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Amarin's Vascepa Positioned For Broad CV Risk Reduction Claim Following US FDA Panel Nod

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A US Food and Drug Administration advisory committee on 14 November unanimously endorsed Amarin Corp. PLC's Vascepa (icosapant ethyl) for a broad cardiovascular risk reduction claim despite many panelists' reservations about the strength of the efficacy data for primary prevention in patients that do not have established CV disease.

Ten of 16 members of the Endocrinologic and Metabolic Drugs Advisory Committee favored approval for an indication encompassing secondary prevention in patients with existing CV disease and primary prevention in diabetics with additional risk factors for CV disease.

Four panelists strongly opposed extending the claim to primary prevention, while the remaining two suggested they were on the fence.

Panelists favoring a broad indication said they were persuaded by the robust efficacy in the overall results of the 8,179-patient REDUCE-IT trial. Although the majority of patients in the study had existing CV disease, the magnitude of benefit was less robust in the approximately 30% of lower risk patients with diabetes and an additional risk factor for CV disease. However, REDUCE-IT was powered to show an effect on major adverse CV events in the overall population, not specifically in the lower risk cohort.

Marvin Konstam, a cardiologist at Tufts Medical Center, said he was "just queasy about the primary prevention population." Nevertheless, he voted for a broad indication in both secondary and primary prevention for several reasons, including statistical considerations involving the single trial and the underlying biology of CV disease.

However, clinicians should be mindful that as they think about treating the lower risk patients for secondary prevention, Vascepa's risks of bleeding and atrial fibrillation/flutter "may be catching up to the benefit," Konstam said.

"I'm still comfortable with this being approved for both primary and secondary prevention," said Susan Ellenberg, a biostatistician at the University of Pennsylvania. "I think that if there's sufficient hesitation in the community about the primary prevention indication, that may show up in terms of a reluctance to prescribe it. There might be a motivation then to do another trial" in the primary prevention setting.

On the other side were panelists unpersuaded that REDUCE-IT showed Vascepa to be effective in preventing CV events in individuals who do not have established CV disease.

"I believe there's insufficient data to establish a primary prevention population that will truly have adequate and acceptable benefit more than risk, particularly given concerns over the robustness of the therapeutic effects in the primary prevention population versus the risk of bleeding

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Gottlieb On Pursuing Legislative Reform: Start Small, Build Later

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Former US FDA commissioner Scott Gottlieb encouraged stakeholders at the Association for Accessible Medicine's GRxBiosims 2019 meeting to start small in scope when pushing for legislative changes, which makes it easier to build on later.

GSK Seeks To Halt Boehringer Promos That 'Denigrate' Effectiveness Of Ellipta, Diskus Inhalers

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US FDA's wariness of taking enforcement action against Rx drug promotions may lead to more suits like GSK's. Complaint says healthcare providers are switching COPD patients to BI's Respimat inhaler in response to BI's marketing campaign.

England's NICE Backs Epidyolex For Seizures, Sativex For MS Spasticity

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Health technology assessment body NICE has given the thumbs-up to Epidyolex and Sativex, which become the first plant-derived medicinal cannabis products to secure routine NHS funding. It has also issued positive guidance on other products including nabilone, but turned down the use of cannabis-based drugs in chronic pain.

International Horizon Scanning Initiative To Level Pricing Playing Field

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and atrial fibrillation," said Thomas Weber, an endocrinologist at Duke University.

"In the secondary prevention population the data are overwhelming and convincing … but they are wholly unconvincing in the primary prevention" population, said James de Lemos, a cardiologist at UT Southwestern Medical Center.

"I do not think we should reward sponsors for enrolling small subsets of primary prevention patients in secondary prevention trials, reporting an interaction that's not significant, and then giving them a broad indication for which we really don't have enough evidence," de Lemos said. "It well may be a great primary prevention drug, they just haven't established that yet."

INDICATION STILL MAY FACE LIMITATIONS

The advisory committee's recommendation positions Vascepa for a labeling expansion significantly beyond its approved use to reduce triglyceride levels in adults with severe (≥500mg/dL) hypertriglyceridemia.

"Vascepa is positioned to be the first approved treatment to reduce cardiovascular events in the group of at-risk patients studied in the landmark REDUCE-IT clinical trial," CEO John Thero said in a press release after the meeting. " We look forward to anticipated labeling discussions with the FDA, and we continue to prepare for the launch of Vascepa assuming FDA approval of our sNDA on or before the target PDUFA date of December 28."

Nevertheless, the panel's comments suggest Vascepa's new indication may be more limited than Amarin would prefer.

Amarin seeks approval to reduce the risk of CV death, myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization as an adjunct to statin therapy in adults with elevated triglyceride levels (≥135mg/dL) and other risk factors for CV disease.

However, numerous panelists suggested the indication should more closely match the inclusion and exclusion criteria of REDUCE-IT, including a requirement for either established CV disease or diabetes with other CV risk factors. Some panelists also favored a higher triglyceride threshold and minimum age limit, as well as language stating that patients should be on maximally tolerated statin therapy.

Notably, several panelists recommended against a claim for reduction of CV death because the magnitude of benefit on that endpoint was not as large or statistically robust (HR 0.80, p=0.03) as other components in the five-point composite primary endpoint.

Based on the REDUCE-IT results, treatment of 1,000 patients for five years would prevent 76 revascularization procedures, 42 myocardial infarctions, 14 strokes and 12 CV deaths, according to Amarin data.

Panelists generally agreed the effect of the mineral oil placebo on the overall REDUCE-IT results was unclear. While it likely had some impact on the study's efficacy results, it was probably not enough to negate the overall benefit, which included a 25% reduction in five-point MACE and a 26% percent reduction in three-point MACE.

As for safety, committee members agreed the increased risks of bleeding and atrial fibrillation/flutter seen in REDUCE-IT could be adequately managed through labeling, but they also called for postmarketing studies to look at those events.

USING ASCVD RISK SCORE AS TREATMENT GUIDE

Going into the meeting, the FDA had raised concerns about the breadth of Amarin's proposed indication. The REDUCE-IT population represented a higher risk group than the target population in Amarin's indication, which also was not limited by presence or absence of CV disease, diabetes in patients without CV disease, age, LDL-cholesterol or optimization of statin therapy, the agency said. *(Also see "Amarin's Vascepa: US FDA Panel To Scrutinize Breadth Of CV Risk Reduction" - Pink Sheet, 12 Nov, 2019.)*

"As written, the indication for Vascepa would apply to a group of patients with a potentially different benefit/risk consideration than those studied in REDUCE-IT," said John Sharretts, acting deputy director of the Division of Metabolism and Endocrinology Products (DMEP). In REDUCE-IT's lower risk cohort of diabetics, the number of patients with a medical history consistent with established CV disease "was not insignificant," and the majority of patients in this cohort had diabetes plus two or more risk factors for CV disease, said Iffat Nasrin Chowdhury, a medical officer in DMEP.

"Taken together, the baseline characteristics of risk category 2 defined a higher risk population than the applicant's proposed indication," she said. "It would be challenging to extrapolate the results of the trial to patients without established CVD or diabetes on low-intensity statins, with triglycerides levels greater than or equal to 135."

Amarin acknowledged the magnitude of benefit in the second risk cohort was lower than in the higher risk group, but this was not surprising given the lower overall event rate in this group of patients.

The risk/benefit profile for primary prevention is most positive in diabetics at highest risk of CV events, and a 10-year atherosclerotic CV disease (ASCVD) risk score can be used to identify these individuals for Vascepa treatment, Amarin said.

In the overall population of the second risk cohort, the number needed to treat to avoid one CV event was 96, but this number dropped to 36 when limited to those patients who have a predicted ASCVD risk of 10% or more, said Ann Marie Navar, a cardiologist at Duke University and a consultant for Amarin.

As CV risk increases in patients with diabetes so does benefit of Vascepa therapy, and "the risk/benefit equation becomes much more compelling when we focus on those with the highest risk," she said. "In clinical practice, clinicians are already used to thinking about using predicted

ADVISORY COMMITTEE VOTE

Has the applicant provided sufficient evidence of efficacy and safety to support the approval of Vascepa for an indication to reduce the risk of cardiovascular events?
Y – 16, N – 0

cardiovascular risk to guide therapy in primary prevention."

Current professional guidelines use the 10-year ASCVD risk score to stratify adults with and without diabetes for guiding statin therapy and intensity, as well as initiation of pharmacologic therapy for blood pressure, Navar said. This score can be calculated easily, is available online, and most electronic health records allow auto calculation of a patient's risk score at point of care, she said.

"I am confident that using something like the 10-year risk score to help guide therapy for icosapant ethyl can easily be incorporated into clinical practice, because it's something that we're already doing," Navar said.

However, Peter Wilson, a cardiology epidemiologist at Emory University, noted that cut-offs and algorithms for risk scores can change over time, and a more practical approach to treatment could be based on the number of risk factors for a given patient.

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Jardiance Likely Needs Another Trial After Rebuke By US FDA Panel

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Boehringer Ingelheim International GmbH will likely need to conduct another trial for Jardiance (empagliflozin) after the US Food and Drug Administration's Endocrinologic and Metabolic Drugs Advisory Committee voted 14-2 that the benefits do not outweigh the risks as an adjunct to insulin to improve glycemic control in adults with type 1 diabetes mellitus.

Many panelists at the 13 November meeting said the existing data were promising, but they also felt that a larger trial of a longer duration is necessary to better characterize the risk of diabetic ketoacidosis (DKA) and the durability of benefit.

Boehringer is specifically seeking a supplemental approval for a distinct 2.5mg dose of Jardiance for type 1 diabetes patients, which is smaller than the 10mg and 25mg doses recommended in its existing label for type 2 diabetes patients.

In EASE-3, the single pivotal Phase III trial supporting approval, 2.5mg Jardiance demonstrated a statistically significant -0.26% reduction of hemoglobin A1c (HbA1c) from baseline versus placebo over 26 weeks and also demonstrated modest benefits on weight and blood pressure.

However, only 241 patients received the 2.5mg dose of Jardiance; the FDA recommended the company explore a lower dose for type 1 diabetes patients because of a different risk/benefit profile expected in this population. The agency questioned in its briefing documents whether the sample

size and 26-week length of the trial were adequate to assess the safety and efficacy. *(Also see "Boehringer's Jardiance Heads To Advisory Cmte. With Questions On Treatment Effect" - Pink Sheet, 11 Nov, 2019.)*

The panel shared these concerns.

