagliptin as Istavel and the sitagliptin +metformin combination under the brand name *Istamet* under its alliance with MSD.

GLENMARK LEADS PACK

Glenmark's teneligliptin brands *Zita Plus* and *Ziten* currently lead the teneligliptin pack which has over 50 brands (excluding the combination) on the market.

In May 2017, the teneligliptin molecule registered overall sales of INR234m, of which Zita Plus and Ziten notched a 16.5 % share, followed by **Zydus Cadila**'s *Tenglyn* (9.1%) and the Delhi-based **Mankind Pharma**'s *DynaGlipt* (7.5%), among others. In the teneligliptin and metformin combinations space Glenmark's *Zita Met Plus* and *Ziten M* notched a share of about 30% in the same month.

Significantly, the plethora of brands and competition has meant a further fall in prices; data on online medical stores in India indicate that teneligliptin brands are now available as low as INR6.6-7.9 per tablet for the 20mg version.

Glenmark confirmed its top-ranking for teneligliptin and told Scrip that the total number of diabetics in India on gliptin therapy had increased from 1.9 million to 2.9 million.

"Out of this 2.9 million, almost one million patients are currently on teneligliptin," the Mumbai-based company claimed.

Though the patient numbers represent a small fraction of India's overall diabetic population, which is estimated at around 63 million, analysts say it's probably significant given that some leading physicians have in the past suggested that only around 6 million Indian patients get "appropriate" treatment.

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Scrip Awards Finalists 2017

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Best Partnership Alliance

This award recognizes the importance of pharmaceutical and/or biotech companies working together to develop new medicines.

AstraZeneca and Pieris Pharmaceuticals for Anticalin-based inhaled biologics for respiratory diseases

This creatively structured, multi-program collaboration combines Pieris' platform for inhaled Anticalin-based biologics with AstraZeneca's expertise in inhaled formulation technologies to address unmet needs in respiratory disease. With potential payments of around $2.1bn it could prove one of the largest respiratory alliances in history.

BioNTech and Genentech for mRNA-based cancer immunotherapies

Genentech paid $310m up front and near-term milestones to enter the mRNA cancer immunotherapy space with this deal with BioNTech in which the two companies will share equally all development costs and any potential profits. BioNTech gained a partner with a huge experience in the US oncology market while retaining significant decision-making rights.

Cancer Research UK and Bicycle Therapeutics' agreement to trial BT1718 for cancer

This collaboration provides Bicycle with access to CRUK's extensive oncology expertise to robustly test its lead asset – the first-in-class bicyclic peptide BT1718 – in patients for the first time, and allows CRUK to be at the forefront of the development of a whole new and potentially disruptive class of anticancer agents.

F-star with Denali Therapeutics for delivery of medicines across the blood-brain barrier

This collaboration brings together Denali's expertise in the blood-brain barrier and CNS therapy development with F-star's capabilities in the development of bispecific antibodies. The flexible business model offers Denali an option to acquire the platform through the buyout of F-star Gamma or have the right to use it to develop bispecifics under license.

Merck KGaA and Avillion for anti-IL-17 A/F Nanobody in inflammatory diseases

Merck and Avillion's agreement for Merck's investigational nanobody in inflammatory diseases sees Avillion responsible for its development and financing up to Phase III, when Merck would take over for registration and commercialization, paying royalties to Avillion. These types of collaborations are relatively new in Europe and could serve as a model for others.

Takeda and Ovid Therapeutics for TAK-935 in rare epilepsies

Takeda has completed Phase I with this CH24H inhibitor and has selected Ovid as partner of choice, leveraging its agility and focus on rare neurological disorders. Ovid will lead clinical development and commercialization in the US, EU, Canada and Israel, and Takeda lead commercialization in Japan. Costs and profits will be split equally.

WuXi AppTec's Biotech Company of the Year Award

This award honors outstanding achievement by biotech companies over the qualifying 12 months.

AC Immune

A successful IPO raising about $70.5m was the high point in a landmark year for the Swiss-based neurodegenerative disease company, AC Immune - the financial resources will support its next growth phase as it builds on pipeline progress. The company also entered into a new collaboration with another major partner, Essex Bio-Technology.

Avacta

In the qualifying 12 months, Avacta made significant progress with its therapeutic program, taking its Affimer technology from an almost standing start to being a revolutionary next-generation therapeutic platform, demonstrating significant technological benefits that will ultimately allow the company to deliver differentiated immune-oncology therapies.

