Allergan’s Back In The (M&A) Saddle Again Post Pfizer Breakup

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Allergan PLC never really left the market for biopharmaceutical mergers and acquisitions after it entered into a $160bn merger agreement with Pfizer Inc., but now that the deal has been called off the company is free to buy assets large and small that fit its “growth pharma” focus.

Since there was always a chance that the US government would propose new tax rules to prevent the mega-merger, it’s likely that Allergan never stopped looking at deals. Now the company is free to buy anything that suits its interests with its $150m from Pfizer plus $36bn in cash from the sale of its generics business to Teva.

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In fact, after the stock market closed, Allergan and Heptares Therapeutics, a wholly-owned subsidiary of Sosei Group Corp., revealed a partnership worth up to $3.34bn plus royalties. Allergan will license exclusive global rights to a broad portfolio of novel subtype-selective muscarinic receptor agonists to treat major neurological disorders, including Alzheimer’s disease.

The company agreed to pay $125m up front, up to $665m in development and product launch milestone fees, and as much as $2.5bn for sales milestones, plus royalties. Allergan also will provide up to $50m for a joint research and development program that will advance multiple drug candidates through Phase II clinical trials. Allergan will take over development starting with Phase IIb trials and handle all manufacturing and commercialization for future products. Heptares recently completed a Phase I study for the program’s lead drug candidate HTL9936.

‘RECHARGED, EXCITED, READY TO GO’

Allergan president and CEO Brent Saunders said in a conference call regarding the end of its merger agreement with Pfizer that “we are recharged, excited and ready to go” in terms of executing the company’s growth pharma strategy. That strategy relies on mostly later-stage research and development programs for product candidates with high sales potential as well as acquisitions of companies or assets that may contribute to Allergan’s double-digit revenue growth target.

Allergan fell 14.8% to $236.55 per share on April 5 as investors responded to the Treasury rules on tax inversions, US President Barack Obama’s endorsement of the rule.

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How the mighty fall. Pfizer, already nudged from the number one spot in the most recent Scrip 100 league table by Novartis, has twice failed to secure a major transformative merger that simultaneously re-establishes its market dominance and releases it from the controlling strictures of its US tax domicile. The prospects of it succeeding now look vanishingly slim.

CEO Ian Read, hitherto gung-ho for a tax inversion deal that would free Pfizer to use the deep pools of cash it has accumulated outside the US without taking a US tax hit, seems to have accepted this. Until the Allergan deal collapsed, he had been deferring discussion of a potential break-up of the company. Now Pfizer says it will make a decision by the end of this year on whether to split out its innovative and established product businesses.

If, as looks increasingly likely, that separation happens, the core innovative pharmaceutical business will be a standalone unit with only a tad more than half of the current group’s revenues (looking at 2015 figures), leaving it struggling to remain in the top 10.
Gilead Buys NASH Drug To Dominate 2nd Liver Disease

Mandy Jackson

Gilead Sciences Inc. knows a thing or two about developing successful liver disease therapies, since it owns the world’s top two hepatitis C drugs in terms of sales, and now the company is attempting to dominate another liver disease with the purchase of Nimbus Apollo Inc. for up to $1.2bn.

Nimbus Apollo, a Nimbus Therapeutics LLC subsidiary, has a portfolio of ACC inhibitors, including a Phase II-ready non-alcoholic steatohepatitis (NASH) program known as NDI-010976. Gilead’s acquisition of the assets gives the biotech giant a fourth NASH drug candidate — one that is designed to stop or reduce the liver’s production of fat thereby preventing new inflammation and fibrosis as opposed to compounds that reduce fat buildup, inflammation and fibrosis after they’ve occurred.

‘We hadn’t been proactively soliciting partners for this [ACC inhibitor] program,’ Nimbus CEO Don Nicholson told Scrip

Gilead, which has generates more than $20bn dollars in sales from its hepatitis C medicines Sovaldi (sofosbuvir) and Harvoni (sofosbuvir and ledipasvir) since late 2013, agreed to pay Nimbus Therapeutics $400m up front and up to $800m in development-based milestone fees.

Nimbus was considering an initial public offering to fund Nimbus Apollo’s mid-stage NASH clinical trials, but now the Cambridge, Massachusetts-based biotech firm plans to use cash from the Gilead transaction to fund other early-stage drug development programs.

“We hadn’t been proactively soliciting partners for this [ACC inhibitor] program,” Nimbus CEO Don Nicholson told Scrip. “There are several pharma companies that have been trying to decide if they want to have a NASH program; we haven’t been going into discussions with those companies, but we certainly have been getting into discussions with the companies that want to be and are in this field.”

Foster City, California-based Gilead, with three NASH programs in Phase I and II development, emerged as an ideal partner for the development of NDI-010976 and Nimbus’s other ACC inhibitors.

THREE NASH ASSETS BECOME FOUR

Gilead’s lead NASH asset simtuzumab inhibits lysyl oxidase-like-2 (LOXL2), an enzyme involved in maintenance and homeostasis of tissues that is highly expressed in liver fibrosis. Gilead acquired the asset in its $225m purchase of Arroto Biosciences in 2010.

Simtuzumab failed in Phase II pancreatic cancer and idiopathic pulmonary fibrosis (IPF) studies in September 2014 and early 2016, respectively, while mid-stage development in colorectal cancer and myelofibrosis were discontinued last year.

The LOXL2 inhibitor remains in development for liver diseases with Phase IIb clinical trials under way in NASH and primary sclerosing cholangitis (PSC) plus an ongoing Phase II trial in primary biliary cirrhosis (PBC), according to Sagient Research’s BioMedTracker database. Results from the NASH study are expected during the first half of 2016.

Gilead is testing its apoptosis signal-reducing kinase 1 (ASK1) inhibitor GS-4997 in combination with simtuzumab in a Phase IIb NASH clinical trial, but the company also is developing the small molecule in mid-stage pulmonary arterial hypertension (PAH) and diabetic nephropathy trials, according to the BioMedTracker database. ASK1 is involved cardiac inflammation and fibrosis.

The company’s third NASH drug candidate is the Phase I farnesoid X receptor (FXR) agonist GS-9674, which Gilead acquired from Phenex Pharmaceuticals for up to $470m at the start of 2015. Phenex initiated a 12-patient, Phase II pilot study for a different small molecule FXR antagonist known as Px104 in December 2013, but Gilead included the earlier-stage GS-9674, not Px104, in its 2015 annual report issued in February.

BIG MARKET, GROWING COMPETITION

There are an estimated 15 million people in the US with NASH, which is expected to become the most common disease requiring liver transplants by 2020. That’s why the competition to develop and commercialize treatments is fierce and growing for the fatty liver disease. The BioMedTracker database lists 32 NASH drugs in clinical development, including 15 Phase I, 10 Phase II, six Phase IIb and two Phase III programs.

 Intercept Pharmaceuticals Inc. began the Phase III REGENERATE clinical trial in September to test its closely-watched FXR agonist obeticholic acid (OCA; INT-747) in the treatment of non-cirrhotic NASH patients with advanced liver fibrosis. The company’s stock soared to more than $300 per share in 2014 based on an investiga
tion-sponsored Phase IIb study in NASH despite cardiovascular concerns, but shares were trading at $133.55 as of April 4.

 Genfit SA also began a Phase III NASH clinical trial for its selective PPAR modulator elafibranor in late 2015 despite a Phase II failure for the small molecule earlier in the year.

Gilead executive vice president of research and development and chief scientific officer Norbert Bischofberger said in a statement! from the company that “the acquisition of Nimbus’s ACC inhibitor program represents a timely and important opportunity to accelerate Gilead’s ongoing efforts to address unmet needs in NASH.”

Bischofberger added: “These molecules will complement and further strengthen Gilead’s pipeline and capabilities to advance a broad clinical program in NASH that includes compounds targeting multiple key pathways involved in the pathogenesis of the disease.”

Gilead’s stock was essentially unchanged by the company’s disclosure of its transaction with Nimbus on April 4. The stock rose 0.13% to $94.24 per share.

Privately-held Nimbus focused on NASH for NDI-010976, and the biotech firm’s CEO Nicholson said Gilead’s main interest in the drug is NASH and hepatocellular carcinoma. However, Nimbus evaluated its other preclinical ACC inhibitors in various cancers, including breast and pancreatic, as well as psoriasis and other autoimmune disorders.

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Move over Zarxio. There’s a new kid in town: Inflectra (infliximab-dyyb), which won the FDA’s nod on April 5 as the first monoclonal antibody biosimilar licensed in the US, although it’s going to be a while before patients have access to the new drug, since Celltrion Inc. and Pfizer Inc. said they won’t put it on the market until after June 29.

The companies have remained mum on Inflectra’s pricing – with Pfizer telling Scrip in a statement it “cannot comment on our future development and commercialization strategies” for the product, which is a biosimilar version of Remicade (infliximab), a tumor necrosis factor blocker sold in the US by Johnson & Johnson Inc. subsidiary Janssen Biotech Inc.

So it’s unclear how much of a discount Inflectra will provide for patients currently getting Remicade. “Each biosimilar molecule has specific drivers that determine market price,” Pfizer said. “The overall cost savings and generally positive reception of Inflectra in other markets to date is consistent with our belief that biosimilars can be an important and a welcome option for patients, prescribers and payers.”

Some have been skeptical Inflectra would provide any real cost savings, including members of the FDA’s Arthritis Advisory Committee, which backed approval of the biosimilar at a Feb. 9 meeting.

After all, Sandoz Inc’s Zarxio (filgrastim-sndz) only has provided a 15% discount to Amgen Inc’s human granulocyte colony-stimulating factor Neupogen.

But some analysts have predicted Inflectra could provide as much as a 25% discount to Remicade, cutting deeply into its $4bn annual US sales.

Inflectra is only the second biosimilar to be approved for the US market – coming just over a year after Zarxio won the FDA’s blessing in March 2015.

Inflectra was licensed by the FDA for the US for rheumatoid arthritis, active ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn’s disease in adults and pediatric patients and ulcerative colitis (UC) in adults – all of the indications Celltrion and Pfizer were seeking.