"I remain optimistic that the regimen will ultimately prove to be useful," said Erica Brittain, a mathematical statistician at the National Institute of Allergy and Infectious Diseases. "There wasn't anything very worrisome about the results of the study, but just that one six-month study was insufficient to assess the tradeoff between benefit and risk."

Duke University Medical Center professor Thomas Weber added that, "I do feel the data are promising and would recommend a more robust assessment of efficacy and safety."

A sodium-glucose co-transporter 2 (SGLT2) inhibitor, Jardiance is currently indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

Mohamed Eid, vice president, Clinical Development & Medical Affairs, Cardio-Metabolism & Respiratory Medicine at Boehringer, said in a statement following the meeting, "We continue to believe the totality of data from the EASE program indicates a favorable benefit-risk profile for empagliflozin 2.5 mg in adults with type 1 diabetes and look forward to continuing to work with the FDA in this review process."

CHARACTERIZING THE DKA RISK

Several panelists laid out specifics about how they would like to see the potential DKA risk studied when explaining their votes. SGLT2 inhibitors are known to increase the risk of

DKA, which occurs due to insulin deficiency.

UT Southwestern Medical Center professor James de Lemos said that a future trial would need to include "several thousand individuals." "I think that the next study that needs to be done has to focus on safety with regard to DKA, and it has to be large enough to do that. ... We need a trial large enough to get a precise signal about DKA rates," de Lemos said.

Other panelists called for expanding the definition of positively adjudicated DKA cases. In EASE-3, DKA events were classified as "certain," "potential," "unlikely ketoacidosis but ketosis," or "unlikely." Only two patients receiving 2.5mg Jardiance had DKA events labeled as "certain" compared with three placebo recipients, although the FDA and the advisory committee raised concerns that DKA rates may be higher in the real world without the intense monitoring that takes place during clinical trials.

Michael Blaha, a professor at the Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, called for a study that focuses exclusively on the DKA safety issue.

"The primary outcome here would be, let's call it broad DKA," Blaha said. "We have to think carefully about what that means. But it would be a safety study."

Blaha also cited a few reasons why such a trial would be beneficial.

"I guess from the company's point of view its certainly worth the investment," he said. But also for the biology. Understanding this disease, it would be extremely worth the investment. It would teach us a lot about type 1 diabetes, DKA. It would teach us a lot about SGLT2 inhibitors, but also just the concept of adding on therapies for insulin reduction in type 1 diabetes, where these seems to be a large gap in knowledge."

Advisory committee members also recommended that the trial test Boehringer's risk mitigation proposals, such as educational materials about ketone monitoring.

In terms of length, Weber recommended Boehringer conduct a clinical trial of at least two years in length that is "adequately powered and adequate to establish efficacy in HbA1c, and also gather adequate patient-year exposure to more definitively and acceptably characterize the risk of diabetic ketoacidosis."

Connie Newman, a professor at the NYU Langone School of Medicine suggested a randomized controlled trial of at least one year "with a consideration to including microvascular outcomes, and also consideration to extending the trial beyond one year, perhaps in an open-label fashion so we get more data about safety."

ADVISORY COMMITTEE VOTE

Do the available data suggest that the benefits outweigh the risks and support approval of empagliflozin 2.5 mg, administered orally once daily, as an adjunct to insulin to improve glycemic control in adults with type 1 diabetes mellitus? **Y - 2, N - 14**

RESULTS AREN'T DURABLE

Many panelists also felt that they couldn't make conclusions about the durability of the HbA1c reduction results for 2.5mg Jardiance with just 26 weeks of data to look at.

"I think we need a larger, longer randomized controlled trial on the 2.5mg dose," said Cecilia Low Wang, a professor at the University of Colorado Anschutz Medical Campus School of Medicine. "I think we do have some evidence that that is the dose. But I think we need to see reproducibility, durability of the benefits both on A1c reduction, possibly other benefits as well, maybe decreased microvascular complications."

Newman offered a similar assessment.

"I feel that this database on the dose of 2.5mg is too small and in too short of a time period to even know what the efficacy in terms of glycemic control may be," she said. "The purported reduction of 0.26 may not actually be clinically meaningful, in my opinion, and that may not be what would happen in year 1 or year 2."

THE 'YES' VOTERS

Anna McCollister, founder of VitalCrowd and the panel's consumer representative, was among the small minority supporting approval. Her "yes" vote came in spite of her calling the patient sample size in EASE-3 "borderline insulting."

On the DKA risk, McCollister, herself a diabetes patient, commented that, "I think that DKA is a big risk as a clinical issue, but I don't know that this drug introduces that much of a greater risk in the relative scheme of things." McCollister added that the DKA risk is one that can be mitigated through education and conversations with physicians.

What's more, McCollister noted that SGLT2 inhibitors are being used off-label and contended that an approval for Jardiance would make its use in clinical practice less risky.

"From my perspective as a patient/consumer, I think the real question that we need to consider is whether we want people to take this class of medications without knowing what's happening and without having any rigorous requirements on the part of manufacturers to track it," McCollister said. "I think I would rather have that happen in a regulated environment where there is a degree of responsibility." But de Lemos pushed back against such an approach.

"This concept of approving a drug so that we can monitor its use when we don't know it's safe and effective seems like an incredibly slippery slope," he said. "Absolutely no would be my answer to that. Our role and the agency's role is to make sure the package that's submitted provides evidence that the risk/benefit is favorable. If we don't have that, putting it on the market so we can learn more about it in a regulated way doesn't seem like the right way to go."

The other vote in favor of approval came from University of Maryland School of Medicine professor Kashif Munir.

"I think at the end of the day, I agree it would have been nice to see more data and a longer trial, but I feel like the data were what I expected them to be," Munir said. "I felt the DKA risk would be there, it's real, but that it would be less than the higher doses. And I felt like the efficacy would be less than the higher doses. And that's exactly what we saw."

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NHS England Hails Biggest CAR-T Uptake In Europe

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England has seen the greatest uptake of cutting-edge CAR-T treatments in Europe so far, according to the National Health Service's chief price and market access negotiator.

Some 250 patients with relapsed or refractory large B-cell lymphoma will have been treated with two cell therapies, Novartis AG's Kymriah (tisagenlecleucel) and Gilead Sciences Inc.'s Yescarta (axicabtagene ciloleucel) by the end of this year, said Blake Dark, commercial medicines director at NHS England.

Kymriah is also used in children and young people with refractory B cell acute lymphoblastic leukemia, and NHS England says it is also set to hit a target of 15-30 patients treated a year.

Dark was speaking in London at the IQVIA Biotech UK conference on 7 November, a meeting that brought together different players in the country's life science "ecosystem" including biotech, pharma, venture capitalists and the payer, NHS England.

The tally of 250 lymphoma patients would put England well ahead of other major European markets, such as Germany and France, which have been slower in negotiating deals with the two companies for their high-priced but potentially life-saving medicines.

Both Kymriah and Yescarta have UK list prices of just under £300,000 ($384,000) per patient, but commercial agreements between the companies and NHS England were announced respectively in September and October 2018.

Dark has been head of NHS England's Commercial Medicines Directorate for a year, and the unit has grown into England's most significant decision-making body for specialized products. It has negotiated a string of major market access deals with pharma based on big price discounts in exchange for fast access. *(Also see "UK NICE Changes Mind On Ocrevus After Roche Drops Price" - Pink Sheet, 9 May, 2019.)*

Kymriah and Yescarta both received EU marketing authorization in August 2018.

Reaching rapid agreements on the CAR-Ts and other innovative medicines is something Dark is clearly proud of – as it demonstrates NHS England's ability to secure major price concessions from pharma (though the final prices remain confidential) while also helping patients gain rapid access to cutting-edge products.

This has helped overcome longstanding problems where health technology assessment body NICE would hit pricing issues with pharma companies, but did not have a mandate to negotiate on costs.

Dark is a "poacher turned gamekeeper" having been recruited to the role at NHS England after a career in pharma, much of it at Sanofi.

He insists that NICE will remain the primary decision-maker for medicines value and access, but it is clear that NHS England will play a key role for those increasingly numerous potentially "transformational" medicines that come with a very high price tag.

Both CAR-T products are being funded via the Cancer Drugs Fund, which will see the clinical and cost effectiveness of the drugs reviewed within a few years, with a final decision to reimburse permanently or end funding taken at that time.

Dark says the CAR-T agreements were "examplars" of how industry could work with NHS England. He notes that only a few potential breakthrough products a year, which also carry uncertainty about their value, are "transactable" and negotiable on price and access.

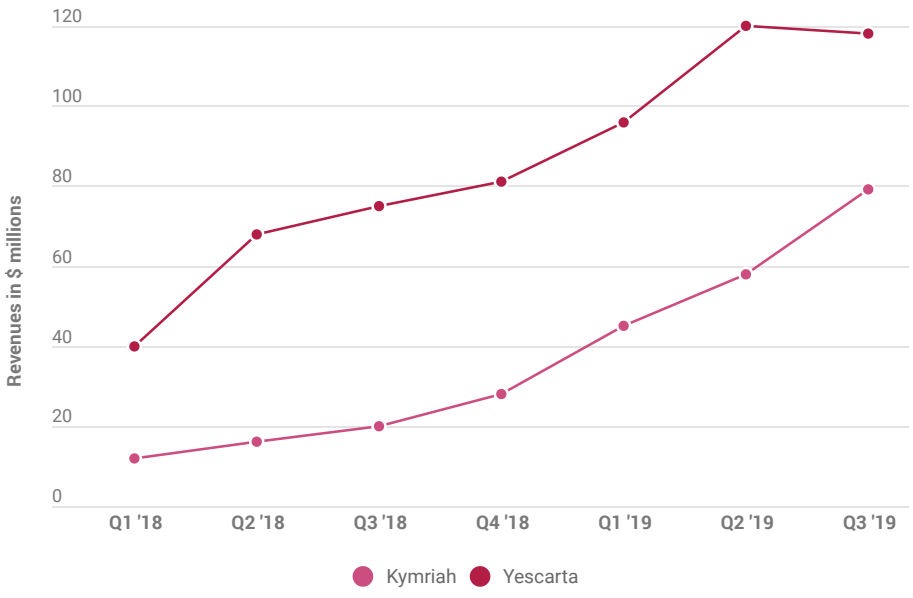
"I'm a real optimist, I'm here to get these products to market as long as companies want to speak the same language as I and my team do."

ADMINISTRATIVE BURDEN OF CAR-TS

However, Dark also highlighted the complexity and administrative burden of introducing CAR-Ts to England's health service. The products have been introduced via a network of specialist hospitals to accom-

Kymriah Versus Yescarta

Global revenues from the CAR-Ts in $ millions since Q1 2018



Source: company quarterly revenues

modate the complex process required to collect cells from patients, with the modified T cells reinfused at a later date.