Bicycle Therapeutics

A year of tremendous progress for Bicycle saw it establish its US subsidiary in Cambridge, MA, and sign two collaboration agreements, a partnership with Cancer Research UK to trial its lead candidate, and a licensing deal with AstraZeneca. It also closed a £40m Series B financing to support development of its multiple bicyclic peptide candidates.

BioNTech

This German company enjoyed a year of outstanding business and development achievements, including a landmark deal with Genentech for individualized mRNA cancer vaccines, in which the partners will equally share costs and profits. It also described in *Nature* the first example of a clinically applicable and systemic mRNA cancer immunotherapy vaccine.

Genmab

It was another vintage year for Genmab – one of Europe's biggest biotechs – as it achieved progress with its two marketed products, Arzerra and Darzalex, as well as its first antibody-drug conjugate in development, tisotumab vedotin. Darzalex in particular impressed with data from CASTOR and POLLUX in combination with other standard treatments.

Tocagen

Tocagen's achievement of several significant milestones over the past year have transformed it from an early stage company advancing Phase I studies into a public company with a potential registrational trial for its lead product candidate, Toca 511 & Toca FC, after it received a breakthrough therapy designation from the US FDA.

Takeda Eyes Irish Opportunities Despite Access Issues

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Although access to new medicines leaves a lot to be desired, Ireland has a lot to offer innovative pharmaceutical companies, according to **Takeda Pharmaceutical Co. Ltd.**, which has plans for further expansion in the country.

Takeda has been in Ireland for 20 years and is looking to expand

Shutterstock: Bennian

> 'Access to all innovative treatments is not yet a given for patients in Ireland'

The country is in "a unique position because of the vigorous ecosystem of companies with manufacturing, shared services or other strategic operations," according to Shane Ryan, country head of Takeda Products Ireland, who told *Scrip* that the country has "an exemplary compliance record with regulatory agencies and a skilled workforce." He added that pharmaceutical companies also profit from strong support through networks such as the Industry Research & Development Group (IRDG), the business and employer association for organizations based in Ireland (IBEC) and BioPharmaChem (BPCI) and the sector offers competitive salaries with a high standard of living for the right talent.

Takeda has been in Ireland for 20 years with its first factory in Bray, which opened in 1997, then serving as the Japanese drug maker's main pharmaceutical production base for the European and US markets. That was followed by the completion of a facility in Grange Castle in Dublin in 2006 and in June this year, construction started at the latter on a €40m standalone facility dedicated to the manufacture of the firm's oral multiple myeloma drug *Ninlaro* (ixazomib), a first-to-market active proteasome inhibitor.

Takeda was a bit surprised to see an article in the UK's *Sunday Times* last month which claimed that the company will invest up to €100m in a new plant at Grange Castle that could eventually add 100 jobs there. It did acknowledge that advance planning permission has been sought to facilitate the potential expansion of the site, but did not disclose further details on proposed plans or levels of investment.

ACCESS TO INNOVATION IS A PROBLEM

However not all is rosy in the Irish garden and Ryan said that "access to all innovative treatments is not yet a given for patients in Ireland." He cited a recent analysis by the Irish Pharmaceutical Healthcare Association (IPHA) which indicated that over 90% of all health technology assessments completed in 2015 & 2016 ended with a negative recommendation from the National Centre for Pharmacoeconomics.

Companies can then enter into negotiations with the Health Service Executive (HSE) which currently take an average of eight months according to the IPHA, and the total average timeline to obtain reimbursement for the majority of specialist medicines in Ireland is now over 18 months. Ryan told *Scrip* that "looking at our EU reference basket of 14 countries, Ireland clearly falls behind the rest of Europe with getting new treatments to patients. In 2016, only one in five oncology medicines launched internationally in 2014 and 2015 were available to Irish patients, compared with 40% in Portugal and 76% in Germany."

He added that "this is very concerning for Takeda, and we are actively committed to working with all stakeholders to improve this situation so that Irish patients are not disadvantaged." Ryan noted an agreement signed last year between the IPHA and the HSE which is supposed to deliver approximately €785m in savings to the Irish healthcare system over its four-year term. The pact is a positive one, Ryan believes, as "it provides certainty from a planning perspective. We are happy to bring value to the Irish state and this financial headroom should mean that there is greater capacity to bring new and innovative treatment to Irish patients."