The only indication that Remicade carries that Inflectra doesn’t is use for pediatric UC, and that’s because Janssen’s branded medicine holds orphan drug exclusivity on that indication until Sept. 23, 2018.

But, insisted Jay Siegel, chief biotechnology officer and head of scientific strategy and policy at J&J, Celltrion’s and Pfizer’s biosimilar is “not identical to Remicade.” He pointed out the FDA approved Inflectra as a biosimilar, but it’s not approved to be interchangeable with Remicade.

“For FDA to determine a biosimilar is interchangeable with its reference product, a manufacturer must demonstrate that the biosimilar is expected to produce the same clinical result as the reference product in any given patient,” he said. “In addition, the manufacturer must demonstrate the risk of alternating or switching between the reference product and biosimilar is no greater than the risk of using the reference product.”

FIRST TO FOLLOW LABELING GUIDELINES

Inflectra also is the first to carry labeling that follows new guidelines set out just last week by the FDA – including a statement of biosimilarity, which declares it’s a “biosimilar” version of Remicade.

Inflectra also is the first biologic to carry an FDA-assigned unique four-letter suffix as part of the nonproprietary name of its active drug substance: dyyb.

When the FDA approved Zarxio in March 2015, the agency designated “sndz” as a four-letter “placeholder.” The FDA wants to change that suffix to “bflm,” but currently, Zarxio’s suffix remains “sndz,” which was derived from the license holder’s name: Sandoz, a unit of Novartis AG.

LAWSUITS

Like Zarxio, Inflectra is caught up in a legal dispute over whether Celltrion and its partner Hospira Inc., now part of Pfizer, followed the requirements of the Biologics Price Competition and Innovation Act (BPCIA) – the law that gave the FDA the authority to approve biosimilars.

Most recently, Janssen on March 22 stipulated to drop its infringement claim against Celltrion and Pfizer involving the J&J subsidiary’s patent ‘396, which expires on June 29.

That agreement came after Celltrion and Pfizer agreed not to market Inflectra before June 30. J&J’s Siegel, however, said the company has other patents on Remicade that “remain valid and enforceable until September 2018.”

“A commercial launch of Celltrion’s infliximab-dyyb in advance of this date would be an infringement of our patents, and we intend to defend our intellectual property rights,” Siegel said.

A spokesperson for Janssen confirmed the company is continuing to pursue the BPCIA questions in its lawsuit, which is being fought at the US District Court for the District of Massachusetts.

In addition to the patent infringement claims, Janssen filed the suit to try to force Celltrion and Hospira to engage in the biosimilar law’s disclosure and negotiation procedures – the patent dance. In Zarxio’s case, it had to wait six months post-approval before it could enter the market because of Amgen’s lawsuit against Sandoz.

Sandoz has petitioned the Supreme Court seeking to overturn a ruling by the US Court of Appeals for the Federal Circuit, which said when a biosimilar applicant does not dance, the BPCIA’s 180 days notice of commercial marketing is mandatory and may only be given after FDA licensure. But Amgen argued in its opposition brief the case is a “poor vehicle” for the high-court’s first interpretation of the 2010 biosimilars law.

Amgen also filed a “conditional cross-petition” with the Supreme Court calling for the justices to also review the other portion of the Federal Circuit’s ruling, in which it said the patent dance was optional and biosimilar makers could choose not to disclose their application and manufacturing details.
Robbing Ebola To Pay For Zika: Playing With Fire?

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ince early this year, the Obama administration has been shift-
ing money around to cover the costs of the work being done
by the National Institutes of Health (NIH), the Centers for
Disease Control and Prevention (CDC), the FDA and other federal
agencies to address the Zika crisis in the Americas and to prepare
the US for the invasion of the virus.

But now, the sources of those funds have dried up and because
the Republican-controlled Congress has been reluctant to grant
President Barack Obama's request for $1.9bn in emergency spend-
ing for Zika, the administration has been forced to dip into a pot of
money officials have long-declared were dollars already commit-
ted to the continued effort to combat Ebola in Africa and keep the
disease from further invading the US.

The White House has identified $589m, including $510m of ex-
isting Ebola resources within Health and Human Services (HHS),
State Department and USAID accounts, which is being redirected
for immediate use for "time-critical activities" to address Zika, Shaun
Donovan, director of the Office of Management and Budget (OMB)
told reporters during an April 6 conference call.

"In the absence of congressional action, we must scale up Zika
preparedness and response activities right now," Donovan said.

But, he said, "these repurposed funds are not enough to support
a comprehensive Zika response, and can only temporarily address
what is needed until the Congress acts on the administration's emergency supplemental request," which Donovan stressed was "urgently needed."

HHS Secretary Sylvia Mathews Burwell warned that the efforts
on vaccines and diagnostics could be jeopardized, even stopped,
without the emergency Zika funding.

And, she said, biopharmaceutical makers and other companies
need to know the government has those funds to stay interested in
collaborating on vaccines and diagnostics – something Anthony
Fauci, director of the NIH's National Institute of Allergy and Infec-
tious Diseases, whose agency is leading the government's pursuit
of those products, has consistently been warning about since the
Zika crisis began.

"We've made important progress to keep Americans safe from
these public threats here and abroad, but these efforts need to
continue, and they can't be stopped or shortchanged," Burwell said.
"We face two real global health challenges – Ebola and Zika – and
we don't have an option to set one aside in the name of the other."

Obama administration officials condemned Congress for failing
to act and leaving the US vulnerable.

"We don't have an option to set one aside in the name of the other.""We need Congress to step up to the plate," he said.

But over that time, "Congress has done nothing," Earnest said during
his daily White House briefing with reporters.

The nearly $600m in "reprogrammed" funds is only a "temporary
fix and not at all a long-term solution," he said.

Donovan said the administration would use some of the $1.9bn
to then replenish the amounts being taken from the Ebola ac-
counts that are being used for the Zika-related activities.

"This will ensure that we have sufficient contingency funds to
address unanticipated needs related to both Zika and Ebola," he
explained.

Earnest stressed the US was facing a "unique scenario" where it's
got an advanced warning a disease will soon be arriving on the
nation's shores.

"That means that we have an opportunity to do something about
it in advance," Earnest said. "But Congress has completely abdicated
their responsibility to follow through on a proposal that the admin-
istration put forward based on the advice of scientific experts."

"There's no reason that Democrats and Republicans should dis-
agree about the need to protect the American people from an
impending epidemic that has serious consequences for pregnant
women in this country," Earnest argued.

"Responsible adults should be able to step back and acknowl-
edge that planning in advance, when you're talking about some-
thing like this, is really important," he said.

"Mark my words," Earnest said, news headlines will be "sounding
the alarm" this summer about the spread of Zika – but it may be
too late by then.

"As you're writing those stories remember this day," he told re-
porters.

"I take no joy in suggesting that Republicans are going to look
back on this time that they've had to act on the Zika virus and
deepl regret it," Earnest lamented. "It's deeply regrettable right
now that they aren't taking the necessary steps to fight this disease."

"We need Congress to step up to the plate," he said.
The White House on April 6 fought back against accusations from Allergan PLC CEO Brent Saunders the Obama administration’s move to institute new rules aimed at thwarting corporate inversion was “un-American” and had specifically been constructed to take down the company’s $160bn merger deal with Pfizer Inc., which had, indeed, fallen apart in light of the US Treasury Department’s actions.

Saunders made his charges during an April 6 morning interview on CNBC shortly after Allergan and Pfizer confirmed they had terminated their deal, under which the combined company would have resided in Ireland, which has a significantly lower tax rate than the US.

In a conference call with investors and analysts, Saunders insisted he was “patriotic,” but argued the Obama administration’s new anti-inversion rules were “incredibly misguided” and an “unproductive policy for the United States.”

But Josh Earnest, the White House press secretary and chief spokesperson for President Barack Obama, shot back.

“It is difficult to have a lot of patience for an American CEO trying to execute a complicated financial transaction to avoid paying taxes in America talking about what it means to be a good citizen of the United States,” Earnest declared from the White House during his daily briefing.

“At this point, it’s hard to have a lot of patience for the commentary on patriotism from a corporate leader who’s prepared to renounce his citizenship just to avoid paying his fair share,” he charged. “That’s part of why I think the American people are strongly on the side of the government in this case.”

Earnest denied the administration launched the rules specifically to bring the Pfizer-Allergan deal before it could be consummated – pointing out Treasury had been working on its actions for “years before these two companies even announced they were considering a corporate inversion.”

“This is a long thought-out strategy here,” Earnest contended.

Under the rules, released on April 4, the federal government would disregard foreign parent stock attributable to certain prior inversions or acquisitions of American companies for the past three years – thereby making mergers like Pfizer-Allergan no longer worthwhile for the US firm.

“The intent of the rule is to close a loophole that allows individual corporations on paper to move their company’s operations overseas to avoid paying taxes,” Earnest said.

The lost revenue associated with US corporations “not paying their fair share” in taxes impacts the nation’s ability to invest in schools, reduce the cost of college education and put people to work building America’s infrastructure, he said.

Most US corporate leaders are “trying to do the right thing for the country” and “understand that a strong American economy is good for their business,” Earnest said.

The Obama administration’s concern, he said, is “with the leaders of some corporations that are looking to take the best of America without making a contribution to the success of our country. And that’s wrong.”

No American would tolerate “a discussion of patriotism from somebody who’s advocating that kind of approach for their company’s accounting practices,” Earnest argued.

Allergan’s Saunders also asserted the US Treasury was “building a wall around the US to keep people in and global companies inverted.”

And, he said, “just foreign domiciles are going to be advantaged in buying US companies as long as this is the tax code and scheme that the US government wants to have.”

But, Earnest said, “just on a factual matter, he’s wrong about that.”

He pointed to provisions in the Treasury’s rules aimed at allowing foreign companies to make “significant investments” in the US.

“The president has talked about how that’s important for our economy over the long term,” Earnest said. “The president has been a leading advocate for companies overseas doing that.”