"In one hospital we had to train 300 members of staff how to use CAR-T," he said, noting that the delivery to patients of the finished CAR-T product is so time-dependent that it is measured in seconds.

He adds that having two separate CAR-T products is a "downside" - as each one has its own supply chain and administrative system (one paper, the other electronic) and its own dedicated fridge.

"We have cell and gene therapies coming through which will need bespoke printers specific to that product. If we have 10 of these products, we're going to need 10 printers in every hospital ward." This is simply not feasible, he declared.

"So it's fabulous to be at the cutting edge of medicine… but very quickly we'll need the industry to come together on supply chain to harmonize. Otherwise patients are not going to get access to these medicines for no more reason than we don't have the space in hospitals for the equipment."

BUT CAUTIONS ON SUPPLY CHAIN COMPLEXITY

Dark says any company with potentially transformational products that also require bespoke training or systems for health care professionals needs to approach NHS England at least two years ahead of market launch.

NHS England has also just launched a consultation on its new Commercial Framework for Medicines, which sets out in greater detail proposed terms of engagement with the industry. *(Also see "Fair Pricing A Key Feature Of NHS England Drug Funding Proposals" - Pink Sheet, 11 Nov, 2019.)*

For Gilead, and especially Novartis, the CAR-Ts look unlikely to be profitable products in their current indications, and firms are relying on further expansion in their indications to help them recoup their costs.

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MYELOMA BCMA THERAPY IN SPOTLIGHT: EMA Considers Fast Tracking GSK Filing

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GlaxoSmithKline should soon learn whether the European Medicines Agency will fast track its planned EU marketing application for belantamab mafodotin, one of several BCMA-targeting therapies being developed to treat multiple myeloma.

GSK's request for accelerated assessment for the antibody-drug conjugate is due to be considered at this week's monthly meeting of the EMA's drug evaluation committee, the CHMP, which is taking place on 11-14 November. The agency is also evaluating a fast-track request from ViiV Healthcare for its HIV treatment, fostemsavir.

BCMA (B-cell maturation antigen) has become an exciting novel drug target in multiple myeloma, and GSK is ahead of other companies developing a BCMA-targeting therapy for the disease.

It is understood that the company is on track to file for US approval of belantamab mafodotin by the end of 2019 and expects to file for EU approval in the first half of 2020.

"With the primary overall response rate (ORR) endpoint met in DREAMM-2, a pivotal Phase II trial, the antibody-drug conjugate belantamab mafodotin is positioned to be the first approved BCMA-targeted therapy," Datamonitor Healthcare analyst David Dahan told the *Pink Sheet*.

Celgene/bluebird bio's BCMA-targeting CAR-T therapy, ide-cel, "will likely be second to market as Celgene expects to file a US biologics license application to the Food and Drug Administration in H1 2020," Dahan said.

Accelerated assessments are not easy to get in Europe. The EMA reserves the fast-track mechanism for products that are expected to be of major public health interest, particularly from the point of view of therapeutic innovation.

An accelerated assessment reduces the time it takes the agency to evaluate a marketing authorization application (MAA) from 210 days to 150 days (not counting clock stops when applicants have to provide additional information). Fast-track requests should be made at least two to three months before the MAA is submitted.

Notably, in 2017 belantamab mafodotin was accepted onto the EMA's priority medicines scheme, PRIME, which is designed to get drugs for unmet medical needs to patients faster. PRIME offers drug developers enhanced scientific and regulatory support from the agency to help optimize their development plans,

as well as the likelihood of having their product reviewed under the accelerated assessment procedure when it is filed for regulatory review.

BELANTAMAB MAFODOTIN VERSUS IDE-CEL

Regarding the competitive landscape for BCMA-targeting therapies, both belantamab mafodotin and ide-cel are being evaluated in fourth-line or later multiple myeloma patients.

"Although quantitative data for DREAMM-2 have not yet been disclosed, in DREAMM-1, belantamab mafodotin reported an ORR of 60% (15% complete remission (CR)) and progression-free survival (PFS) of 12 months. In a cohort of patients previously treated with an anti-CD38 antibody (a requirement in the DREAMM-2 trial), ORR and PFS were 38.5% and 7.9 months respectively," Dahan said.

Meanwhile, in Celgene's Phase I study (CRB-401), active doses of ide-cel outperformed belantamab mafodotin with an ORR of 95.5% (50% CR) and a PFS of 11.8 months, the DMHC analyst observed. "While we still await results from ide-cel's pivotal Phase II trial (KarMMa), these results suggest that ide-cel (formerly known as bb2121) outperforms belantamab mafodotin and that if both are approved, the latter may be reserved for patients too fragile for CAR-T therapy."

Nevertheless, there may be more opportunities for belantamab mafodotin in earlier lines, according to Dahan. "GSK is planning a series of Phase III trials for the product, including four trials in the relapsed/refractory setting (DREAMM-3, -7, -8, and -9) and one trial in the newly diagnosed, ineligible-for-transplant setting (DREAMM-9)."

WAY AHEAD OF CLASS COMPETITORS

Belantamab mafodotin also has a substantial lead over class competitors, according to Dahan.

"While there are several BCMA-targeted CAR-Ts and bispecific antibodies in the clinic, the only BCMA-targeted antibody-drug conjugates in clinical development are AstraZeneca's MEDI2228 and Celgene's CC-99712 which initiated Phase I trials in May 2018 and August 2019, respectively," he said. "These trials have estimated primary completion dates of April 2021 and November 2024, respectively."

In addition, Heidelberg Pharma is this year expected to initiate a Phase I trial of its BCMA-specific antibody-drug conjugate, HDP-101, Dahan noted.

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REIMBURSEMENT

French Industry Denies Influence On Prescribing Practices

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France's pharmaceutical industry body Leem has reacted angrily to a study published in the *British Medical Journal* that claims that French doctors who receive gifts from pharmaceutical companies write "less rational drug prescriptions" with the result that expenditure by the national health insurance system is higher than it should be.

Leem claims the data in the study do not establish a direct relationship between benefits provided by a company and the prescribing of drugs from the same firm, that it fails to distinguish between gifts that are forbidden under the law and those that are permitted, and that it "treats doctors like children."

The study, led by Bruno Goupil of the Department of General Medicine at the University of Rennes, set out to assess a possible association between gifts from pharma firms to French general practitioners and their drug prescribing patterns, using data from two French databases: French Transparency in Healthcare and the National Health Data System. Some 41,257 GPs listed in the latter database were included in the analysis.

> "French GPs who do not receive gifts from pharmaceutical companies have better drug prescription efficiency indicators and less costly drug prescriptions than GPs who receive gifts."
> – BMJ study

This is by no means the first study to look at the impact of company gifts on prescribing patterns, but it adds to the growing body of evidence that there is a correlation. The authors themselves note that the results of the study "are consistent with recent meta-analyses and systematic reviews showing an association between gifts from pharmaceutical companies and more frequent, lower quality and more costly drug prescriptions."

According to the study, gifts are described in French regulations as any type of present or payment given by a company to a health care professional without requiring anything in return, such as carrying out work or a service. They include donations of equipment, invitations, catering expenses, travel expenses, and cash payments such as commissions, rebates, or

reimbursement of expenses.

Under French regulations, all gifts and payments must be declared by companies, starting from €10.00 (US$11.00) including taxes. The date, amount, type of donation, identity of the receiver, and identity of the company must be recorded.

The main outcome measures used in the study were 11 drug prescription efficiency indicators and the amount reimbursed by the national health insurance for drug prescriptions written.

It found that the amount reimbursed for prescribed drugs per patient visit to the doctor was significantly lower for the group that did not receive gifts compared with the groups that received gifts worth €10-€69, €70-€239, €240-€999, and €1,000 or more.

GPs in the no gift group prescribed significantly more generic versions of antibiotics, antihypertensives and statins than the other groups, including those without reported gifts in 2016 but with at least one gift between 2013 and 2015 (pre-2016 gift group). They also prescribed significantly fewer benzodiazepines (for more than 12 weeks) and vasodilators compared with the €240-€999 and €1,000 or more groups, and significantly fewer ACE-inhibitors compared with the €1,000 or more group.

However, differences were not significant when it came to the prescribing of aspirin and generic antidepressants and generic proton pump inhibitors, according to the study.

They say that the generally high proportion of prescriptions for generic proton pump inhibitors and antidepressants and the absence of differences between groups could be explained by the fact that in 2016 proton pump inhibitors did not have a patented originator molecule, and the few patented antidepressants on the market were established drugs and so were not actively promoted by pharmaceutical companies.

"The more frequent use of some drugs, such as benzodiazepines and vasodilators, increases the risk of well known adverse effects of these drug classes, with occasional serious or fatal consequences," according to the authors.

"Our data suggest that prescription of these drug classes increases slowly but progressively from the no gift group to the €1,000 or more group. Prescriptions of brand name drugs instead of generic drugs represent an additional cost for the National Health Insurance with no proved benefit for the patient."

In France, the authors say, the price of a generic drug is at least 60% lower than the price of the original drug. "With an additional €1.2 to €5.3 reimbursed per drug prescription, GPs with gifts reported in the Transparency in Healthcare database are associated with an important additional charge for the National Health Insurance compared with GPs who did not have any gift reported."

> "The data do not allow any direct relationship to be established between the receipt of benefits from a company and the prescribing of medicines from that same company."
> – Leem

"The findings suggest that French GPs who do not receive gifts from pharmaceutical companies have better drug prescription efficiency indicators and less costly drug prescriptions than GPs who receive gifts," the study authors say. They caution, however, that the observational study "is susceptible to residual confounding and therefore no causal relation can be concluded."

They add: "Perhaps the time has come for interventional studies to test the impact of restrictive policies on physicians' drug prescription patterns prospectively."

LEEM SAYS NO

Leem says it has "strong reservations" about the conclusions drawn from the study. For example, the transparency database (www.transparence.sant.gouv.fr) includes composite data on several sectors like the pharmaceutical, medical devices and cosmetics industries, and gathers together under the term "benefits" such things as invitations to scientific or training events, and accommodation, travel and meals.

Analyzing these data is "particularly complex", the association says, noting that its own code of practice committee (Codeem) came up with some proposals in 2016 to improve the structure of the database to make it more user friendly, but that "these recommendations have still not been followed up."

It claims that the study fails to distinguish between the notion of gifts that are forbidden by law since 1993 and benefits that are authorized but strictly governed by the same law. In addition, it says that the study establishes a correlation between the receipt of gifts by doctors and their prescribing behavior.