The HSE finally agreed to fund Takeda's *Entyvio* (vedolizumab) for Crohn's disease and ulcerative colitis in August and Ryan said the company has launched a patient support program in Ireland that offers nutrition advice, personal coaching and more. The program had strong input and validation from specialist IBD nurses who believe it adds well to their activities, he stated. *(Also see "Delayed Medicines To Hit Irish Market, But Uncertainty Remains For Future" Pink Sheet, 3 Aug, 2017.)*

Ryan also noted that Takeda recently partnered with Crohn's & Colitis UK to campaign the main airports, train stations and service stations to adopt accessible toilet signage to give more patients more confidence to travel. He said "we are proud of how well the 'Travel with IBD' campaign has done so far and are hopeful we can bring this to Ireland as well," and added that in oncology, the company recently partnered with the Irish Cancer Society to support 'Living Well With Cancer', a survivorship congress for patients and their support network.

Ryan concluded by saying that "we will continue the evolution of the business here to become an agile specialty-focused organization. I believe we have an entrepreneurial culture that encourages independent thinking by giving autonomy and responsibility to our people."

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Single-Tablet Darunavir-based Combo Effective

Johnson & Johnson may be taking a back seat in the hepatitis C market, but it is looking more competitive in the HIV/AIDS sector, where just-released top-line 48-week efficacy and safety data from the Phase III EMERALD study show a lack of virologic rebound and similar virologic suppression and safety associated with the company's darunavir-based once-daily single-tablet regimen compared with multi-pill therapies being taken by control patients.

In announcing the results, J&J's **Janssen Pharmaceutica NV** and AIDS researchers highlighted the likely better adherence of patients to a single daily tablet, and the high barrier to the development of antiviral resistance represented by darunavir, a HIV protease inhibitor. The darunavir-based once-daily regimen met the study's primary endpoint relating to the lack of virologic rebound.

Although promising, it's unclear how successful the new combination will be. Analysts at Datamonitor Healthcare have previously pointed out the HIV/AIDS market is becoming crowded with various combination therapies. Also, the four-drug combination is likely to cannibalize the market share previously held by Janssen's dual combination, *Prezcobix* (darunavir and cobicistat), the analysts remarked.

Other once-daily anti-HIV tablets on the market include **ViiV Healthcare**'s *Triumeq* (lamivudine, abacavir sulfate and dolutegravir) and **Gilead Sciences Inc.** *Genvoya* (elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide).

Janssen is proceeding with a roster of marketing submissions and approvals, with the darunavir-based once-daily tablet being approved for marketing in Europe, as *Symtuza*, on Sept. 25, 2017.

john.davis@informa.com, 9 Oct 2017

Catalonia In Danger Of Failing Pharma Stability Test

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Leading figures in the pharmaceutical industry in Spain have been reacting to the crisis triggered by last week's referendum in Catalonia, noting that threats of a unilateral declaration of independence would be ruinous for the sector.

A tumultuous week for Spanish politics ended with huge anti-independence demonstrations across the country, most notably in Barcelona, the capital of Catalonia. Organizers of the rally, Societat Civil Catalana, said more than one million people had taken part, although Barcelona police put the turnout at 350,000.

With emotions running high, Spain's pharmaceutical companies have been unsurprisingly reluctant to speak up about the political situation but the economic instability that the illegal referendum and its aftermath have provoked is a cause for considerable concern for the sector. The uncertainty has already led some businesses to move their bases away from Catalonia and Spanish flagship biotech **Oryzon Genomics SA** is relocating its administrative headquarters from Barcelona to Madrid.

It is a delicate situation and a number of pharma companies - both domestic and multinational – have not responded to requests from *Scrip* for comment on how damaging the crisis is for the sector. However, two very senior industry figures did agree to speak, on condition of anonymity.

The first believes that in terms of R&D, companies are not going to just shut up shop and close their facilities in Catalonia, where many drug makers have a presence. Stability is key for the sector and for the good of their workforce and their research efforts, the source said, companies will not be uprooting their R&D centers or manufacturing plants, and certainly not near-term.

TAX REVENUES COULD DRY UP

However, they will take measures to reduce economic risk and quickly if necessary. The source noted that while employment levels within the pharma and biotech sectors in Catalonia will not be affected, the autonomy's government could be in for a shock when money coming into the region through taxes starts to dry up as companies switch their corporate headquarters to Madrid or elsewhere.