He insisted Treasury had “thought through the consequences” and went to “great lengths to ensure that we’re not overly disincentivizing foreign companies who are seeking to invest in the United States.”

Earnest acknowledged, however, the administration’s rules could only go so far in shutting down “this unpatriotic corporate practice” and that it would take Congress to act.

“More precisely, we need Republicans in Congress to stop working so hard to defend corporate interests that are seeking to shirk their basic American responsibility,” he said.

“We can’t get Republicans in Congress to understand the significance of their failure to act," Earnest said.

He acknowledged there is a handful of Republicans that have sided with Obama in seeking to end inversion, noting at least one presidential candidate – Donald Trump, although Earnest didn’t mention him by name.

The two Democratic presidential candidates, former Secretary of State Hillary Clinton and Sen. Bernie Sanders (I-VT), also weighed in on the matter on Twitter.

“Glad to hear Pfizer is calling off the merger. We need to close the loopholes that let corporations escape paying their taxes,” Clinton said.

“Pfizer’s merger was a transparent attempt to dodge US taxes. I applaud President Obama for taking decisive action,” Sanders said, adding in a separate tweet “Corporate greed needs to end. They’re taking advantage of the benefits of America, yet refuse to accept their responsibilities as Americans.”

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change, and the increasing likelihood that the merger with Pfizer would fall through. After Saunders reassured investors on April 6 that the company is focused on growth, including through value-creating M&A, Allergan regained 3.5% to close at $244.74.

Deutsche Bank analyst Gregg Gilbert shed some light on investors’ muted response to reassurances from Saunders in an April 6 note: “[S]tand-alone execution will be key for Allergan, but may be somewhat more challenging in light of what has likely been a distracted employee base. With investor sentiment at poor levels for the [biopharma] space, and the natural skepticism that may follow when a company had agreed to sell itself, some investors may take a more wait-and-see approach.”

Indeed, while the NBI jumped based on the news that two big acquirers are re-focused on deal making with companies of any size, the index still is down 15.6% so far in 2016 and Allergan has fallen 21.7% year-to-date.

VALUATION HITS MAY HELP ALLERGAN’S GROWTH STRATEGY

In terms of how Allergan will execute its growth strategy, Saunders said during the company’s conference call that “our goal is not to be a serial acquirer; our goal is to be the premier growth pharmaceutical company.” He noted that investments in both M&A and R&D are what create “premier companies,” not M&A alone.

However, Saunders conceded that Pfizer and Allergan terminated their agreement at a great time given the decline in biopharma company values that took place between the mega-merger’s announcement in November and now. Since then, he said, “the environment has only improved for us and, if it stays this way, there could be an exceptional period for us to look for growth assets.”

Saunders noted that private companies generally tend to be more realistic about their valuations and they didn’t benefit from the big value surges experienced by publicly-traded biotechs until recently. But while many public company CEOs haven’t stopped seeing their recent stock price declines as anomalies, he said that view is “starting to soften” – just in time for Allergan to deploy the cash from its pending transaction with Teva. That deal is expected to close in June.

“It’s a bit fortuitous, but as we get into the end of the first half of this year and the Teva deal closes, my sense is that people will start to come to grips with the new reality. So, the timing, frankly, couldn’t have winded up any better for us,” Saunders said.

A FULL CIRCLE BUY FOR SAUNDERS?

Saunders didn’t shed a lot of light on which companies Allergan would consider buying, but he didn’t completely rule out an acquisition that would bring his own CEO career back to where it started: Bausch & Lomb. The eye care giant was sold to Valeant Pharmaceuticals International Inc. for $8.7bn in 2013 during Saunders’s tenure.

Valeant has become ensnared in controversy and has seen its stock price drop precipitously this year, so among a spate of recent rumors is speculation that the company may be looking to sell some of its businesses, including Bausch & Lomb.

“Obviously, I have a fondness for Bausch & Lomb that goes beyond my time at Allergan. And, to be fair, Bausch & Lomb is a premier brand in eye care,” Saunders said. “[M] ost of the people there used to work for me. They’re a great team.”

However, it’s not clear that Bausch & Lomb is for sale and it may not fit in with Allergan’s growth strategy.

“I think Bausch & Lomb is interesting at the right price, given that we’re in eye care and it’s a complementary business to us,” Saunders said, noting that it’s hard to tell if the company’s $8.7bn valuation three years ago holds up today.

Our goal is not to be a serial acquirer; our goal is to be the premier growth pharmaceutical company

TARGETS MUST FALL INTO SEVEN KEY AREAS

In terms of other companies that Allergan might buy, there was a lot of speculation about who would be attractive targets after Allergan agreed to sell it generics business to Teva. The targets have to align with the company’s seven key therapeutic areas: ophthalmology, aesthetics/dermatology, central nervous system (CNS), gastrointestinal (GI) diseases, women’s health/urology, anti-infectives and biosimilars.

Large-cap biopharma companies were also mentioned in Evercore ISI’s July survey of investors as potential Allergan targets, including Alexion Pharmaceuticals Inc., BioMarin Pharmaceutical Inc., Vertex Pharmaceuticals Inc. and Shire PLC. However, Saunders said Allergan wouldn’t consider an orphan disease purchase unless the target had a high-growth asset that fit very specifically into one of the company’s seven therapeutic areas.

Alkermes PLC and Acadia Pharmaceuticals Inc. each have CNS drugs and product candidates, and Anacor Pharmaceuticals Inc. has dermatology and anti-infective assets – all of which could be attractive to Allergan – but the company is likely to remain tight-lipped about specific acquisition opportunities until it pulls the trigger on new deals.

Each of those three companies saw their stock prices jump on April 6: Alkermes by 5.3%, Acadia by 9.9% and Anacor by 16.5%. Their market capitalizations ranged from $3.3bn to $5.8bn – reasonably sized deals for Allergan even without the cash from Teva in its pocket.

As Gerberry wrote in his note on the company, “management commented that it ‘would not hesitate for the right opportunity,’ which suggests to us [that] smaller bolt-on transactions aren’t gated by the completion of the Teva deal.”
Allergan ‘Unusual Suspect’ But Pipeline ‘Hunger’ A Perfect Match For Heptares

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With Scrip still reeling from the news last week that Pfizer and Allergan have called off their $160bn mega-merger, news broke that former darling of the UK biotech scene Heptares, now a wholly-owned subsidiary and the ‘R&D engine’ of Japanese company Sosei Group Corp., has secured a notable licensing deal with Allergan. Scrip caught up with Heptares CEO Malcolm Weir to get his take on the fall of Pfizer-Gan (PfAllergan?), and of course the small matter of securing a partnership deal worth up to $3.34bn plus potential royalties.

Under the agreement announced on April 6, Allergan has licensed exclusive global rights from Heptares to a broad portfolio of novel subtype-selective muscarinic receptor agonists to treat major neurological disorders, including Alzheimer’s disease.

Allergan agreed to pay $125m up front, up to $665m in development and product launch milestone fees, and as much as $2.5bn in sales milestones, plus royalties. Allergan also will provide up to $50m for a joint R&D program to push multiple drug candidates through Phase II trials. Allergan will take over development starting with Phase IIb trials and handle all manufacturing and commercialization for future products.

**SCRP:** Congratulations on a securing a great deal with Allergan, but I have to start by asking what your thoughts are about the Pfizer-Allergan deal falling apart…

**MALCOLM WEIR:** In truth, we’ve been working with Allergan on this deal all along. We didn’t stop working on it because they had some discussions ongoing with Pfizer. Allergan remained committed to us throughout that process so we’ve been a bit blinkered. Pfizer is a partner of ours and they’re both great companies. Would it have worked if they had come together? Very possibly, it was just a meeting of minds really.

**SCRP:** Was securing this deal with Allergan a competitive process?

**MW:** There wasn’t really a process. We have been talking to a number of pharmaceutical companies over the years and keeping them apprised of progress. [The muscarinic program] is a leading program for us and it attracted a lot of interest. But we haven’t been aggressively pushing to partner it. It was just a meeting of minds really.

**SCRP:** What stage are the lead candidates that Allergan has licensed?

**MW:** We’ve got two molecules in Phase I right now, and they’re both of interest in terms of taking them forward. Within a program like this you are going to have to make prioritization decisions, ultimately, but at the moment we have those two. These are against M1, so they’re for cognition.

In Phase I, they look very promising at doses which suggested that they will be efficacious. At those doses we are not seeing the side effect problems that people have seen in the past with muscarinic drugs, and that’s because they are selective: we’ve got rid of the bad side effects of M2 and M3 and kept the efficacy. So they are promising to take into Phase II studies for proof of concept in Alzheimer’s.

Then we’ve also got M4 agents which should be in the clinic early next year, and dual M1/M4s as well. M4 is directed towards psychosis in Alzheimer’s, which is the behavioral disturbances and delusions and agitation that you see in people with Alzheimer’s. We plan to move the M1 products into Phase II towards the end of this year.

**SCRP:** How does a broad-based deal such as this fit in with your positioning at Sosei?

**MW:** It fits very well. This is a program that we always expected to partner at some point, because we can’t take drugs to market in Alzheimer’s ourselves as the investment is absolutely enormous. We have partnered much of our pipeline that was historic Heptares pipeline.

What we’re doing now is building a new pipeline of targets, many of which are not listed yet on our website, in a limited but well-chosen range of therapeutic areas, including neurology. Some of those targets will be partnered, just as we’ve done here, and there will be huge deals to come from them. But some we will look to take to market ourselves. That way we can see us – Sosei – able to sustainably move forward and build value, and build the company into a genuine pharmaceutical player.

**SCRP:** What do you say to suggestions that Allergan is not the most obvious partner for you to match up with?

**MW:** That’s an interesting point, because we did talk to the usual suspects. Some people might say that Allergan is a slightly unusual suspect. But when you look at Allergan and see how Brent [Saunders] is leading the company, then we sit perfectly within his open science agenda.