"As the authors of the study indicate, this correlation cannot be used to deduce a causal link. In fact, the available data do not allow any direct relationship to be established between the receipt of benefits from a company and the prescribing of medicines from that same company."

Leem says that of the 219,382 benefits given to doctors in 2016, "only 306 exceeded €1,000." Moreover, the classes of medicines taken into account in the study are "largely genericized and generally are no longer promoted by pharmaceutical companies."

It "strongly denounces this new denigration" of the pharmaceutical industry, saying that the study "treats doctors like children." No other sector, it asserts, "is subject to such extensive obligations in terms of transparency and controls as the pharmaceutical industry," adding that the legislation and regulations in this area have been considerably strengthened over the past 10 years.

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Gene Therapy Payment Models Could Be One Focus For 'Cures II'

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Key Republicans on the US House Energy & Commerce Oversight Subcommittee used an accountability hearing with Centers for Medicare and Medicaid Services Administrator Seema Verma to highlight their desire to work on new models to pay for transformative therapies in the next iteration of the "21st Century Cures" Act.

Texas Republican Michael Burgess brought up the subject directly in his questioning of Verma. "We'll be working on the next version of the Cures bill at some point over the coming months, and we really do want to involve you and your office" in talks about gene and cell-based therapies, he explained.

"We have to have a way of value-based purchasing or amortizing that cost over a longer period time and certainly look forward to your help as the committee develops" legislation.

The bipartisan leaders of the original 21st Century Cures effort (Colorado Democratic Rep. Diana DeGette and Michigan Republican Rep. Fred Upton) recently announced plans to push for a "Cures II" bill – and CMS policies are likely to be one area of focus. *(Also see "Cures 2.0: Can Congress Recapture The Legislative Magic?" - Pink Sheet, 19 Aug, 2019.)*

The focus of the 23 October hearing was reflected in the title: Democratic concerns about the administration of the Affordable Care Act, where they see HHS/CMS policies as a form of deliberate "sabotage" of the program. Those arguments have been in play from the start of Verma's tenure, but she had not previously been called to testify. That did not lend itself to bipartisan conversations about potential areas of agreement.

Questioning from Democrats was predictably aggressive, focusing on the impact of the Trump Administration's changes to the ACA and resulting reductions in coverage. On the Republican side, members pointed out the irony of Democrats expressing outrage over Trump Administration policies in the context of their drug price "negotiation" bill, HR3.

"I wish you could have been here during our markup, when nearly every Democrat was holding up posters of what President Trump had said about bringing down drug prices," Rep. Greg Walden, R-OR, said.

"While we may have some disagreements about the policy, they were certainly the President's advocates last week when we were dealing with drug costs," Walden, who announced his plans not to seek reelection a few days after the hearing, said. *(Also see "Medicare Part D Redesign Backed By House Republicans Retools Manufacturer Discount" - Pink Sheet, 20 Oct, 2019.)*

Republicans also tried to focus on areas where there has been bipartisan agreement involving CMS policy, including in the context of the opioid response and in the need to develop new payment models for curative therapies. Ranking Republican Brett Guthrie (Kentucky) raised that issue specifically during his initial questioning of Verma.

Verma agreed that current payment systems are not "set up to handle" such therapies, but her answer was cut off by Oversight Subcommittee Chair DeGette, who declared Guthrie's time expired. That prompted Burgess to return to the subject when it was his turn for questions – but also underscored that the Democratic majority was not looking to use the hearing to advance new ideas.

As part of its bipartisan drug pricing bill, the Senate Finance Committee included some initial proposals to enable installment plan payment models for one-time use gene therapies. However, a committee staffer acknowledged that it had been difficult to translate the broader interest in enabling innovative payment models into specific proposals at this point. *(Also see "Value-Based Contracts: Medicaid Best Price Concerns Could Be Eased With CMS Guidance" - Pink Sheet, 17 Sep, 2019.)*

Republicans tried to focus on areas of bipartisan agreement involving CMS policy, including the opioid epedemic and in the need to develop new payment models for curative therapies.

That suggests that the topic may indeed be held over for something like the "Cures II" process, even if some form of a bipartisan drug pricing bill is enacted this Congress.

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A Reflection On BTD And RMAT Designations

The continuing interest in cell and gene therapies is reflected by the 800+ active investigational new drug (IND) applications within the field that are on file with the US Food and Drug Administration (FDA).[1] This trend is only set to increase, with the FDA foreseeing the approval of 10–20 cell and gene therapy (CGT) products per year by 2025.[2]

To increase the number of therapeutic options for treatment of conditions for which there is currently no cure, there are two FDA expedited pathways: the Regenerative Medicine Advanced Therapy (RMAT) designation and the Breakthrough Therapy designation (BTD). Both are well suited to the development of cell and gene therapies. This article reflects on the usage of these designations and, throughout, Keith Webber, Vice President, Biotechnology at Lachman Consultant Services, Inc., provides insights and advice regarding the two accelerated pathways for cell and gene therapies.

BTD Versus RMAT

Being the earlier of the two designations (2012), BTD holds the majority of product approvals. This pathway was followed in 2017 by the RMAT, which has a particular focus on cell and gene therapies, tissue engineering products, and human cell or tissue products. This differentiates it from the BTD, which is also applicable to other types of therapies if they address serious or life-threatening conditions. Table 1 provides an overview of the number of requests for each designation, as well as the success rate across 2019.

Despite the number of BTD requests exceeding quadruple the number of RMAT applications, the success rates are comparable, at around 35–40%. This has also been the case for cumulative data that show all submissions since each designation was introduced (refer to **this** 2018 *Pink Sheet* guide for cumulative information, plus further trends including therapy areas and sponsor types). However, there are certain differences in evidentiary criteria for applying for both pathways that may affect decision-making regarding which designation to apply for. With the BTD, sponsors must provide evidence that the treatment is likely to be a substantial safety or efficacy improvement over existing therapies, which is not the case for RMAT.[5] As

a result, if a product candidate is eligible, Webber notes that it could be beneficial to gain both designations as, "if you can apply for both, you can choose the most advantageous if you receive both, so it opens up more opportunities."

Inevitably, there are certain challenges associated with applying for either designation. According to Webber, one factor to be mindful of: "Often the clinical development is more advanced than the chemistry, manufacturing and controls (CMC) development. The CMC and product development can be a rate-limiting component for a Biologics License Application (BLA) submission or approval. So that is something to keep in mind. You don't want this to hold you back as you move through development." Ensuring all elements of the research and development process are aligned is therefore an important factor for boosting chances of rapid product approval.

Post-Approval Safety And Efficacy Studies

Post-approval requirements can be another consideration when determining which pathway is most suitable. For an accelerated approval under BTD, there is a requirement to perform a post-approval confirmatory study when the approval has been based on a smaller data set or surrogate endpoints. The post-approval requirements for the RMAT are not as rigid; Webber notes that "the accelerated approval may allow the use of historical controls, retrospective studies, monitoring data or real-world evidence – there are more opportunities for that confirmatory evaluation. This may be because the BTD is for all products, including traditional pharmaceuticals, whereas RMAT is only for the more complex biological products. As such, RMAT products are often times more challenging to design clinical studies for."

The topic of post-approval and surrogate endpoints can raise concern around treatments being ineffective, or possibly toxic, upon being marketed.[6] In terms of advice, Webber said, "Communicate with the FDA early and often when designing your trials or planning approval." There is an FDA guidance document, called "Interacting with the FDA on Complex and Innovative Trial Designs," which provides sound advice for developing successful clinical protocols. The recommendation is to get both FDA input and acceptance as early as possible on trial design. To support these critical interactions, the FDA has set a goal of recruiting 50 new clinical reviewers for CGT products.[7]

FDA Submissions – What To Look Out For

The recent development of Medicaid expanding coverage for products receiving accelerated approvals signifies the interest and investment in cell and gene therapies.[8] This is in tandem with a growing trend of larger companies being increasingly keen to own gene therapy technologies rather than partnering. Historically, gene therapies have been spearheaded by small biotechnology companies (typically in partnership with larger pharmaceutical firms). In fact, 90% of gene therapy development is by companies with fewer than 500 employees.[9] From his experience in carrying out due diligence for larger organizations interested in investing or acquiring smaller biotechnology companies, Webber noted: "Be vigilant in your due diligence assessments when considering buying or investing into a company. You should watch out for gaps in product development. For example, there may be deficiencies in the establishment of the master cell bank or working cell banks."

Look out for poorly characterized components in the product and qualification of materials. In addition, watch out for any lack of standardization, which can create issues further on in the process. Webber explains that "There may be a lot of variability in how the manufacturing processes are performed during development and that can be a challenge in terms of establishing what is the consistent product that's coming out of that manufacturing process. In many

TABLE 1. 2019 COMPARISON OF BTD[3] AND RMAT[4] FDA DESIGNATIONS

Designation	Total Requests Received	Granted	Denied	Withdrawn	Success Rate (%)
BTD	157*	54	63	18	34%
RMAT	37*	15	18	2	41%

*Requests that are still pending a decision are included in the total requests received column. Numbers are for US federal fiscal year 2019, ended 30 September 2019.

cases, the product is the process. So if the processes are changing continually, and the product is difficult to fully characterize (as often the RMAT products are), you can have considerable uncertainty with regard to the interpretation of any preliminary clinical data."

Data integrity can also be an issue, for which Webber suggests paying close attention to the ALCOA principles (Attributable, Legible, Contemporaneous, Original and Accurate). "Those principles should be in place, and if they aren't it can be challenging to be reliant on that data for presentation to the FDA during inspection."

Webber indicates that manufacturing is a final area of the process that can come under scrutiny: "Sometimes there are manufacturing changes during development that have not been qualified. So, the company makes changes where they haven't really evaluated the impact (of those changes) during development of the manufacturing process."

What Will The Future Look Like?

The direction of growth in cell and gene therapies is moving further toward personalized medicines. At this point, it is difficult to predict how the regulatory landscape will accommodate these advancements. One of the largest challenges to anticipate may be in assessing clinical outcomes, where variances could be due to patient-to-patient differences or product-to-product differences. "It might be necessary to develop methods to assess the *in vivo* product performance, for example, gene incorporation and gene expression, in addition to the assessment of clinical outcome, to further understand the relationship between clinical performance and product performance *in vivo*." Webber continued, explaining that the FDA's Center for Biologics Evaluation and Research (CBER) has released many new guidances regarding CGT, covering everything from certain therapeutic areas such as hemophilia to evaluations of devices used in regenerative medicine.