As well as the Oryzon move, the source cited the examples of La Caixa, Spain's third largest bank, shifting its legal base to Valencia and Banco Sabadell moving to Alicante. Whether pharmaceutical companies, many of which have been high-profile firms in Catalonia, will do the same remains to be seen but the source says none of them want to find themselves outside the European Union in an area not recognized by any other states, which would be the case if the independence activists continue to dominate the political discourse and act unilaterally.

The source also noted that the Spanish government is proposing a royal decree to change the law to facilitate the relocation of Catalan companies. Seeing that option on the table should make the local government think twice about endangering the region's economy, the source added.

The second senior source to speak to *Scrip* also stressed the importance to pharma companies of stability on a commercial, scientific and regulatory level, so if the turmoil continues in Catalonia, the logical step is for domestic firms to relocate their headquarters in Madrid or other parts of Spain. As for the multinationals, the source believes that they will stay put but they are not going to make substantial investments in the north-east region as they cannot afford to take the risk of setting up or expanding in a non-European Union zone.

The source added that the independence movement has several factions, saying some elements are anti-system and others take a more emotional approach, even if it means that Catalonia will find itself much worse off economically. The individual added that to have the voices of these leaders drown out what is being referred to as 'the silent majority' in the region would be a great shame for the life sciences sector there which has emerged as a leading center for biotechnology in southern Europe.

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Majority Of Indian Firms "Beginners" In Digital Journey

PENELOPE MACRAE

Big Indian pharmaceutical players employ armies of salesmen to sell their drugs. But using salesmen as foot-soldiers to get physicians to prescribe their company's drugs is fast becoming an outdated marketing model, says a just-released EY report.

Digital technologies now are the driving force in a rapidly shifting healthcare landscape with tech-aware doctors relying far less on pharmaceutical sales representatives and more on new independent online channels for information, says the report entitled "Reinventing pharma sales and marketing through digital in India."

Nowadays, marketing "is more than just selling the pill," Sriram Shrinivasan, EY global life science emerging markets and generics leader, told Scrip.

Digital disruption globally has shaken industries from music and retail to travel and since 2000 has led to 52% of Fortune 500 companies becoming bankrupt, being acquired or going out of business, the report warns.

The Indian government, under Prime Minister Narendra Modi, has been aggressively pushing digitization in all areas of the economy from banking and retail to taxation.

Still, most Indian pharmaceutical companies remain at the early stages of digital adoption even as worldwide drug companies are moving — albeit cautiously as they look at factors such as return on investment (ROI) — toward being "digital practitioners," the global consultancy says. *(Also see "As Digital Channels Grow In Importance, AZ, Lilly, GSK Seen As Key Engagers" Scrip, 12 Jul, 2017.)*

INDIAN DRUG FIRMS AT EARLY STAGE OF DIGITAL ADOPTION

According to a five-point digital-maturity scale developed by EY, some 93% of Indian pharma companies fall into the early-stage category and are yet to develop any clear digital strategy and have limited digital channels to find and engage customers.

"We compared what Indian companies are doing with regard to digitization to what global companies are doing and there is a significant gap," said Shrinivasan.

There are more than 600,000 medical sales representatives in India, according to industry estimates, and they have long been considered as being among the greatest assets of Indian pharmaceutical firms. There is always a clutch of young men with bulging briefcases in doctors' consulting rooms, waiting for a chance to make their pitch.

But only 11% of healthcare professionals in India now prefer in-person visits from a company representative, says a 2016 study by Health Link Dimensions2. Time-squeezed doctors, large private healthcare chains and increasingly online savvy patients, want Internet platforms to provide clinical information.

Already, there are a host of online communities for sharing patient experiences, apps and sensors to monitor the impact of therapy on a patient's daily life and data aggregation and analysis to generate insights into drug efficacy and safety. Experts say pharma companies must rapidly build their own digital capabilities if they want to remain the main source of authority on product performance. "Data needs to become the currency of marketing," the report says. Looking at the US experience gives an idea of how digital is transforming the way the healthcare industry does business. Nearly 70% of US consumers use an online channel to manage health and wellness, more than 50% of US healthcare providers are digital "omnivores" using three or more connected devices professionally, and one in five of the top pharma companies now has a chief digital officer or equivalent position, and many others are creating senior management digital roles, according to a recent McKinsey report. *(Also see "Six Questions For McKinsey's Fox On Pharma's Digital Struggle" Scrip, 28 Oct, 2016.)*

DOCTORS MAY LOSE ROLE AT CENTER OF DRUG PURCHASE DECISIONS

"The rules of engagement need to be redefined (in India)," says the EY report, which foresees the advent of "super consumers" and corporate hospital chains being at the core of drug-purchase decisions. The report suggests physicians' role being "at the center of the pharma ecosystem may become a thing of the past."