Allergan is looking to build pipeline – early, mid and late stage – not just products ready to go [to market]. They don’t have big in-house discovery activities, but they have a tremendous development machine so Allergan is a very good partner for us. They are very knowledgeable in Alzheimer’s, they have memantine on the market and have developed drugs for Alzheimer’s before. They know the space, and they’re hungry for pipeline.

That’s an advantage in many ways compared to a situation where the partner company has large internal capability in a similar area. Sometimes those things get a bit difficult. Some might say it’s an unusual partner but this is the way that a lot of the industry is going to move. That’s good for both biotech and pharma.

**SCRP:** Heptares was acquired by Sosei in early 2015 as its ‘R&D engine.’ How does a broad-based deal such as this fit in with your positioning at Sosei?

**MW:** It fits very well. This is a program that we always expected to partner at some point, because we can’t take drugs to market in Alzheimer’s ourselves as the investment is absolutely enormous. We have partnered much of our pipeline that was historic Heptares pipeline.

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**SCRP:** What stage are the lead candidates that Allergan has licensed?

**MW:** We’ve got two molecules in Phase I right now, and they’re both of interest in terms of taking them forward. Within a program like this you are going to have to make prioritization decisions, ultimately, but at the moment we have those two. These are against M1, so they’re for cognition.

In Phase I, they look very promising at doses which suggested that they will be efficacious. At those doses we are not seeing the side effect problems that people have seen in the past with muscarinic drugs, and that’s because they are selective: we’ve got rid of the bad side effects of M2 and M3 and kept the efficacy. So they are promising to take into Phase II studies for proof of concept in Alzheimer’s.

Then we’ve also got M4 agents which should be in the clinic early next year, and dual M1/M4s as well. M4 is directed towards psychosis in Alzheimer’s, which is the behavioral disturbances and delusions and agitation that you see in people with Alzheimer’s. We plan to move the M1 products into Phase II towards the end of this year.

**SCRP:** Congratulations on a securing a great deal with Allergan, but I have to start by asking what your thoughts are about the Pfizer-Allergan deal falling apart…

**MALCOLM WEIR:** In truth, we’ve been working with Allergan on this deal all along. We didn’t stop working on it because they had some discussions ongoing with Pfizer. Allergan remained committed to us throughout that process so we’ve been a bit blinkered. Pfizer is a partner of ours and they’re both great companies. Would it have worked if they had come together? Very possibly, it was just a meeting of minds really.

**SCRP:** Was securing this deal with Allergan a competitive process?

**MW:** There wasn’t really a process. We have been talking to a number of pharmaceutical companies over the years and keeping them apprised of progress. [The muscarinic program] is a leading program for us and it attracted a lot of interest. But we haven’t been aggressively pushing to partner it. It was just a meeting of minds really.

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Life After Pfizer Will See Allergan Make Waves In Alzheimer’s

MAHA ELSAYED maha.elsayed@informa.com

With patent expiries threatening Allergan plc’s position as a current leader in the Alzheimer’s disease market, and following the failed attempt at gaining direct access to Pfizer Inc’s resources, Allergan’s decision to partner up with Heptares Therapeutics (subsidiary of Sosei Group Corporation) can help reinforce its commitment to developing treatments for Alzheimer’s and other neurological disorders.

Through a series of dynamic acquisitions, Allergan plc. (the product of a recent merger of the Actavis and Allergan businesses) has transitioned from a generic firm into a growth-oriented pharmaceutical company – made up of companies including Watson Pharmaceuticals, Forest Laboratories and Warner Chilcott, all of which represented multibillion-dollar deals. While Allergan’s acquisition of Forest helped to secure its place as a global leader in the development and commercialization of treatments for central nervous system (CNS) diseases, Allergan looks set to strengthen and grow this area of its portfolio without any input from Pfizer.

Namenda/Namenda XR (memantine HCl) is a key CNS product for Allergan. With global sales reaching an ultimate high at $2.3bn in 2014, the product enabled Allergan to be a market leader in the Alzheimer’s space. The success of Namenda was a result of its novel mode of action and positioning as an add-on therapy for patients with moderate to severe Alzheimer’s disease. While Allergan’s lifecycle management strategy – the launches of Namenda XR and Namzaric (memantine HCl extended release and donepezil HCl) – will likely lessen sales erosion in the US, they will be unable to prevent the inevitable sales decline that accompanies patent expiries. Indeed, a generic version of Namenda IR was launched in 2015, and with future expected launches of the generic Namenda XR in January 2020 in the US, Allergan will be unable to maintain its position as the market leader for Alzheimer’s disease without a fresh boost.

With a failed attempt to join forces with Pfizer and gaining access to its resources, Allergan risked losing its global commercial footprint in Alzheimer’s market. However, the day after announcements of Pfizer-Allergan merger collapse, the latter pharma struck a deal with Heptares, a move that could help maintain its position.

Allergan Pharmaceuticals International Limited (wholly owned subsidiary of Allergan) and Heptares entered into a definitive agreement under which Allergan will license exclusive global rights to a broad portfolio of novel subtype-selective muscarinic receptor agonists in development for the treatment of major neurological disorders, including Alzheimer’s disease. These products include M1, M4 and dual M1/M4 selective muscarinic agonists.

M1 selective compounds are in development for the potential treatment of symptomatic cognitive deficits in Alzheimer’s patients, with the potential upside of better tolerability and a more pronounced effect compared with available treatments.

Heptares’ M1 muscarinic receptor agonist is in Phase I studies and is a first selective muscarinic M1 receptor agonist in clinical development for treatment of Alzheimer’s disease and other disorders of cognitive impairment. Heptares reported promising results in early development in their ability to selectively target the M1 receptor without also activating the M2 or M3 receptors, which are associated with undesirable side effects. In a recently completed Phase I study, M1 selective compound was reported to exhibit good brain penetration. It also exhibited robust and significant changes in brain electrical activity measured using multiple electroencephalography (EEG) biomarkers relevant to cognition. According to Heptares these pro-cognitive effects were seen at low doses and low blood concentrations that were safe and well tolerated.

M4 selective compounds, which are currently in preclinical stages of development, were suggested to potentially provide a novel approach to treat the neurobehavioral symptoms (psychoses) associated with Alzheimer’s disease and related neurological disorders, through a different mechanism of action than available antipsychotics. The clinical symptoms associated with Alzheimer’s disease are quite variable and fall under multiple domains. One domain in particular, behavioral/neuropsychiatric symptoms, is very common among dementia patients and causes a significant amount of distress to dementia sufferers and their caregivers. Neuropsychiatric symptoms experienced by patients with Alzheimer’s disease include depression, psychosis and agitation. Hallucinations and delusions are the most salient and serious neuropsychiatric symptoms associated with Alzheimer’s disease and if experienced early in the disease, a more rapid deterioration of cognitive function is generally precipitated. Combining M1/M4 agonists may thus be able to treat both cognitive impairment and neurobehavioral symptoms, an indication that lacks any approved therapy.

The degeneration of cholinergic neurons and cholinergic hypofunction are common pathologies in Alzheimer’s disease. While acting on the cholinergic system is not a novelty in the field of Alzheimer’s disease treatment, we are seeing very few pipeline drugs that target specific cholinergic receptors, namely, encenicline, an alpha7-nicotinic receptor agonist. And in this case muscarinic receptors. By acting on specific acetylcholine receptors rather than ubiquitously boosting acetylcholine synaptic levels, these features could be unique to these pipeline products unlike the case with marketed drugs. Encenicline whose clinical development has recently been placed on hold, is designed to target patients with mild to moderate Alzheimer’s disease. Should muscarinic receptors demonstrate efficacy in Alzheimer’s disease patients with neuropsychiatric symptoms, this could place M4 and dual M1/M4 drugs at a commercial advantage.

Dr. Maha Elsayed, based in New York, is an analyst at Datamonitor Healthcare focused on CNS disorders.
Ironwood Holds Firm To Failing Faster

Cake and champagne are likely being had this week at Ironwood Pharmaceuticals – that’s how the company celebrates the failure of its clinical candidates. Yes, you read that correctly – failure. The Massachusetts biotech revealed to investors on April 5 that topline data from a recent Phase IIa study of IW-9179 for diabetic gastroparesis showed the drug was unable to meaningfully reduce symptoms compared to a placebo. Patients were given IW-9179 or a placebo once or twice daily for four weeks. The most serious adverse event was diarrhea. The disappointing results have prompted Ironwood to abandon development of the drug in diabetic gastroparesis, which is a delayed emptying of the stomach contents. IW-9179 is still being studied in dyspepsia, also known as indigestion. Analysts at BioMedTracker give it a 24% likelihood of approval. Ironwood’s willingness to drop a program so quickly is not the typical attitude you see at most biotechs; although failing fast is a cardinal rule for big pharma. Ironwood chief scientific officer Mark Currie told Scrip in December that the company would rather fail quickly and move on. The company is firmly entrenched in the gastrointestinal space. It has two drugs on the market, both partnered with Allergan – one for irritable bowel syndrome (IBS) with constipation and another for IBS with diarrhea.

Nimbus Puts Off IPO A While Longer With $400m From Gilead

Nimbus Therapeutics LLC was considering an initial public offering to fund its early-stage development programs, but with $400m up front from Gilead Sciences Inc. from the sale of its subsidiary Nimbus Apollo Inc., the company can hold off until the market is more favorable for biotechnology IPOs. Nimbus Therapeutics probably could have raised a significant amount of venture capital based on the company’s portfolio of acetyl-CoA carboxylase (ACC) inhibitors, including a non-alcoholic steatohepatitis (NASH) drug candidate that’s yielded favorable Phase I results, without selling the assets to Gilead for up to $1.2bn. Instead, the company capitalized on its ACC inhibitors, including NDI-010976 for NASH, bringing in new money to fund other early-stage compounds without diluting existing investors. For Gilead, the transaction fit nicely into the big biotech company’s liver disease portfolio and growing NASH pipeline, but for Nimbus Therapeutics the deal highlights the flexibility built into the private firm’s structure.