Given that the cell and gene therapy accelerated pathways are relatively new, and with the stance of Medicaid reimbursing such products, applications for accelerated approval pathways are set to skyrocket. The possibilities that cell and gene therapies may unveil could be truly profound. That being said, approval for CGT is undoubtedly going to become more complex with the advancement of personalized medicine, and this could create further complications when conducting studies and assessing clinical outcomes (due to individual variance).

A closing remark from Webber: "The FDA has a great interest in bringing new and effective treatments to patients, so I encourage sponsors to take advantage of this willingness, to meet with the FDA early and during product and clinical development phases. Also, work with consultants as needed to get guidance on preparing submissions and product development as you move forward."

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Importation, Pricing Policies Raised Concerns For US FDA's Project Orbis

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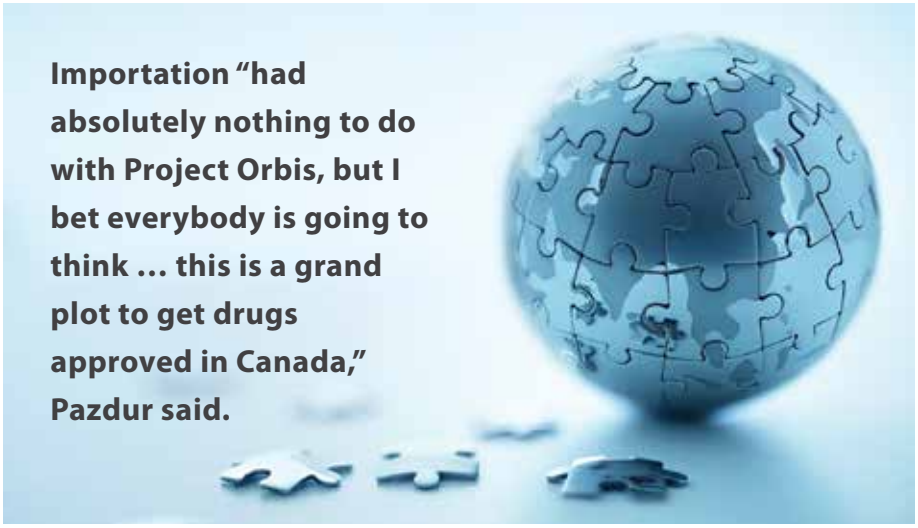

Richard Pazdur worried that his program allowing simultaneous submission and assessment of drug applications in the US and other countries would be improperly linked to, and potentially damaged by, White House plans to allow drug importation from Canada.

The director of the US Food and Drug Administration's Oncology Center of Excellence also was concerned that ex-US drug pricing issues could emerge and prevent Project Orbis, Pazdur's program to allow simultaneous submission and collaborative review of drugs in Canada, Australia and the US, from gaining a foothold.

During a 12 November session of the Friends of Cancer Research Annual Meeting, Pazdur commented on some of the problems that prevented companies from participating in the program, as well as the external forces that he worried may impact it.

Drug importation was one of the issues Pazdur thought may create problems. Just as US, Canadian and Australian regulators were working on the first application, HHS announced a pathway allowing states to import drugs from Canada, ideally at a significantly lower price.

Pazdur said his reaction was, "Oh shit. How did this happen?"

"I said this had absolutely nothing to do with Project Orbis, but I bet everybody is going to think that the reason why we're doing this is because this is a grand plot on the part of the FDA and the administration to get drugs approved in Canada so they can be imported," Pazdur said. "Strange coincidences occur. It was, let me guarantee you, never, ever, ever on the radar."

HHS released an action plan for a potential regulatory approach to drug importation from Canada in July *(Also see "Canadian Importation Option May Be Hindered By Product, Savings Restrictions" - Pink Sheet, 31 Jul, 2019.)*, and recently Florida submitted a proposal that is under consideration. *(Also see "Trump Pushes Importation, Claims Success In Lowering Prices" - Pink Sheet, 3 Oct, 2019.)*

Drug pricing issues also potentially threaten the long-term use of Project Orbis outside the US. Pazdur said the program will include new molecular entities and since Canada and Australia potentially could approve those applications before regulators in Europe, their pricing benchmarks would not be available.

"Usually Canada and Australia benchmark on European drug pricing, and especially if we got into a new molecular entity this would be waters uncharted," Pazdur said.

Pazdur said he was not sure what role drug pricing would ultimately play in future Project Orbis work. He said the issue is "purely theoretical" and must be addressed, but is not insurmountable.

The issue also may have scared some sponsors from participating in Project Orbis. Kelly Robinson, Health Canada director of the Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics, said during the session that Canada was reviewing its drug pricing regulations, which may have contributed to some sponsors' anxiety about the program.

Indeed, the FDA and others may have to find a solution if Pazdur's aspirations for the program are to be fulfilled. He wants the program to speed access to breakthrough-designated products and novel treatments for the participating countries. *(Also see ""Project Orbis' Oncology Pilot Eventually Will Target 'Major Impact' Applications" - Pink Sheet, 7 Oct, 2019.)*

The first product to participate in Project Orbis was Eisai Inc.'s kinase inhibitor Lenvima (lenvatinib), seeking an indication for use in combination with Merck & Co. Inc.'s PD-1 inhibitor Keytruda (pembrolizumab) for some patients with endometrial cancer. The FDA granted accelerated approval to the application, Australia's Therapeutic Goods Administration gave provisional approval, and Health Canada gave a Qualifying Notice for the Notice of Compliance with Condition. *(Also see "US FDA's Project Orbis Could Streamline Global Clinical Trials In Cancer" - Pink Sheet, 17 Sep, 2019.)*

SUPPLY WORRIES DISCOURAGED SPONSORS FROM PARTICIPATING

FDA officials usually made a cold call to sponsors to gauge their interest in participating in Project Orbis. A small number refused to participate, Pazdur said, for a number of reasons.

Among them was that there was not

sufficient drug supply for Canada and Australia in addition to the US. Pazdur seemed to shoot down the premise, arguing that Canada and Australia combined had about 20% of the US population.

"I felt like saying 'Really? You don't have a delta of 20% of your drug?'" he said.

Pazdur also said that companies were against participating because they did not have a regulatory component in the country, although he wondered why that was the case.

"I was like, 'Don't you think you should find one?'" Pazdur said rhetorically during the conference session.

EU NOT LIKELY TO JOIN PROJECT ORBIS

The Project Orbis collaboration may be growing soon, as Singapore and Switzerland have shown interest in joining.

Pazdur said Singapore in particular was chosen as another potential partner because it is a hub for health care in southeast Asia and Canada has prior experience working with them. In addition, Pazdur also performed research for the Singapore health care system early in his career.

Both countries already participate in a collaborative review consortium that also includes Australia and Canada. Each country leads the evaluation a portion of the application to decrease the time needed to reach a decision and reduce review costs. *(Also see "Dual Approval For Verzenio Under International Review Scheme" - Pink Sheet, 18 Apr, 2019.)*

Pazdur was not sure whether Project Orbis could be expanded to the European Union. He said the EMA application review process does not lend itself to the Project Orbis structure and that EMA does not generally see a substantial delay in gaining access to novel drugs.

Pazdur added that the program is not intended "to establish some global consensus" similar to the EMA review.

The FDA is working with other regulators to harmonize standards in many areas, in part to streamline the development process. Among the recent developments was execution of the mutual recognition agreement with the EU to share inspection information. *(Also see "Mutual Recognition's Next Evolution May Be Sharing Info On India And China Inspections" - Pink Sheet, 11 Jul, 2019.)*

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US FDA Oncology Leadership Shuffle Moves Patricia Keegan To OCE; Gootenberg Takes On Recruitment

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The reorganization of oncology functions in the US FDA's "modernized" Office of New Drugs will result in Patricia Keegan, the long-time director of Division of Oncology Products II in the former Office of Hematology & Oncology Products, moving to the Oncology Center of Excellence.

Keegan will serve as an acting associate director in OCE, and will continue to report to Richard Pazdur, who remains director of both the Oncology Center of Excellence and the newly-organized Office of Oncologic Diseases (formerly OHOP). FDA announced the new oncology leadership positions as part of the second phase of the OND restructuring. *(Also see "Drug Review Reorganization At US FDA Coming Into Focus" - Pink Sheet, 6 Nov, 2019.)*

At OCE, Keegan will join approximately a dozen associate directors. OCE works on cross-cutting oncology issues, including the development of programs like "Project Orbis," Real-Time Oncology Review, and the oncology Assessment Aid.

Pazdur announced the most recent OCE pilot at the Friends of Cancer Research annual meeting on 13 November: "Project Point/Counterpoint" will use advisory committee briefing documents to highlight areas of agreement and disagreement between sponsors and FDA on an application.

Keegan joined FDA in 1990 as part of the oncology group within the Center for Biologics Evaluation & Research. When therapeutic biologic reviews transitioned to the Center for Drug Evaluation & Research in 2003, she became a division director in OHOP responsible for biologics under Pazdur. In 2011, OHOP more fully integrated reviews by indication rather than the legacy biologic/pharmaceutical divide, and Keegan became DOP II director.

As part of the new reorganization, Keegan's former division is divided into two new divisions. The new "Division of Oncology II" will be responsible for thorac-

ic, head and neck, neuro-oncology, rare cancers and pediatric solid tumors, while DO III will oversee gastrointestinal, superficial cutaneous cancers, melanoma and sarcoma.

DO II will be led by acting director Harpreet Singh, while DO III will be led by Steven Lemery. Division of Oncology I will remain intact, led by director Julia Beaver and focusing on breast, gynecologic and genitourinary cancers, as well as on cancer supportive care products.

OOD RECRUITMENT EFFORTS

Also as part of the oncology leadership reshuffling, Joseph Gootenberg will become acting associate office director in the Office of Oncologic Diseases, where he will continue to work on oncology recruitment and retention efforts. He previously served as deputy director in the Division of Oncology Products II under Keegan, and is a pediatric hematologist-oncologist.

At OHOP, Gootenberg has made it a personal priority to recruit new staff via medical school fellowship programs and shepherd those individuals through the long and convoluted government hiring process. Speaking the Prevision Policy/Friends of Cancer Research Biopharma Congress in 2016, Pazdur said Gootenberg was "better than a headhunter or professional personnel person" in recruiting new oncology reviewers.

At OOD (which Pazdur says should be pronounced "double-O-D"), Gootenberg joins four acting supervisory associate directors: Gideon Blumenthal, Paul Kluetz, Tamy Kim (regulatory affairs), and Meredith Chuck (safety). Marc Theoret is the acting deputy director.