"Companies are getting the FDA approval for their apps to help patients that will be a paradigm change in the way medicine is sold and practiced," noted Shrinivasan. "You have an Alphabet (Google) working with GSK (to develop bio-electronic medicines)… That is totally disruptive."

EY says 53% of Indian pharmaceutical companies are at the "beginners" stage with no digital marketing strategy at all in place and limited use of technology to capture interaction of sales representatives with physicians and other customers. A further 40% of companies have limited channels of customer digital engagement.

There are a just a few companies in what EY calls the "explorers" category, which have partly defined their digital strategies and are looking at ways to scale up to digitally link back-ends and front-ends and offer omni-channel interaction with customers.

'CULTURE CHANGE REQUIRED'

Many of the key hurdles to digital advancement are not technological, but organizational, cultural and regulatory. In the EY report, 67% of the pharmaceutical executives surveyed cited "people resistance," 80% cited lack of value proposition in solutions, 75% cited lack of authentic and sufficient data and 60% cited physicians' mindsets and inertia as barriers.

"In our conversation with the companies, it was clear that they viewed making the move to digitization as very important… the technology, ambition and the desire is there. But there is a culture change that's required. There are a number of barriers out there and they exist across the company hierarchy," said Shrinivasan.

Indian pharma companies will have to create "hybrid" marketing teams including sales, medical, training and supply chain specialists to "seamlessly cater" to customer needs, the report says.

EY says Indian companies will also need to adopt a "fail fast and fail cheap" approach to allow quick learning cycles.

"The next three-to-four years will be crucial for companies to get out of their comfort zone and embrace disruption to avoid being disrupted… the strategic moves that companies make today will determine their survival," the report says.

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Traditional Vs. Digital: Merck And GSK Battle For HPV Vaccines In China

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Merck & Co. Inc. is readying the launch in China of *Gardasil*, the second HPV vaccine approved in the country. As it strives to catch up with competing product *Cervarix* from **GlaxoSmithKline PLC**, with the help of local partner **Chongqing Zhifei Biological Products Co. Ltd.**, it has won one more bid in Jiangxi province.

Just a day before China's national holiday week, the partners added the fifth province to the successful procurement bidding list, which also includes Henan, Yun'nan, Chongqing and Heilongjiang. The procurement bidding price for Gardasil is CNY780 per shot.

At the same time, Zhifei Biological also announced it had received customs clearance for the first batch of the vaccines in Beijing, and is awaiting the release certification from China National Institutes for Food and Drug Control, which could take up to three months.

Zhifei Biological has exclusive rights to sell Gardasil in China under a strategic agreement with Merck. After the vaccine was approved by the China FDA in May this year, Zhifei Biological began to prepare for the bidding process in different provinces, and it is accelerating the filings and bids having received customs clearance.

In China, nonprofit healthcare institutions set up by government above the county level must procure most of their drugs through a bidding process centralized at the provincial level. Zhifei Biological said it expects Gardasil to enter bidding lists in most provinces by year-end, when it also hopes be able to complete the product inspection and get the approval to launch the vaccine nationwide.

Zhifei Biological said a strong marketing network is one of its core competitive advantages. As of the end of 2016, the company had established the most comprehensive direct sales channel in China, with about 1,000 sales reps, covering 327 cities in 30 provinces, 2,248 counties, and more than 25,400 vaccination sites. And the number could continue to rise, the company said. Zhifei is also the exclusive distributor for Merck's *Pneumovax*, *Vaqta* and *Rotateq* brands and has deep roots in the Chinese vaccine market.

GSK was ahead of Merck to launch its HPV vaccine in August, but it chose the digital path to promote Cervarix. Through a collaboration with China's e-commerce giant Alibaba, the companies are using the online commerce site Taobao to provide information on Cervarix and links to community health clinics for vaccination consultation and appointments. The program is planning to cover 1,500 community clinics at the end of this year, and will extend to other vaccine products.