MedDay Raises €34m For US Trial As EU Filing Of MS Drug Nears

MedDay of France, which is preparing a European filing for its progressive multiple sclerosis product MD1003, has raised €34m in a Series B financing round. Edmond de Rothschild Investment Partners (EDRIP) led the new investment round alongside existing investors Sofinnova Partners, the company’s largest shareholder, and In-noBio (Bpifrance). Large Venture (Bpifrance) also participated. MD1003 is highly-concentrated pharmaceutical-grade biotin. The new funds will enable MedDay to conduct a confirmatory Phase III study – to be called SPI2 – in the US. MedDay has already reported data from the successful Phase III SPI study which completed in 2015 in progressive multiple sclerosis patients. The cash will also be used to fund pre-launch activities of MD1003 in Europe where the drug is currently being supplied by MedDay on a named-patient basis. “The SPI2 study is expected to confirm, in a large North American population, the results of our prior European MS-SPI study,” Frédéric Sedel, CEO of MedDay, told Scrip. The trial is being conducted at the request of the FDA, he added, and is slated to begin at the end of 2016 and will enroll only progressive multiple sclerosis patients.

Depomed Slapped By Shareholder Discontent

After a grueling battle to fight off unwanted acquirer Horizon Pharma last year, Depomed finds itself in another precarious position. The pain drug maker is now facing a battle with an activist investor that says it’s shirking its fiduciary duties. Starboard Value LP, which holds 6.8% of the company as of April 8, said in a filing with the US Securities and Exchange Commission that it’s interested in supplanting the current Board of Directors at Depomed. The activist investor believes both the board and management at the biotech have been acting in their own interest with “shareholder-unfriendly” moves and taking steps to “entrench” themselves in the company. Furthermore, Starboard believes Depomed’s decision to fend off Horizon’s advances was the wrong move for shareholders.
UK Firms Lead As EU Biotechs Complete Best Ever 1Q VC Fundraising

MIKE WARD mike.ward@informa.com

Europe's biotech sector has just registered its best ever 1Q fundraising from venture capital sources. While the opportunities for conducting initial public offerings have all but dried up, European biotechs announced VC commitments of more than $600m – almost double the amount raised in the equivalent quarter in 2015 – with UK firms taking three of the top 10 slots.

Each of the leading fundraisers have recently enhanced their management teams, but interestingly, the two UK-based companies hired experienced non-British CEOs.

Top of the pile was Mission Therapeutics, a UK-based a drug discovery and development company focused on selectively targeting deubiquitinating enzymes (DUBs) to treat cancer, neurodegenerative and other diseases, which raised £60m. Funds will be deployed in the discovery and development of first-in-class, small molecule drugs that selectively target DUBs which are involved in multiple cellular processes, including DNA damage and cell proliferation. The financing was jointly led by Imperial Innovations Businesses LLP and included new investor Woodford Patient Capital Trust Plc (WPCT). Previous investors Sofinnova Partners, SR One, Roche Venture Fund and Pfizer Venture Investments also participated in the round.

Switzerland’s Cardiorentis AG raised CHF60m in a series B financing to support the commercial build-out of Ularitide, the company’s Phase III candidate drug for acute decompensated heart failure (ADHF). The company anticipates top-line results from the TRUE-AHF Phase III trial in spring 2016 and expects to file a US new drug application and European marketing authorization application in the second half of the year. The US FDA granted Ularitide fast track status in December 2015. The company said the round attracted three new private investors but did not disclose their identities.

The final podium place goes to Autolus, a UK biopharmaceutical company founded in 2015 and focused on the development and commercialization of next-generation engineered T-cell therapies for hematological and solid tumors. The London-based firm secured £40m in a series B round from Woodford Investment Management LLP and Perceptive Bioscience Investments Ltd. The company had previously raised previous £30m seed and series A investment from founding investor Syncona LLP.

Boosting Management

Each of the leading fundraisers have recently enhanced their management teams. Interestingly, the two UK-based companies hired experienced non-British CEOs. Mission hired Dr. Anker Lundemose as its CEO in September 2015, while Autolus asked its chair Dr. Christian Itin to also assume the CEO position.

Lundemose’s previous positions include CEO of Norwegian vaccine company Bionor Pharma ASA and co-founder and CEO of Prosidion, the UK spin-out of OSI Pharmaceuticals’ diabetes and obesity assets, which subsequently reversed into OSI. Itin previously served as president and CEO at Micromet Inc., a former NASDAQ-listed biopharmaceutical company that was acquired in 2012 by Amgen, and from November 2012 to January 2016 he served as CEO and chair of Cytos Biotechnology Ltd. He continues to serve as chair of Autolus and Kuros Biosciences AG, and is on the board of Kymab Ltd.

Top EU Biotech VC Financings 1Q 2016

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<td>Mission Therapeutics</td>
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<td>Petah Tikva, Israel</td>
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Inside The Sun-Novartis Japanese Deal

ANJU GHANGURDE anju.ghangurde@informa.com

Like all pharma transactions, the Sun-Novartis deal in Japan took its time to come to fruition – around six months from conceptualisation is perhaps a fair guesstimate.

After all, the deal concerned one of industry’s toughest markets to crack and one where business needs to get a good grasp of the cultural undercurrents before taking the plunge.

Japan is a market dotted with several local firms that have deep-rooted “self-pride” said an industry source tracking the developments. “It’s almost like the Indian equivalent of not wanting to marry off your daughter to a man of a different caste,” was the analogy the official used to Scrip.

The net result: very few local Japanese candidates are available for partnering or buyouts. This is despite Japan’s Ministry of Health, Welfare and Labour encouraging local generic firms, which cannot ramp up manufacturing to meet government targets, to consolidate.

This might explain, at least in part, why a transaction with a foreign firm keen to shed its brands was preferred by Sun.

Late last month India’s Sun Pharmaceutical Industries Ltd made its entry into Japan when it snapped up a portfolio of 14 established prescription brands from Novartis for $293m.

Here Scrip brings a deep dive on the Sun-Novartis deal covering aspects including: why the acquired brands perhaps need limited marketing push; whether recent regulatory issues that have dogged Novartis in Japan could have any spill-over effect on the divested brands; and what Sun needs to steer clear from as it builds its base in the land of the rising sun.

VOLUME SHARE

First, a bit on why Sun chose the long-listed Novartis products. While specifics on the brands covered under the deal remain sketchy, what perhaps drew Sun’s attention was that typically long-listed brands in Japan, despite being on the market for several years (decades in some cases) still command significant volume share (30-40% is not uncommon, the official says). And brands command better price realisations in the brand-conscious Japanese market.

Long-listed brands in Japan are typically backed by limited sales promotion after five years of patent expiry - Sun will probably, thus, need to undertake only very minimal promotional efforts. That will also give Sun time to get useful experience to study the intricacies of the Japanese generic market, while it readies its own portfolio for future launch.

The acquired brands have combined annualized revenues of approximately $160m and, as per a Sun statement, Novartis will continue to distribute these brands, for a certain period, pending transfer of all marketing authorizations to the Indian firm’s subsidiary.

But why did India’s top ranking firm steer clear from the traditional joint venture entry model in the $73bn Japanese market?

One explanation, based on recent data, is that joint ventures with local Japanese firms generally appear to have had a low success rate, the official said. The Teva-Kowa alliance didn’t last and there have been some aborted Indian ones. In 2011, Teva Pharmaceutical Industries paid $150m to acquire the 50% of its Japanese generics joint venture with Kowa that it did not already own.

Last year Teva and Takeda formed a joint business venture to boost the supply of generics to the Japanese market.

India’s Zydus Cadila had previously shut up shop in Japan, following a business review, while others like Dr Reddy’s Laboratories scrapped plans for an exclusive partnership with Fujifilm for generic drugs in Japan.

Finally, given that few Indian firms, except for Lupin, have really made headway in Japan, what’s the one thing that Sun should perhaps guard against, at least in the short term?

The official underscored that the quality of the product, which also includes packing and outer finish, consistency of supply and service are the mantra to success in Japan. In comparison, lower cost/prices are important determinants to success in the US, the UK and Germany. Sun probably will be better off if it does not try to play the cost arbitrage card in the Japanese market, the official added.
LUCIE ELLIS: When seeking external innovation through partnerships or acquisitions, what do you look for first?

DR. IVANA MAGOVCEVIC-LIEBISCH: Teva is a very patient-centric business so when I look for innovative partners or deals I always try to understand the real need of the patient that the technology or product might address. I always ask “Are we really the party that can generate the most value with this project?” I try to look for assets that can make a difference, that address patient need but products that also align with our expertise and strategy.

LE: What helps you make a final decision on whether to invest or make a deal?

IML: I always start with the patient view but ultimately what I look for in an acquisition or collaboration is a good fit strategically. It is important that Teva is aligned with its partners on understanding what we are trying to accomplish. Strategically we have to feel that we can bring value and that we have the right people working together to take an asset forward because we all know what the challenges are for bringing a new drug to market.

LE: What are the biggest changes you have effected at Teva since joining in 2013?

IML: Teva used to focus on acquisitions: we would acquire companies and then we would move on. Now, we are concentrating on building collaborative partnerships in the specialty side of the business. It is very important to us to ensure every partnership is the right fit and that we start from a place of trust because doing a deal is easy, the challenges start once the ink has dried.

LE: What are some examples of the more collaborative deals Teva has signed?

IML: Teva has been very active in signing interesting partnerships over the past year. We did a deal with Microchips, a company based in Lexington, Massachusetts; it’s a very interesting collaboration for the development of microchips for sustainable drug delivery. We forged this relationship very early on, unusually early, actually, because in the past Teva has tended to wait and go with technology that has been de-risked. However, we really believe in the power of this technology. With Microchips’ capacities in devices and Teva’s understanding of patient needs and our clinical capabilities, we will be able to do something amazing here for patients by changing the way chronic care is given.

LE: Why has Teva started to focus on earlier stage deals now?

IML: Teva has made a commitment to the specialty-side of the business and we recognize in order to deliver on that commitment Teva has to forge these relationships and become a part of this innovation ecosystem much earlier. We want to be recognized as a trusted partner that can really help biotechs move novel products and technologies forward.