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US FDA Revokes Orphan Drug Designation For Indivior's Sublocade

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Orphan drug designation for Indivior PLC's Sublocade (buprenorphine extended-release) was improperly granted 25 years ago under the Orphan Drug Act's cost recovery provision and should be revoked, the US Food and Drug Administration said in a first-of-its kind decision.

Based on the facts and circumstances at the time buprenorphine first received orphan drug designation for opioid addiction in 1994, it was unreasonable to conclude that there would be no cost recovery from the product's sales in the US during its first seven years on the market, the agency said in a 7 November response to a citizen petition from Braeburn Pharmaceuticals Inc., which is seeking to bring Brixadi, a competing buprenorphine product, to market.

It was not reasonable for the FDA to assume that the market size would remain constant for the first seven years of buprenorphine's marketing for opioid use disorder because it was not reasonable to assume that the laws restricting access to treatment of opioid use disorder (OUD) with opioids were unlikely to change during the relevant timeframe, or that the number of treatment facilities would not increase, the agency said.

In addition, the FDA's original cost recovery analysis did not account for buprenorphine products other than the sublingual tablet (subsequently approved as Subutex) in estimating potential costs and revenue, the agency said. "Therefore FDA did not have the information necessary for the agency to properly evaluate the designation request."

The agency's decision means that Sublocade, which was approved in November 2017, does not qualify for seven years of orphan drug exclusivity.

Indivior's orphan drug designation for Suboxone (buprenorphine/naloxone sublingual film) also is at risk of revocation.

"Because FDA granted the orphan-drug designation for buprenorphine with naloxone the same year and under a similar set of facts and circumstances as the designation for buprenorphine, we intend to reconsider whether the orphan-drug designation for buprenorphine with naloxone was also improperly granted," the FDA said.

> The FDA is reconsidering whether orphan designation for Indivior's buprenorphine/naloxone product Suboxone also was improperly granted.

Nevertheless, Braeburn will not be able to launch the monthly formulation of Brixadi in the US until December 2020 because, in a separate same-day decision, the agency reaffirmed its view that Brixadi is blocked by Sublocade's three-year Hatch-Waxman exclusivity that expires on 30 November 2020.

'TWO VERY RARE THINGS'

The agency's decision to revoke Sublocade's orphan drug designation is unusual in two respects, experts said.

The buprenorphine active moiety received designation under the rarely used cost recovery prong of the Orphan Drug Act. In addition, revocation of an orphan drug designation is an "extraordinarily unusual event," Tim Cote, former director of the agency's Office of Orphan Products

Development, told the *Pink Sheet*.

"In this case you have two very rare things that are occurring simultaneously," Cote said.

Nevertheless, Cote said it sounds like the agency's action was an appropriate one from a policy perspective, particularly given the current opioid epidemic.

"It sounds like a one-off," Cote said. "I don't believe this is going to cause major changes in orphan designation practices or revocation practices."

Braeburn counsel Scott Lassman of Lassman Law+Policy said that with the revocation of Sublocade's orphan drug designation, the agency "has gone back and corrected an error, and I think it's a huge win for patients."

The case highlights a loophole for orphan drugs, Lassman said, noting that once a sponsor gets a cost recovery-based designation, the designation does not expire even if financial conditions change dramatically.

"I think the loophole needs to get closed, and I think there may be efforts to close that loophole," he said.

The Fairness in Orphan Drug Exclusivity Act (HR 4712), introduced in the House on 17 October by Rep. Madeleine Dean, D-PA, would require the sponsor of a drug previously designated under the cost recovery provision to demonstrate at the time of approval that the product still satisfies those requirements to qualify for seven-year orphan exclusivity.

SEEKING REMEDIES AT THE FDA AND THE COURTS

Braeburn has been fighting on both the legal and regulatory fronts to bring Brixadi to market.

Brixadi, a monthly and weekly depot formulation of buprenorphine, received tentative approval in December 2018 but was blocked from coming to market by Sublocade's three-year new product exclusivity, which expires in November 2020.

In April, Braeburn sued the FDA over the scope of Sublocade's exclusivity. *(Also see "Blocked By Sublocade: Braeburn Sues To Get Brixadi Buprenorphine Formulation Onto Market" - Pink Sheet, 10 Apr, 2019.)* The company also filed a citizen petition asking that the agency revoke Sublocade's orphan drug designation and refuse to grant the Indivior drug seven-year orphan exclusivity. *(Also see "US FDA's Transfer Policy For Orphan Drug Designation Under Scrutiny" - Pink Sheet, 10 Apr, 2019.)*

> "Not only was it conceivable at the time of designation that the laws could change in the future and allow significant additional patient access to buprenorphine, but there is also no evidence that the total number of treatment facilities would remain constant." – FDA

The citizen petition challenged the agency's policy of allowing sponsors to transfer orphan drug designation granted for an active moiety in one formulation (in this case, Subutex in 1994) to a subsequent formulation (Sublocade) without submitting either a separate request for designation, or a plausible hypothesis that the follow-on drug is clinically superior to the first drug. Braeburn also took issue with the basis for Subutex's original grant of orphan drug designation under the cost recovery provision.

RARELY USED PATH TO DESIGNATION

Under the Orphan Drug Act, a product may qualify for designation if it is intended for a disease that affects less than 200,000 persons in the US, or if the condition affects more than 200,000 persons but there is no reasonable expectation that the cost of developing and making the drug for such a disease will be recovered from US sales.

This cost recovery provision has been little used. In its citizen petition, Braeburn said only three drugs have been designated under this provision: Indivior's (previously Reckitt & Colman Pharmaceuticals) Subutex and Suboxone, both designated in 1994 for treatment of opioid addiction; and Eli Lilly & Co.'s Evista (raloxifene), designated in 2005 for reducing the risk of breast cancer in postmenopausal women.

The cost recovery provision requires sponsors to submit documentation regarding the expected costs of the drug's development and projected sales revenue in a product's first seven years. However, companies generally are reluctant to open up their books on development program expenses and sales projections to the FDA. *(Also see "FDA Orphan Drug Requests Could Start To Rely More On Non-Profitability Criteria" - Pink Sheet, 3 Nov, 2015.)*

ERRONEOUS ECONOMIC ASSUMPTIONS

In its response to Braeburn's petition, the FDA said it will not revoke a cost recovery-based designation solely because the drug has become profitable.

"However, FDA may revoke a cost recovery orphan-drug designation if new information demonstrates that the drug did not meet the cost recovery standard at the time of the designation request," the agency said. "For example, such new information can show that the economic assumptions underlying the agency's analysis at that time were erroneous or were not reasonable."

In the case of buprenorphine, the agency said the information submitted by Reckitt & Colman in 1993 did not support the assertion that the sponsor would not recover its development costs in the first seven years after approval.

First, the agency said it was not reasonable to assume that the market size would remain constant for the first seven years of marketing buprenorphine for OUD.

In 1993, the sponsor's estimates of expected revenue relied on several assump-

tions, including that the maximum population eligible for treatment of addiction with any narcotic was limited to 115,000 patients, which was the number of slots in methadone maintenance programs. The estimates also assumed relevant laws that strictly regulated methadone treatment programs would not change during the product's lifetime.

"However, not only was it conceivable at the time of designation that the laws could change in the future and allow significant additional patient access to buprenorphine, but there is also no evidence that the total number of treatment facilities would remain constant," the FDA said.

It would have been unreasonable not to recognize that buprenorphine is materially different from methadone in a way that potentially could support a different regulatory approach, the agency said, pointing to evidence at that time that buprenorphine could be used with potentially less toxicity even for nontolerant individuals.

The agency also points to evidence indicating that when Indivior's predecessor requested the designation, it already had considered the possibility that the regulatory framework would change to expand the market, and the company factored the benefit of that potential change into its business plans.

In addition, the FDA's own sensitivity analysis performed at the time of designation looked at different scenarios based on timing of approval, market share and sales price. "Notably, in four out of nine scenarios, FDA's analysis indicated that buprenorphine would provide a positive return on investment following the first seven years of sales in the US," the agency said.

REVENUE FROM OTHER FORMULATIONS NOT CONSIDERED

The agency's original cost recovery analysis also failed to take into account the costs and revenue associated with other potential buprenorphine products.

Because orphan drug designation generally covers an active moiety for a specific condition, a cost recovery analysis should not be limited to just the particular product described in the designation request. Rather, it should consider the costs and revenue that can reasonably be expected from all products with the activity moiety that the sponsor may potentially market during the first seven years.

The agency noted that a parenteral dosage form of buprenorphine was approved for treatment of pain in 1981, and there also was evidence at the time of designation that subcutaneous administration was potentially effective in treating addiction.

"Without analyzing the possibility of marketing other products, FDA did not obtain or consider all the information necessary for the agency to properly conduct the cost recovery analysis," the agency said.

In a statement, Indivior said it had requested that FDA review Sublocade's eligibility for orphan drug exclusivity, given its orphan drug designation. "We are reviewing FDA's decision in this matter," the company said of the designation revocation.

"We recognize the urgent need for new and effective treatments and are grateful that patients have access to more than a dozen medications currently on the market, including multiple generic versions of buprenorphine. Indivior continues to invest in developing innovative treatments for addiction and to demonstrate real-world outcomes of patients treated with Sublocade as part of an evidence-based treatment program."

NEW PRODUCT EXCLUSIVITY SCOPE REAFFIRMED

While the revocation of Sublocade's orphan drug designation is a win for Braeburn, the agency's reaffirmation of the scope of the drug's three-year exclusivity is a win for Indivior.

In a July ruling in Braeburn's lawsuit against the FDA, a federal judge said the agency failed to define the limits of Sublocade's innovation in determining whether Hatch-Waxman exclusivity blocked approval of Brixadi. The court remanded the case to the agency to reconsider whether Braeburn's application for a monthly depot formulation is eligible for approval. *(Also see "US FDA Must Explain How It Defines 'Innovation' In Awarding Hatch/Waxman Exclusivity, Court Says" - Pink Sheet, 23 Jul, 2019.)*

On remand, the agency reaffirmed its earlier finding that the Brixadi monthly formulation is blocked by Sublocade's exclusivity.

The FDA interprets the scope of exclusivity to be related both to the underlying new clinical investigations that were essential to approval, and to aspects of the approval that were supported by those new clinical investigations.

The agency "concludes that the innovation supported by Sublocade's new clinical investigations essential to approval is the effective delivery of buprenorphine in a depot formulation to treat moderate-to-severe OUD over a month-long period in patients who have initiated prior treatment with a buprenorphine product," the remand decision states.