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GSK disclosed that the company had completed bids in 18 provinces in August, and that people had been able to make appointments for vaccination in more than 40 cities by that time.

GETTING CROWDED?

Before this year, China was an untapped market for HPV vaccines, and yet it has a huge market potential, given its large female population of 172 million between the ages of 9 and 26, and 208 million between the ages of 27 to 45. The market value could be worth more than CNY10bn.

Given the current processes of product launch in China, Cervarix ceding the US market to Gardasil last year will not have a significant impact on its sales in China, but the greater impact will come from competition after marketing, a regulatory officer at the local FDA told *Scrip*. "From the point of view of pricing strategy, marketing focus and target population, as well as sales channel integration, two products have their own advantages in the early stage of the competition," the officer said. "GSK is moving faster by leveraging the e-commerce channel to achieve high growth in sales, but Merck's vaccine has wider preventative coverage."

Merck will have more advantages in future competition, since its Gardasil 9 is likely to get approval by China FDA in the next few years, the officer predicted. Merck told local media that launching Gardasil 9 in China is already being planned, but it has not entered clinical trials yet because of the complicated registration process for vaccines.

Domestic companies are also competing to seize market share. According to the Center for Drug Evaluation, 11 companies have filed clinical trial applications, including Chengdu Institute of Biological Products Co., Beijing Institute of Biological Products Co., Shanghai Zerun Biotechnology, Xiamen Innovax Biotech, Jiuzhou Pharmaceutical and Shanghai Bovax Biotechnology.

The front runner, Zerun Biotechnology, is already in Phase III trials for its quadrivalent HPV vaccine, and is awaiting clinical approval for a nonavalent HPV vaccine.

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From the editors of PharmAsia News

Merck & Co Calls It Quits On Anacetrapib

MARY JO LAFFLER & EMILY HAYES

Merck & Co. Inc. is making the prudent choice in opting not to pursue regulatory approval for the CETP inhibitor anacetrapib, avoiding the commercial quagmire of the cholesterol market that has hindered uptake of the PCSK9 inhibitor class.

"The decision follows a thorough review of the clinical profile of anacetrapib, including discussions with external experts," the firm said in its Oct. 11 announcement.

"Unfortunately, after comprehensive evaluation, we have concluded that the clinical profile for anacetrapib does not support regulatory filings," Merck Research Laboratories President Roger Perlmutter said in the statement.

The company has been signaling this may be the fate for anacetrapib ever since the surprise success of its massive cardiovascular outcomes study, REVEAL.

Merck announced in June that anacetrapib met the primary endpoint in REVEAL, with a significant reduction in a composite of major coronary events compared with placebo, and with a safety profile in line with previously released studies. *(Also see "Big REVEAL: Merck's Anacetrapib Surprises With Success, But What Next?" Scrip, 27 Jun, 2017.)* At the time, however, the company's lack of guidance on filing plans raised questions about whether the drug would ever see the light of day.

The firm followed up in August with a full presentation of results at the European Society of Cardiology meeting, with simultaneous publication in the *New England Journal of Medicine*, but signaled that it was consulting with experts about next steps, including whether to file for regulatory approval.

REVEAL tested the drug against placebo in 30,449 patients at high risk of a cardiovascular event and already well-managed on intensive standard of care lipid-lowering therapy with **Pfizer Inc.**'s *Lipitor* (atorvastatin). Anacetrapib significantly improved the primary endpoint, reducing the risk of a composite of major coronary events (coronary death, myocardial infarction or coronary revascularization) by 9% over placebo. The baseline LDL in the trial was very low at 61 mg/dL, which is below the traditional 70 mg/dL target for high-risk patients, and baseline HDL was 40 mg/dL. Patients in the test arm got an additional 17 mg/dL of LDL lowering (18%) while HDL was up by 43 mg/dL (104%).

Researchers also reported that there was no significant improvement for anacetrapib on the secondary composite outcome of major atherosclerotic events, which included myocardial infarction, coronary death or ischemic stroke.

The benefit seen in the study was consistent with LDL-lowering effects but not HDL-raising benefits, REVEAL investigators reported. While statistically significant, 9% was a lower reduction than desired and raised questions with analysts about whether it was robust enough to spur prescriptions of the drug.