LE: What is your long-term vision for the area of business you lead at Teva?

IML: In the past the pharma industry was all about managing diseases but Teva is moving away from this approach and we are not just managing diseases, we are trying to manage the individual patient. It’s no longer about drug life cycle management; it’s about patient life cycle management. Patients are becoming a lot more sophisticated; they are demanding more information and the data available to everyone have increased in volume and value. Patients want more personalized treatment so we have to be able to understand what their challenges are. Teva is moving to a very patient-centric business model, the patient is an anchor and we are producing different options to enable them to manage that life cycle of their illness.

LE: What developments outside of the pharma world do you think have made new challenges for businesses like Teva?

IML: There have been a lot of technology advancements and we are seeing other companies move into this space, like computer hardware company IBM, Google and Apple, and these tech giants are trying to figure out how they can play in this space. Pharma needs to be forging the right relationships here, as well as working out how we as an industry can work with technology businesses. The e-health evolution is a challenge and pharma needs to figure out how to position itself to be in the right place with the right information and the right attitude. By the right attitude, I mean the willingness to do things differently than we have done in the past.

LE: Is Teva investing in biosimilars and what are the biggest challenges in this area?

IML: Teva is active in biosimilars already and we remain very interested in strengthening our portfolio in this area, both on our own and through possible partnerships. We want to position Teva to be a major player in the biosimilars space. That said, the company is still selective in investment.
BMS’ Opdivo Heading Towards Indian Debut?

Bristol-Myers Squibb’s PD-1 immune checkpoint inhibitor Opdivo (nivolumab) appears to be on course to a potential Indian debut, after a key local expert panel recommended the product for marketing. A subject expert committee (SEC), which advises the Indian regulator on trial-related permissions as part of a layered approval process, recommended marketing authorization for the product, permitting BMS to import and market the drug in India for certain indications. The SEC approval also permits a waiver of local clinical trials, in view of “the non-availability of any standard effective treatment” for the specified indications in India.

IQWiG: Added Benefit Not Proven For Elocta

Swedish Orphan Biovitrum AB (Sobi) is preparing to respond to an “added benefit not proven” decision on its long-acting recombinant Factor VIII product Elocta (efmoroctocog) from Germany’s HTA body, IQWiG, a negative ruling that the company was expecting. The response will be submitted by April 22, just before a scheduled oral meeting with IQWiG in May, with a final decision by the top HTA body, the Federal Joint Committee (G-BA), expected later this year. Germany’s mandatory AMNOG process requires that, without head-to-head data, the Institute for Quality and Efficiency in Health Care can only hand down a “no additional benefit proven” decision, Sobi noted.

Positive PhIII Data For Pfizer’s Xeljanz

Pfizer has reported positive top-line data from the first of three Phase III trial of Xeljanz (tofacitinib) in psoriatic arthritis. The product has been approved for rheumatoid arthritis since 2012 but sales had initially struggled to take off in a category dominated by blockbuster injectable tumor necrosis factor inhibitors. However, 2015 saw worldwide Xeljanz revenues increase by 72% to $523m. Pfizer said in October that it was deprioritizing development of the oral Janus kinase inhibitor in Crohn’s disease, ankylosing spondylitis and potentially psoriasis, and would focus further development of the drug on psoriatic arthritis and ulcerative colitis.

AZ, Lilly’s BACE Inhibitor Clears Safety Hurdle

AstraZeneca and Eli Lilly are to plough straight ahead with the Phase III part of the AMARANTH study testing their oral beta secretase cleaving enzyme (BACE) inhibitor AZD3293 in early Alzheimer’s after an encouraging interim safety review, building confidence in this potential disease-modifying drug class. AMARANTH will continue into the Phase III of the Phase II/III seamless trial, the companies said after the independent data monitoring committee recommended the study continue without modification. The analysis was not designed to review efficacy. The development is obviously very good news for both the product and the drug class, commented Datamonitor Healthcare senior analyst Daniel Chancellor. Other oral disease-modifying drugs have failed this safety hurdle, he pointed out, notably two other Lilly drugs LY2886721 (other BACE inhibitor) and semagacestat (which has a related mechanism, gamma secretase inhibitor). AstraZeneca and Lilly tied up back in 2014 jointly to develop and commercialize AZD3293 in a deal worth up to $500m.

Regeneron’s Oncology R&D Boosted

US biotech Regeneron Pharmaceuticals Inc. has licensed rights to the use of MedImmune’s “warhead and linker” technology for developing antibody-drug conjugates (ADCs) against a number of undisclosed cancer targets, the companies announced April 5. The deal will add to Regeneron’s research efforts in oncology, a therapeutic area it wants to exploit that is beyond its current successes in ophthalmology with the macular degeneration therapy Eylea (aflibercept) and in heart disease with the antihypercholesterolemia agent Praluent (alirocumab).

Shire On Course For Launch Of ‘Adderall Beads’

Shire’s positive topline data from a pediatric Phase III trial of SHP465 (triple-bead mixed amphetamine salts) addresses the US FDA requirements for a class 2 resubmission for the product’s NDA, said the company. The product is slated for US launch in 2017.
Lilly’s Evacetrapib Raises More Doubts For HDL Theory
LISA LAMOTTA lisa.lamotta@informa.com

The obituary has been written on Eli Lilly & Co’s cholesterol drug evacetrapib and likely for the class of CETP inhibitors as a whole. While the big pharma stopped development of the drug in October, data released at the American College of Cardiology shows the class and the theory behind it might be faulty.

Results from the ACCELERATE study were released at the conference in Chicago on April 3, showing that evacetrapib lowered bad cholesterol, or LDL-C, by 37%, while improving good cholesterol, or HDL-C, by 130%. Despite the astounding positive effects on cholesterol levels in the 12,000-patient study, the trial was stopped early for futility in October because a Data Safety Monitoring Board determined that the drug was having no impact on cardiovascular health compared with a placebo.

The findings were both surprising, but consistent. Two other big pharma have previously abandoned the development of cholesteryl ester transfer protein (CETP) inhibitors due to problems with toxicity and a lack of cardioprotective benefits.

Pfizer dropped development of the lead CETP inhibitor, torcetrapib, in 2006; the big pharma had been testing the drug in combination with its uber-blockbuster Lipitor (atorvastatin) in hopes of extending Lipitor in 2006; the big pharma had been testing the drug in combination and a lack of cardioprotective benefits.

Nevertheless, NICE does not think that Vidaza represents a “step change” in treatment and said that there was a “high degree of uncertainty about its effectiveness relative to current conventional chemotherapy treatments.”

Roche had a similar experience with its own CETP inhibitor in 2012, when it chose to discontinue development of dalcetrapib due to a lack of clinically meaningful efficacy. Dalcetrapib – like the other CETP inhibitors – all helped increase HDL cholesterol, but didn’t improve cardiovascular outcomes. Evacetrapib was expected to perform better than its predecessors because it didn’t have the toxicity issues of the older iterations, but ACCELERATE proves those hopes were unfounded.

The premise behind the CETP inhibitors is that by dramatically raising HDL levels and lowering LDL levels the drugs would provide a cardiovascular benefit to patients with heart troubles. Scientists and big pharma have both been enthusiastic about the idea of raising good cholesterol in an effort to protect the heart. Yet, those benefits haven’t been bearing fruit in clinical trials and could mean that the HDL number is less important than once believed.

“The trial raises questions about the benefits of raising HDL and the future of this class of drugs,” said A. Michael Lincoff, director of the Cleveland Clinic Coordinating Center for Clinical Research (C3Research) and a principal investigator on the study.

NICE Says No To Celgene’s Vidaza
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NICE, England’s health technology appraisal institute has said no to Celgene’s Vidaza (azacitidine) for some NHS patients with acute myeloid leukemia. Among NICE’s concerns was Vidaza’s effectiveness compared with conventional care.

Celgene is disappointed by the news but says it will work with NICE during the appraisal process to try to get the drug to patients.

NICE is not recommending the drug within its marketing authorization for treating acute myeloid leukemia with more than 30% bone marrow blasts in patients aged 65 years or older who are not eligible for hematopoietic stem cell transplant, says the preliminary guidance, published April 8.

Acute myeloid leukemia is an aggressive cancer and little has changed in the way patients are treated over the past three decades. Treatments include intensive chemotherapy or stem cell transplantation, which are particularly difficult for older AML patients to withstand.

Nevertheless, NICE does not think that Vidaza represents a “step change” in treatment and said that there was a “high degree of uncertainty about its effectiveness relative to current conventional chemotherapy treatments.”

Celgene presented data from the AZA-AML-001 trial. Although the committee acknowledged the study demonstrated gains associated with Vidaza in overall survival, it said that it did not show statistical significance when comparing the drug with the combined conventional care regimen. “The committee concluded that the degree to which azacitidine was more effective than any of the individual conventional care regimens was very uncertain,” says the institute. The appraisal committee also pointed to concerns over the company’s economic modelling.

Vidaza’s list price is £321.00 per 100 mg vial, and the cost of a cycle of treatment is £4,494.00 (excluding VAT) assuming the list price, seven treatments in a cycle, vial wastage and a body surface area of 1.8 m2. NICE’s appraisal committee concluded that the most likely cost-effectiveness estimate compared with a conventional care regimen is £240,000 per quality adjusted life year. This is well above the £20-30,000 per QALY threshold that NICE usually deems cost effective. Vidaza also failed to meet the institute’s end-of-life criteria that allows it to consider a higher significance when comparing the drug with the combined conventional care regimen. “The committee concluded that the degree to which azacitidine was more effective than any of the individual conventional care regimens was very uncertain,” says the institute. The appraisal committee also pointed to concerns over the company’s economic modelling.