Differences in how Sublocade and Brixadi address the risk of precipitated withdrawal upon initiation of treatment for OUD are not clinically meaningful to the use of the monthly products themselves in a way that would take Brixadi Monthly outside the scope of Sublocade's exclusivity-protected conditions of approval, the agency said.

"The sponsors of both Sublocade and Brixadi Monthly addressed the risk of precipitated withdrawal in different ways in their clinical investigations essential to approval," the agency said. "The clinically meaningful characteristic of Sublocade for exclusivity purposes is not how the applicant addressed the issue of precipitated withdrawal in its development program, but that it did so with new clinical investigations supporting approval of the monthly depot formulation."

However, the agency also reiterated its view that the weekly formulation of Brixadi falls outside the scope of Sublocade's exclusivity, and it rejected Braeburn's assertion that the monthly and weekly formulations function as an integrated system that cannot be treated as two separate products.

In a press release, Braeburn said it "is pleased to confirm that it will seek, and is eligible for, marketing approval for Brixadi (buprenorphine) weekly and monthly extended-release injection for the treatment of OUD as of December 1, 2020."

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Vaccine Maker Bankruptcy Shows Regulatory Perils Of Business In China

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As one of China's major publicly traded vaccine manufacturers, Changchun Changsheng Biotech is abruptly ending its rapid growth trajectory with a shocking insolvency announcement.

One year after revelations that the Northeastern company had several good manufacturing practice (GMP) violations, Shenzhen Stock Exchange-listed Changsheng Bio formally declared its bankruptcy on 8 November.

The announcement, despite being speculated about for months, sent shock waves across the vaccine and wider health sector in China.

Amid a fast-changing regulatory environment, embodied by two laws that have already been issued and one on the way, legal experts see several important take-aways from the development. The first relates to the increasingly severe punishments, including hefty fines, that are being levied on violators of GMP standards.

Changsheng Bio was fined CNY9.1bn ($1.3bn) by China's National Medical Products Administration, the figure representing three times its illegal revenues from the sales of affected vaccines, plus an additional fine of CNY12.03m. *(Also see "Unbearable Lightness? China Levies Record $1.3bn Fine Amid Vaccine Scandal" - Pink Sheet, 18 Oct, 2018.)*

The Changchun province-based firm in July 2018 was found to have forged data and changed product expiration dates. The fine for the transgressions surpassed the CNY3bn levied on GlaxoSmithKline PLC in 2014 when the UK drug and vaccine producer was charged with compliance violations, and was the largest fine at the time in the pharma sector.

The new penalty also burned a big hole in the balance sheets of Changsheng Bio, which had total capital of CNY3.985bn and net capital of CNY3.41bn, making the company essentially financially insolvent.

By 8 October, the company had been put on notice of market delisting, which will take effect on 16 October. Once officially designated as a "high-tech enterprise" in Changchun City, Changsheng Bio was the number two maker in China of rabies vaccines and a rising star, being a non-state-owned entity in a sector where production of Category 1 (state-purchased) vaccines is dominated by large state-owned makers.

Changsheng Bio had seen its sales grow rapidly, surging by over 50% to CNY346m in the first quarter of 2018 before the violations were unveiled by an unannounced inspection.

RISING CALLS FOR INVESTOR PROTECTION

The second lesson from the affair is the rising call to protect the rights of investors - companies should prepare for potential class actions after a major product and safety scandal.

Small investors in Changsheng Bio, facing the company's sudden fall and subsequent delisting, have seen the value of their shares plummet and essentially wiped out. Those affected could potentially resort to class actions seeking compensation, commented Tsinghua University law professor Xin Tang.

Unlike in the US, large class action lawsuits are rare in China, given a fear of public anger and mass protests, but that could change.

Tang suggested a delay in the collection of the official fines to allow the company to compensate small investors first. Civil compensation should be prioritized and punishment should be dealt appropriately, Tang stressed. "For one, violators and acts of violations should be punished accordingly to make them feel the pain," the professor commented in an interview with China state-owned broadcaster CCTV.

"Victims should get their share of compensation, including [through] class actions and a multi-channel settlement mechanism," he suggested.

FAMILIARITY WITH NEW REGULATIONS IS KEY

The third lesson from the Changsheng Bio bankruptcy is the need to get familiarized with new regulations. The China Drug Administration Law and Vaccines Administration Law have been recently issued and aim to significantly raise the bars for manufacturing, distribution and sale of vaccines and drugs in the country.

A direct result of the Changsheng Bio scandal, the Vaccines Administration Law is the first such dedicated legislation and an elevation from the previous regulation status, showing the increasing importance being placed on the sector by the government.

The new law increases sector entry requirements and imposes even stricter standards than for drugs, while analysts have pointed to the fact that it prohibits the contract manufacturing of vaccines.

Additionally, executives and heads of vaccine manufacturers must meet certain industry background and experience requirements and maintain a good credit record. The new law levies potential fines as high as 30 times any revenues obtained from illegal operations.

Meanwhile, the Drug Administration Law, released on 26 August and taking effect on 1 December, is China's most comprehensive ever legislation governing pharmaceutical affairs. *(Also see "China's New Pharma Law Leaves Key Questions Unanswered" - Pink Sheet, 4 Sep, 2019.)*

The new law emphasizes more dynamic inspections, including unannounced checks to be conducted of pharma manufacturers and distributors. Notably, it explicitly states that both domestic and international drug manufacturers, as well as their local vendors and suppliers, should be prepared for more frequent inspections.

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Ex-Sun Employee Alleges Reprisal For Opposing US Off-Label Practices

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A former executive of Sun Pharmaceutical Industries Ltd. in the US has alleged that she was directed to "facilitate and solicit" off-label marketing for certain medicines and that when she declined to toe the line, she was "disciplined and retaliated against."

In a complaint filed in the US District Court For The Middle District Of Florida, Sandra Hagenbrock, a former national account director for Sun, alleged that the Indian firm's "policy" complied with the law but its "practice" violated these statutes, and that both she and her colleague Damian Frantz had objected to what they viewed as unlawful practices.

Hagenbrock said that she opposed the company's solicitation and off-label marketing practices and told the company that these alleged initiatives violated the Federal and State False Claims Act (FCA) and Anti-Kickback Statute. In response, the complaint alleges, Sun retaliated against her for her failure to engage in what she "reasonably believed" was unlawful conduct.

Frantz is also reported to have earlier filed a retaliation suit against Sun, claiming, among other charges, that he was asked to solicit opportunities to push off-label uses of certain drugs.

Hagenbrock's complaint further alleged that Sun's senior vice-president of sales in the US, Janet Sharp, went on to engage in "name calling" and also made other "insulting comments" against her. Hagenbrock claims she was "deprived" of compensation, passed over for promotion, harassed and then eventually "constructively discharged" in July 2019.

"The defendant's conduct violated the anti-retaliation provision of the FCA," Hagenbrock stated in the complaint, filed earlier this month.

Sun, however, dismissed the allegations as baseless. "We believe the allegations made in this lawsuit are without merit and we will continue to vigorously defend against it," Sun told the *Pink Sheet*. India's top-ranked firm underscored that it is committed to conducting business "honestly, ethically, and in compliance with laws and regulations."

ALLEGATIONS OF UNLAWFUL INCENTIVES

Hagenbrock's complaint alleges that Sun violated the Federal and State FCAs and the Federal Food, Drug and Cosmetic Act by engaging in a range of alleged activities from "at least 2014 to the present", involving the marketing, selling, and prescribing of Ilumya (tildrakizumab), Yonsa (abiraterone acetate), and Absorica (isotretinoin).

These activities, the executive claimed, include conspiring to create unlawful incentives to provide in exchange for patient referral and prescription business; conspiring to make and use false records and statements to get false claims paid by the government; and the illegal off-label marketing of its drugs to obtain increased payments from the government for non-indicated reasons.

> "We believe the allegations made in this lawsuit are without merit and we will continue to vigorously defend against it," Sun told the Pink Sheet.

Notably, however, while Hagenbrock alleges that Sun's scheme caused false claims to be submitted to the government and further believes that the government paid those false claims, the complaint states that the plaintiff "does not have sufficient detail to support that allegation at this time." But she adds that in raising those concerns to Sun, she was disciplined and retaliated against.

Hagenbrock, aged 57, had filed a charge of discrimination, alleging violations of the Age Discrimination in Employment Act and retaliation, which was lodged with the US Equal Employment Opportunity Commission (EEOC) on 4 September. The EEOC closed its file citing that, based upon its investigation, it is "unable to conclude" that the information obtained establishes violations of the statutes.

"This does not certify that the respondent is in compliance with the statutes. No finding is made as to any other issues that might be construed as having been raised by this charge," the EEOC noted. Hagenbrock was then issued her Right to Sue on 11 September.

OFF LABEL PROMOTION TOUGH TO PROVE?

Industry experts maintain that off-label promotion is both complex to prove and then not necessarily always unhealthy.

They explained that such promotion is "very difficult" to establish because most of pharma promotion happens "in-clinic or in closed groups" where groups of doctors are addressed in continuing medical education programs; even these are closed groups as entry is through invitation only and is outside public scrutiny.

"Therefore, unless such promotion is captured on printed promotional material or in-clinic calls are recorded, it is very difficult to prove it. Companies are very careful to not do this brazenly as it can come up in marketing audits and cause problems," one industry pundit told the *Pink Sheet*, adding that there have been cases where sales managers have directed their teams to verbally promote off-label to drive sales to meet "difficult sales quotas."

> Sun will probably prefer to move quickly to settle such complaints, experts believe, indicating that another regulatory probe is something that the company will want to avoid.

But importantly, the observer also sought to differentiate between "wanton" off-label promotion to drive up sales versus cases in practice where doctors find the drug to be quite effective in indications for which it isn't formally approved.

"Not all off-label [promotion] can be labelled as bad. There have been cases where governments have tried to regularise off-label usage for certain drugs," the person noted.

SETTLEMENT THE WAY FORWARD?

Nevertheless, experts believe that Sun will probably prefer to move quickly to settle such complaints and that another regulatory probe is something that the company will want to avoid.

"Also, it is possible that such off-label promotion could have come from local managers who claim to have tacit approval from senior management. If written documents, recorded conversations exist, then this can blow up quickly and Sun will want to do everything possible to avoid it," the industry pundit added.

Sun has over the recent past been battling allegations of market-related and governance lapses in India, though an initial inquiry by the Securities and Exchange Board of India (SEBI) is believed to have yielded little to support these charges. *(Also see "Concerns Over Alleged Lapses By Sun Fading?" - Scrip, 30 Aug, 2019.)*

On 5 September, Sun confirmed that a forensic audit had been ordered by SEBI with reference to its financial statements for the fiscal years ending March 2016/2017 and 2018 and said that the audit was ongoing at the time.