ROUGH ROAD

Seeking approval would have been a tough regulatory road, given the prior history of failure in the class – starting with **Pfizer Inc.**'s torcetrapib in 2006, with **Roche**'s dalcetrapib following in 2012 and **Eli Lilly & Co.** ending evacetrapib development in 2015. *(Also see "Big REVEAL: Merck's Anacetrapib Surprises With Success, But What Next?" Scrip, 27 Jun, 2017.)*

Even though it has been argued that there are mechanistic differences between the molecules, anacetrapib did show some increase in blood pressure in REVEAL (the issue behind the torcetrapib failure) and had mixed results on secondary endpoints – issues that could have been stumbling blocks with the US FDA.

And the commercial environment is different than it would have been when the CETP class first came onto the scene, more than a decade ago. Now the entire statin class is available as inexpensive generics, and the lack of success for the injectable PCSK9 inhibitors (**Amgen Inc.**'s *Repatha* and **Sanofi/Regeneron Inc.**'s *Praluent*) shows how challenging it can be to introduce a pricey new therapy in the cholesterol field. *(Also see "PCSK9 Sales Still Slow, But May Get Boost From Label, Guideline Changes" Scrip, 4 Aug, 2017.)* In addition, the theory that raising HDL improves heath has been damaged along the way, with disappointing results from outcomes trials of fenofibrates and niacin. *(Also see "More Disheartening News For Abbott Cholesterol Franchise: Niaspan/Statin Study Halted Due To Lack Of Added Benefit" Scrip, 26 May, 2011.)* and *(Also see "HPS2-THRIVE Post-Mortem: Lessons Learned For CV Drug Developers" Scrip, 18 Mar, 2013.)* The emphasis on increasing HDL through CETP inhibition had been muted and the class had been repositioned for its broader effects, but at this point PCSK9 inhibitors can achieve very low LDL levels – and that hasn't been enough to capture market share.

FINAL NAIL IN THE COFFIN

Merck's decision not to file anacetrapib may be the final nail in the coffin for the CETP class and could have broader implications for HDL-raising drugs. According to the Biomedtracker database, development of most CETP inhibitors has already been suspended.

Amgen Inc.'s AMG 899 is the only other new CETP inhibitor in clinical development. The company told *Scrip* it is "currently evaluating its development plan for AMG 899."

Using private financing, **DalCor Pharmaceuticals** is testing Roche's dalcetrapib in a genetic subgroup of patients with acute coronary syndromes – in the dal-OUTCOMEs study the 20% of patients with an AA polymorphism at the rs1967309 location in the ADCY9 gene had a much lower rate of events compared with placebo, according to the company. *(Also see "DalCor To Develop Failed Roche CETP Inhibitor In Genetic Subgroup" Scrip, 22 Apr, 2016.)*

Merck noted that it will continue research in cardiovascular diseases. The company currently has only one other CV program in clinical development, per its August pipeline update. Vericiguat, a stimulator of soluble guanylate cyclase (sGC), is in a Phase IIb trial in patients with heart failure and preserved ejection fraction suffering from worsening chronic heart failure. The company also still markets *Zetia* (ezetimibe) and *Zocor* (simvastatin), both of which are available as generics.

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Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.