Charles Craddock, professor of Haemato-Oncology at University of Birmingham hopes NICE will reconsider its position as Vidaza as he believes Vidaza is an important “new treatment modality that demonstrated significant activity” in clinical trials.
After the FDA’s glowing review on paper and even more so at the meeting of the agency’s Gastrointestinal Drugs Advisory Committee, it was highly likely the panel would back a speedy approval of Intercept Pharmaceuticals Inc’s Ocaliva (obeticholic acid) as a treatment for primary biliary cholangitis (PBC), a rare and potentially fatal liver disease.

And it did – voting 17-0 Intercept had provided substantial evidence to support an accelerated approval of Ocaliva as a treatment for PBC, also known as primary biliary cirrhosis, in combination with ursodeoxycholic acid (UDCA) – the standard of care and the only medicine approved in the US for the disease – in adults with an inadequate response to that drug or as monotherapy in adults unable to tolerate UDCA, based on its effect on alkaline phosphatase (ALP).

Shares of Intercept climbed 11% in after-hours trading, gaining $17.92.

The panel’s backing all but assures FDA approval by May 29, Ocaliva’s Prescription Drug User Fee Act action date.

Based on the positive outcome at the advisory committee meeting, analysts from Sajant Research’s BioMedTracker increased their likelihood of approval for Ocaliva in PBC by 1% – from 98% to 99%.

Wall Street has estimated $400m peak sales for the drug in PBC.

But the real question for Ocaliva is what lies ahead for the drug, given the potential broader use in the much more lucrative indication of nonalcoholic steatohepatitis (NASH).

The positive prospects in NASH makes Intercept a good acquisition target for a number of companies with a presence in liver diseases, such as Bristol-Myers Squibb Co, AbbVie Inc, Johnson & Johnson Inc, Merck & Co. Inc and Shire PLC, said Morningstar analyst Stefan Quenneville.

Ocaliva’s future in NASH will become clearer when data from Intercept’s Phase III REGENERATE trial are revealed in the first half of 2018.

Next up for the drug is the release in the second half of this year of the results from the Phase II CONTROL trial, which is examining the changes in lipid particle size specifically in NASH patients.

While there were increases in low-density lipoprotein (LDL) cholesterol and decreases in high-density lipoprotein (HDL) cholesterol in Intercept’s studies of Ocaliva, BMO Capital Markets analyst Ian Somaiya said the FDA’s and the advisory committee’s acceptance of the drug’s safety profile “should begin putting to rest lingering questions” about the experimental medicine’s impact on LDL and any implications on longer-term CV safety.

There was a consensus from the panel that ALP could be used as a surrogate endpoint reasonably likely to predict clinical outcomes in early PBC, although there were some reservations. Some of the panelists said changes in total bilirubin would be helpful, but they noted that in early PBC, it’s generally normal.

The committee also backed Intercept’s proposed starting dose for Ocaliva at 5mg, titrating up to 10mg after three months.

A key consideration for Ocaliva’s future on the US market is whether its benefit in PBC will be confirmed in an ongoing trial, which got underway in 2014 but is expected to take up to eight years to complete.

The global randomized placebo-controlled trial, known as Study 747-302, plans to enroll 350 PBC patients with a mean bilirubin of 1-3x ULN and/or a mean ALP > 5x ULN.

The study, which consists of a two-year recruitment, with a six-year follow-up with quarterly visits, will be conducted at 170 sites across 28 countries, Intercept officials noted, saying that so far, 73 patients have been randomized or are in screening.

The study population in 747-302 will represent a more advanced PBC population, the company said.

Intercept said it needed to get concurrence with the European Medicines Agency about the design of 747-302 because the study also will be used for the conditional approval the company is seeking in the EU.

Intercept said it’s in discussions with the FDA about what potentially could be modified in the design and protocol to make the trial a stronger postapproval commitment study for the US.

Amy Egan, deputy director of the FDA’s Office of Drug Evaluation III, emphasized the agency was still working out details with Intercept of the sample size and total number of events for the confirmatory trial – pointing out “that has not been agreed on yet.”

The FDA’s panelists, however, raised concerns about the difficulty in getting patients enrolled in postapproval studies when the medicine already is on the market, with one of the committee members asking his colleagues whether they’d be willing to randomize their patients into an eight-year trial for which there was a chance they could end up taking the placebo.

Intercept officials noted they plan to also use an historical control relying on two clinical databases – the Global PBC Study Group, which has information on more than 6,100 patients, and the UK-PBC Research Cohort, which is a prospective study group with data on more than 5,900 patients.

While Intercept sponsored the efforts of both databases, they are independent, academically run initiatives. The company said it was not involved in study design, data collection, analysis or publication.

Intercept, however, has collaborated with both groups to confirm that ALP and bilirubin can be used as acceptable surrogate endpoints to support regulatory approval.

The historical control groups would – separately and in combination – be used as a comparator to the randomized Ocaliva treatment group.

But panelist Michael Proshchan, a mathematical statistician at the National Institute of Allergy and Infectious Diseases, said combining historical with the control data gave him “great concern.”

“That is almost always disastrous to rely on historical control data,” Proshchan said. “I have a lot of concern about the postmarketing design.”

Intercept said that while the postapproval study was designed with a placebo control, it is using the multiple controls in the event the placebo cannot be maintained.

Some on the committee thought the confirmatory trial should include cardiovascular changes in LDL and HDL levels.

Intercept, however, said 747-302 was not powered to detect CV events, but that if a signal is observed, it would evaluate cardiovascular safety in a separate study. © Informa UK Ltd 2016
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Mark Timney has been president and CEO of US specialty company Purdue Pharma for just over two years but he's playing a long game to pull the business away from its single-track R&D model towards other opportunities outside pain therapy – its mainstay development area.

Timney, who was previously president of Merck US but joined Purdue in January 2014, spoke with Scrip's Lucie Ellis during partnering conference BIO-Europe Spring, held in Stockholm, Sweden, April 4-6, about Purdue's interest in European partnerships and its target of achieving a transformational deal by the end of 2016 – not anywhere near oncology.

**LUCIE ELLIS:** Why is Purdue expanding its key development areas now?

**MARK TIMNEY:** I was brought in to diversify the company and plan for a life after opioids, our current key portfolio area. To build this plan Purdue has fundamentally changed its business model; we are now doing less internal discovery and have instead built up a business development group so that people know what Purdue is and that we are open for business.

Purdue has a very narrow focus in abuse-deterrent opioids with extended-release formulations. While this is a tapered interest, we have been very successful. However we are going broad with our reach to the full landscape of pain therapy and then we will look at adjacencies. This will mean looking at central nervous system disorders, but we are not talking depression or schizophrenia – which are high-risk development areas – we are thinking movement disorders like Parkinson's disease, and areas like ADHA and sleep conditions. These areas are natural fits for us. Outside of CNS, based on the leadership team I have built, we can go anywhere.

[In late 2015 Purdue named ex-CEO of Panacos Pharmaceuticals and Metaphore Pharmaceuticals, Dr. Alan W. Dunton, senior vice president of R&D. Dutton is responsible for Purdue's overall scientific development strategy, including management of the pipeline, early clinical development programs and setting the scientific direction for the company. Early in the year Purdue appointed Jean-Jacques "JJ" Charhon executive vice president and chief financial officer. Charhon joined Purdue from Cnova, one of the largest global eCommerce companies, where he was also CFO.]

**LE:** Looking ahead then, where else would you look outside of CNS disorders?

**MT:** I can't give that away but I can tell you what we are not looking at. We are not interested in vaccines or large-scale primary care type businesses, and we are not looking in oncology because everyone else is there already. We are going to be driven by the asset and let the asset lead us onwards, rather than say we want to enter a pre-specified therapeutic area. This method is throwing up much more interesting ideas in science for us. If you become therapeutic area-driven you tend to go where everybody else ends up because the analysis will lead you to the same place. It's a lot more work doing it the way we are, for example: in the latest round of evaluation we have been through more than 6,000 potential assets and we are just getting to a point where we can say "Okay, we have some areas of real interest here."

**LE:** Why is Europe a key market for Purdue and what does the company have to offer to potential partners?

**MT:** Europe is really an untapped area for us as Purdue is based in, and predominantly focused on, the US. We do already have a relationship with Mundipharma, it's one of the family companies, but currently when people think Purdue they think US pain therapy company and that's it. Events like BIO-Europe Spring acts as an introduction for us. We are looking for interesting science and late-stage assets at the moment. Purdue has very good cash flow and hope to attract someone who is looking for a commercial and development presence in the US. We have manufacturing capabilities and a very strong intellectually property group.

We also have a field force of more than 600 representatives, one of the largest specialty field forces in the industry. Furthermore, as a private company we have the ability to structure things flexibly. Europe has some great science that can be hidden and it's got some great private companies that we could work well with.

**LE:** Purdue has highlighted a platform deal as its preference over single assets. Why is this?

**MT:** We have a very broad interest at the moment. My hope is that we can find a platform to build on and add our own value too. If we find a really cool asset, I want to know that there is unmet need we can target and build a research team or research alliances around.

**LE:** Purdue is a private company, how is it funded now and is the company seeking more financing?

**MT:** We have a strong balance sheet but we are actively looking to raise funds, not out of necessity but to give me more flexibility to do the deals I want to do, when I want to do them.

**LE:** How is Purdue future-proofing itself as a specialty pharma?

**MT:** The work we are doing now is this idea exactly. I would describe Purdue at the moment as a bit of a one-legged stool because we are so narrow in our focus; I am trying to add three more legs to the stool. This will be achieved through business development because I don't believe we can get there quick enough internally. We are entering a period of investment for Purdue that will continue over the next four to five years.

I am hoping we will do a transformative deal by the end of this year. Everyone keeps saying I am leading with my chin, but that's what I want and what I am here for. We are open for business that is the key. The new Purdue is here.

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**HEADLINE NEWS**

**Introducing The New Purdue Pharma**

**LUCIE ELLIS** lucie.ellis@informa.com

Mark Timney has been president and CEO of US specialty company Purdue Pharma for just over two years but he's playing a long game to pull the business away from its single-track R&D model towards other opportunities outside pain therapy – its mainstay development area.