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Mylan Warning Letter Exposes Challenges In Valsartan Supply Chain Chemistry

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A warning letter to Mylan NV is yet another indication that in response to last year's discovery of carcinogenic nitrosamines in active pharmaceutical ingredients for certain blood pressure medications, US Food and Drug Administration investigators are turning their attention further up the pharmaceutical supply chain.

There has been a growing focus on suppliers of APIs; now the spotlight is turning to the suppliers of the API suppliers.

NITROSAMINE CHALLENGES EVOLVE

The Mylan warning letter, sent on 5 November and posted to the agency's website on 12 November, also shows what a difficult challenge the nitrosamine issue poses to supply chains for valsartan and other angiotensin II receptor blockers, sometimes called ARBs or sartans.

After Mylan identified recovered solvents as the source of nitrosamines in its valsartan API, the firm dropped contract solvent recyclers like Lantech Pharmaceuticals Ltd. and recycled its own solvents.

The FDA hit Lantech with a warning letter in August *(Also see "US FDA Warning Letter Draws Indian Solvent Recycler Into Valsartan Crisis" - Pink Sheet, 16 Aug, 2019.)* and one of its other customers, Aurobindo Pharma Ltd., in June. *(Also see "Aurobindo Faulted In US FDA Warning Letter For Poor Root Cause Investigations" - Pink Sheet, 3 Jul, 2019.)*

It's all part of an uphill effort by the FDA to inspect better process chemistry into the supply chain for ARBs and other pharmaceuticals. *(Also see "Enforcing A Belated Chemistry Lesson – The Nitrosamines In Sartans Saga" - Pink Sheet, 22 Aug, 2019.)*

But doing its own solvent recycling hasn't fixed the problem, probably because of contaminated tanks, so Mylan is relying on fresh solvents for now.

The Mylan warning letter called not only for better control of raw materials but also for improved cleaning validation to prevent cross-contamination in API manufacturing.

A HUNT FOR THE SOURCE OF CONTAMINATION

The warning letter stems from a 27 May through 5 June 2019 inspection at the Mylan Laboratories Ltd. Unit 8 plant along Highway 16 in Gaitula Chodavaram, a village in eastern India's state of Andhra Pradesh.

Mylan's 26 June 2019 response to the inspection's Form 483 ob-

servations lacked enough detail or evidence of corrective actions to satisfy the FDA. The firm's 21 November 2018 investigation and a 1 January 2019 addendum had concluded the contamination came from certain recovered solvents.

But in the FDA's view, Mylan's conclusion that high contaminant levels in some of the solvents would not result in significant levels in its API lacked adequate scientific justification.

A field alert report Mylan sent the FDA on 13 September 2019 suggested that nitrosamine-contaminated solvent from Lantech and other solvent recovery vendors was one likely root cause of the contamination in Mylan's rejected API batches.

HOW IMPURITIES GOT INTO MYLAN'S PLANT

Although Mylan did not document which solvents it stored in which tanks, the firm tried to retrospectively determine the number, identification and usage of its solvent tanks.

The warning letter noted that Mylan stopped making the API with solvents recovered by contractors, switching to in-house solvent recovery to prevent further contamination.

However, despite Mylan's certainty that the in-house solvent recovery process would not produce any of the nitrosamine impurities, the firm detected just such an impurity at levels exceeding its specification limit according to its solvent recovery process performance qualification report.

Mylan attributed that surprising finding to its use of equipment it had previously used to store materials intended for destruction.

For the time being, Mylan told the FDA it would continue to use fresh solvents until it can validate in-house solvent recovery.

That's fine, the FDA told Mylan, but only if the firm commits to testing solvents, whether fresh or recovered, for nitrosamines prior to release for use in API manufacturing.

> Mylan told the FDA it would continue to use fresh solvents until it can validate in-house solvent recovery. FDA still insists on testing prior to release.

REQUEST FOR 'MATERIAL SYSTEM REVIEW' CASTS BROAD NET

In the warning letter, the FDA requested information about Mylan's investigations on recovered solvents, its program for qualifying the performance of API manufacturing and solvent recovery processes, its raw materials controls, an analysis of storage tanks, related specifications and test methods, and a comprehensive, third-party review of its material system.

The information request is quite broad, applying to all APIs that Mylan manufactures and to all its material suppliers.

As part of the material system review, Mylan must report on the adequacy of its oversight of the quality of all the firm's material suppliers. That includes the qualification standards for supplier selection and lifecycle evaluations for ensuring their continued acceptability.

CROSS-CONTAMINATION QUESTIONS

The cross-contamination concerns raised by the warning letter focused on inadequate cleaning of non-dedicated equipment.

Lint-free cloths became stained with API residue after someone wiped certain chutes with them. Mylan responded by grinding and polishing the chutes, updating its cleaning procedures, reviewing investigations into complaints and out-of-specification results, and testing batches for "extraneous matter."

But this wasn't enough, the FDA said, because "cross-contamination cannot be assumed to be uniformly distributed and testing alone is insufficient to mitigate the observed contamination hazards."

The warning letter went on to call for an independent assessment of cleaning effectiveness and improvements to Mylan's cleaning validation program.

The FDA addressed the warning letter to Mylan CEO Heather Bresch with a copy to Chinnikrishna Reddy, head of API site operations at the plant.

DESPITE REDACTIONS, WARNING LETTER GIVES AWAY API'S IDENTITY

The FDA redacted all mention of specific drug products, APIs, solvents and impurities from the public version of the Mylan warning letter that the agency posted online.

However, the redacted warning letter make it clear that it concerns nitrosamine contamination of valsartan because it says Mylan recalled all batches of the undisclosed API from the US market in December 2018, and the FDA's weekly enforcement report says Mylan only had one recall event that month, which was for the recall of all US lots of valsartan-containing products within expiry due to traces of a nitrosamine impurity, N-nitrosodiethylamine, or NDEA, in the valsartan API that the firm had manufactured.

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Recent And Upcoming FDA Advisory Committee Meetings

TOPICS	ADVISORY COMMITTEE	DATE
Boehringer Ingelheim's Jardiance (empagliflozin) as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus	Endocrinologic and Metabolic Drugs	Nov. 13
Amarin's Vascepa (icosapent ethyl) to reduce the risk of cardiovascular events, as an adjunct to statin therapy, in adults with elevated triglyceride levels (135 mg/dL or greater) and other risk factors for CV disease	Endocrinologic and Metabolic Drugs	Nov. 14
Correvio International Sarl's vernakalant for rapid conversion of recent onset atrial fibrillation to sinus rhythm	Cardiovascular and Renal Drugs	Dec. 10

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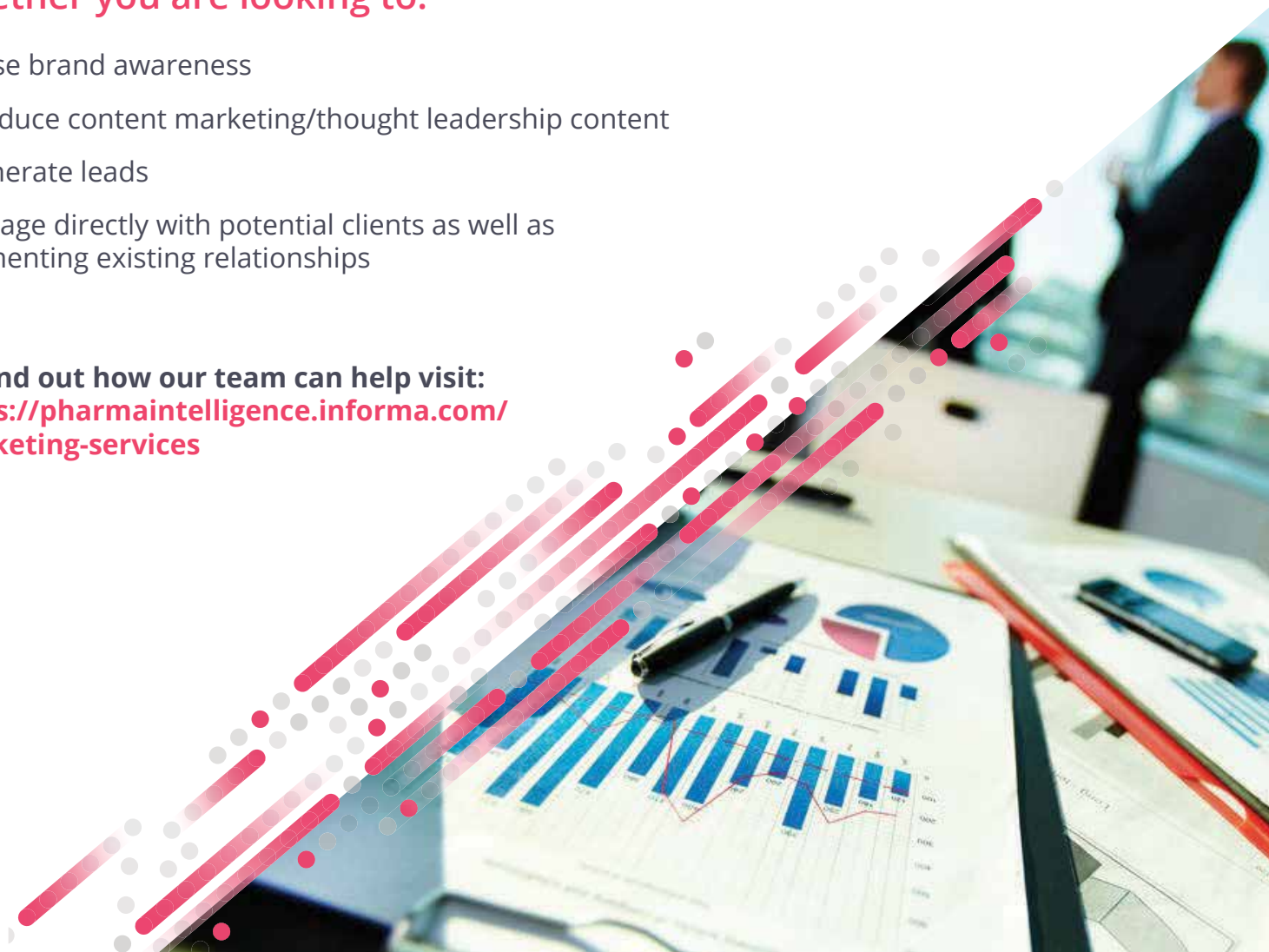

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