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Selected clinical trial developments for the week 6–12 October 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Suspended			
Sun Pharma Advanced Research Co. Ltd.	baclofen GRS once daily	spasticity in multiple sclerosis	Missed primary endpoint.
Phase III Results Published			
Johnson & Johnson	*Symtuza* (duranavir/ cobicistat/emtricitabine/ tenofovir alafenamide)	HIV/AIDS	EMERALD; single once daily tablet, *The Lancet HIV*, online, Oct. 6, 2017.
Bristol-Myers Squibb Co.	*Opdivo* (nivolumab)	gastric cancer	ATTRACTION-2; *The Lancet* online, Oct. 6, 2017.
Zosano Pharma Corp.	zolmitriptan, dermal	acute migraine	ZOTRIP; *Cephalalgia*, online Oct. 12, 2017.
Updated Phase III Results			
Paratek Pharmaceuticals Inc.	omadacycline	skin and skin structure infections, community acquired pneumonia	OASIS-1, OPTIC; effective and well tolerated in patients with comorbidities.
Merck & Co. Inc.	*Gardasil 9* vaccine	HPV prevention	001; sustained efficacy for 6 years.
Neurim Pharmaceuticals Ltd.	PedPRM (melatonin) prolonged release	pediatric insomnia in autism	Effective and well tolerated.
Recro Pharma Inc./Alkermes PLC	meloxicam iv	pain following surgery	Reduced pain, opioid use.
Allergan PLC	*Avycaz* (ceftazidime/ avibactam)	pneumonia, nosocomial	REPROVE; non-inferior to meropenem.
Merck & Co. Inc.	V212, herpes zoster vaccine	chickenpox, shingles following stem cell transplant	001-AM2; shows immunogenicity.
Phase III Interim/Top-line Results			
Ardelyx Inc.	tenapanor	irritable bowel syndrome with constipation	T3MPO-2; met endpoints, NDA filing in 2018.
Eli Lilly & Co.	*Verzenio* (abemaciclib)	KRAS-mutated advanced NSCLC	JUNIPER; missed primary endpoint, but active against sec. endpoints.
Evolus Inc	prabotulintoxinA	glabellar lines	Showed benefits and well tolerated.
Phase III Initiated			
Otsuka Holdings Co. Ltd./ H. Lundbeck AS	*Rexulti* (brexpiprazole)	manic episodes in bipolar disorder	Two global studies.
AveXis Inc./REGENXBIO Inc.	AVXS-101	spinal muscular atrophy	STRIVE; a gene replacement study.
Phase III Announced			
GlaxoSmithKline PLC	*Nucala* (mepolizumab)	hypereosinophilic syndrome	A long-term extension study.
Regeneron Pharmaceuticals Inc.	fasinumab	arthritis pain	FACT OA2; in the knee or hip.

Source: Biomedtracker

Translate Bio, a company focused on developing RNA therapeutics for genetic diseases, has appointed ***Daniella Beckman*** to its board of directors – effective immediately. With more than 15 years' experience, Beckman provides consulting and interim chief financial officer services to early-stage biotech companies, including Tango Therapeutics and Neon Therapeutics.

Vincent Miller has joined **Revolution Medicines Inc.**'s board of directors and will replace ***Michael Bonney***, who has recently joined Kaleido Biosciences as CEO and chair. Miller is chief medical officer of Foundation Medicine.

Bristol-Myers Squibb Co. has appointed ***Saurabh Saha*** senior vice president and global head of translational medicine. Saha joins BMS from Atlas Venture, where he held leadership positions with its portfolio biotech companies, including chief medical officer of Synlogic Inc., and CEO of Delinia Inc.

Gadeta BV., a Dutch start-up focused on cancer, has elected ***Shelley Margetson*** CEO and ***Thomas Davis*** chief medical officer (CMO). Margetson joins Gadeta from Merus NV, where she was chief financial officer until Nov. 2016, and chief operating officer until Aug. 2017. Davis was CMO at Celldex Therapeutics Inc. and previously held the same position at GenVec Inc.

Scancell Ltd. has named ***Cliff Holloway*** CEO – effective Jan. 10, 2018. Holloway will be succeeding ***Richard Goodfellow***, who will remain on the company's board of directors. Holloway joins the company from Benitec Biopharma Ltd., where he was chief business and operating officer. Previously he was CEO and managing director of Sienna Cancer Diagnostics.

Zafgen Inc., a company focused on metabolic diseases, has elected ***Jeffrey Hatfield*** CEO – effective immediately. The current CEO, ***Thomas Hughes***, will continue as the company's president and assume the newly-created role of chief scientific officer. Most recently, Hatfield was CEO of Vitae Pharmaceuticals Inc., until its recent acquisition by Allergan PLC.

Gilead Sciences Inc. has promoted ***Alessandro Riva*** to executive vice president, oncology therapeutics. Riva joined the company in January 2017 as senior vice president, hematology and oncology therapeutic area head. He was previously head, global oncology development at Novartis.

Former FDA commissioner ***Andrew von Eschenbach*** has been appointed **Malin Corp. PLC**'s chief medical adviser – effective immediately. Von Eschenbach is the president of Samaritan Health Initiatives Inc., and is an adjunct professor at Houston's University of Texas MD Anderson Cancer center. He is also a member of the Prostate Cancer Foundation board of directors and a senior fellow at the Milken Institute. From 2006 to 2009, von Eschenbach was the commissioner of the FDA and he was director of the National Cancer Institute (NCI) at the National Institute of Health for the four years before his position with the FDA.

Giles Kerr has been named **Arix Bioscience Plc**'s non-executive director and chair of the board's audit committee – effective immediately. He brings 36 years of finance experience to the company and is a director of finance at the University of Oxford.


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