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**Zika: A Research And Development Cat And Mouse Game**

At two key US conferences focused on strategies to combat the Zika virus – the latest international public health crisis threatening the globe – one resounding message was clear: It’s going to take a lot of money and collaboration between industry, academia, government and other groups. But Nicole Lurie, the assistant secretary for preparedness and response at the Department of Health and Human Services (HHS), told reporters the US government is caught in a “game of cat and mouse” because industry is reluctant “to put skin in the game until they know there’s going to be money to support those efforts.”

Lurie insisted it was time to put the “pedal to the metal” on Zika, like the US did with responding to Ebola, before it’s too late. So far, however, the US Congress has been unwilling to put up the cash, which officials said has created a climate of uncertainty for innovators in pursuing treatments and vaccines for Zika, a mosquito-borne flavivirus that’s been rapidly spreading across the Americas in recent months. The World Health Organization (WHO) said 33 countries and territories in the region have reported widespread transmission of the virus, which has been linked, although not definitively, to an increase in microcephaly and other central nervous system malformations, as well as Guillain-Barré syndrome.

**Searing FDA Review Reveals More Clovis Credibility Slips**

A negative review by the FDA of Clovis Oncology Inc.’s application for its experimental lung cancer drug rociletinib not only spelled more trouble for the future approvability and marketability of the product, but also revealed more questionable behavior by the company – dealing another blow to the firm’s credibility, which could be a bigger problem for the Colorado biotech in the long run. The bad news came in briefing documents released ahead of the April 12 meeting of the FDA’s Oncologic Drugs Advisory Committee (ODAC) – hitting Clovis’ shares on April 8, which fell almost 18%, before closing at $15.77, down $3.40, or 17.7%. A major hurdle Clovis is facing is the potential the FDA may require the company to complete its ongoing open-label, randomized, multi-national Phase III CO-1686-020 trial, also known as TIGER-3, before regulators consider approving rociletinib, which likely would doom any chances the drug would have to compete in the marketplace. In fact, the FDA wants the ODAC to weigh in on that very matter – the one and only voting question the agency plans to ask the committee.

Also potentially damaging for the drug’s commercial opportunity is the FDA has recommended the inclusion of a black-box warning on rociletinib’s labeling alerting prescribers and patients about the risk of QTc prolongation leading to Torsades de pointes (TDP), an abnormal heart rhythm that potentially could lead to sudden cardiac death. Regulators said the risk of QTc prolongation leading to Torsades de pointes (TDP), an abnormal heart rhythm that potentially could lead to sudden cardiac death. Regulators said

**Inter Partes Reviews Just Got More Expensive**

Under new final rules from the US Patent and Trademark Office (US PTO), patent owners will have a more level playing field for inter partes reviews (IPRs) – trial proceedings convened by the Patent Trial and Appeal Board (PTAB) intended to be a faster and more affordable way for third parties to challenge patents than going through the American court system – but the process just got more expensive for everyone. The new rules, which were released in an April 1 Federal Register notice and are set to be finalized on May 1, will give patent owners the ability to submit declarations from expert witnesses as part of their preliminary response in the IPR proceeding to rebut challengers, who currently are allowed to include the testimonial evidence in their petitions. Patent owners have complained they’ve been hamstrung by being shut out from being equally able to provide the testimonial evidence in their responses before the PTAB makes a decision about whether to institute a trial on the IPR challenge, explained Washington lawyer Eleanor Yost, a partner in Goodwin Procter LLP’s intellectual property litigation group. IPR petitions involving drug makers have become increasingly popular – especially with hedge fund manager Kyle Bass, who has filed more than 30 of them against biopharmaceutical firms, with more than half of them granted, most recently for those challenging patents held by Acorda Therapeutics Inc. and Biogen Inc. on their multiple sclerosis drugs. But while the new rules, which were proposed by the US PTO this past August, may provide patent owners a more equal chance to succeed in the preliminary IPR process, “all the parties should be aware that the budgets they’ve been using up to this point are going to be materially affected,” Yost told Scrip. Putting together the testimonial evidence is not an easy task, Yost said. “And experts are expensive,” she declared. So for both sides, Yost said, “it’s going to increase the costs of the overall proceedings significantly, not immaterially, because those declarations are pricey – in the tens of thousands of dollars sometimes.”
Court Probes Rationale Of Biosimilars’ 180-Day Notice

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There was a lot of inside baseball being played at the US Court of Appeals for the Federal Circuit during April 4 oral arguments when Amgen Inc. battled Apotex Inc. over whether Congress intended for it to be mandatory for biosimilar makers to provide 180 days notice of commercial marketing (NCM) to the reference product sponsor (RPS) after the FDA licenses a copycat product.

But a three-judge panel at the appeals court – Circuit Judges William Bryson, Evan Wallach and Richard Taranto – were more interested in cutting through the lawyers’ jargon in attempting to make heads or tails of the 180-day NCM provision of the Biologics Price Competition and Innovation Act (BPCIA), which gave the FDA the authority to approve biosimilars.

In the earlier case, in which Amgen sued Sandoz Inc. in a lawsuit involving the latter company’s biosimilar Zarzio (filgrastim-snzd), a version of the California innovator’s Neulasta, a three-judge panel in July 2015 ruled 2-1 the patent dance was optional and biosimilar makers could choose not to disclose their application and manufacturing details. But in Amgen v. Sandoz, the court also ruled 2-1 that when a biosimilar applicant does not dance, 180 days notice of commercial marketing of biosimilars is mandatory and may only be given after FDA licensure.

In Apotex’s case, the company wants the Federal Circuit to overturn a preliminary injunction imposed this past December by a Florida district judge blocking the Toronto-based company from marketing its yet-to-be-approved biosimilar version of Amgen’s long-acting human granulocyte colony-stimulating factor Neulasta (pegfilgrastim).

Apotex contended that because it already provided a copy of its pegfilgrastim biosimilar application, known as a 351(k), and technical details to Amgen more than a year ago – triggering the BPCIA’s so-called patent dance – the Canadian firm was under no obligation to provide the 180-day NCM.

Apotex also asserted that because Amgen has the 351(k) application and already has sued on all of the patents it identified as relevant, the innovator doesn’t need the 180 days to assess its rights or gain information about the biosimilar.

Apotex insisted that when a biosimilar maker has engaged in the patent dance, the BPCIA’s “(l)(9)(B)” provision ‘contemplates’ such a situation and provides a remedy: the opportunity for the RPS – in this case Amgen – to seek a declaratory judgment action.

Apotex provided Amgen a statement of the biosimilar maker’s intentions about marketing its pegfilgrastim product in April 2015. But Amgen called that a violation of the BPCIA – arguing that companies that want to copy an innovator’s biologic must provide the RPS with a 180-day notice before first commercial marketing, with that notice coming after the FDA licenses the biosimilar. But Apotex argued the 180 days essentially constitutes an additional six-months of unwarranted exclusivity protection on top of the 12 years already granted to innovators under the BPCIA.

“What incentive would an applicant have to participate in an information exchange if the 180-day provision was imposed no matter what?” Wallach asked during the oral arguments.

FITTING IT ALL TOGETHER

Elaine Herrmann Blais, a partner and head of litigation in the Boston office of Goodwin Procter LLP, said the judges were focused on trying to figure out how the BPCIA’s application and manufacturing disclosure provision, known as “(l)(2)(A), and the NCM measure, known as “(l)(8)(A), fit together “and if coming out one way or the other was going to render one of them meaningless.”

Herrmann Blais noted that the parties gave the judges an answer that could give meaning to both provisions, “because they both conceded that a party, who’s exceptionally concerned about an at-risk launch and wants early certainty, might opt to provide the information early.”

“Amgen argued that the notice mechanism provides further certainty to the parties and prevents hurried litigation from overburdening the judiciary or potentially pulling products from the shelf,” added Charlie Cox, an associate in Goodwin Proctor’s Washington office.

Removing the 180-day NCM, contended Amgen’s lawyer Nicholas Groombridge, a partner at Paul Weiss Rifkind Wharton & Garrison, essentially tells the RPS to “seek a preliminary injunction immediately when you file your lawsuit because you have no idea when the biosimilar is going to be launched, and your only alternative would be to wait, risk irreparable damage to the market, and when that irreparable damage begins, run into court and seek a [temporary restraining order].”

But, he said, that would have been a “complete and utter waste of time” since the district court in Amgen’s case has already scheduled a hearing for July involving its last remaining patent on Neulasta.

Apotex’s lawyer Kerry McTigue, co-chair of intellectual property at Cozen O’Connor, however, insisted the “elephant in the room” is whether Amgen can have 12 and a half years of exclusivity.

New York lawyer Robert Cerwinski, a partner in the intellectual property litigation group at Goodwin Procter, told Scrip the Federal Circuit was rightly curious in questioning whether the 180-day NCM should be mandatory in a case like the Apotex’s pegfilgrastim biosimilar in which the company “danced” with Amgen and that latter firm has a copy of the 351(k) application and already knows what patents it could assert.

“IT’s a pretty good archetype of a situation where the 180 days doesn’t really serve much of a purpose,” Cerwinski said.

Herrmann Blais noted Groombridge “danced around” Bryson’s question about whether the NCM still had a purpose if the patents expired during the 180-day period and if it would still be fair to impose it.

Groombridge’s response arguing Congress “drew a bright line” mandating the 180-day NCM in all cases – even if Amgen loses on the merits at the July patent infringement trial – “was an unsatisfactory answer to a really probing question that got right to the heart of the problem,” Herrmann Blais remarked.
Casualties From The War On Inversions

ANDY SMITH

In a surprise move last week, the US Treasury signalled its capacity to prevent any further inversion transactions and, with the public endorsement by President Obama, ended the proposed merger of Pfizer, Inc. and Allergan Plc that would have seen Pfizer relocate its tax jurisdiction to Ireland and access much of its offshore cash without a tax penalty.

Now that the war on inversions is over and the guns have fallen silent from the investment landscape, the winners and losers can be identified. Obviously any funds that held Allergan were losers and any holding Pfizer were winners. When the market opened on Apr. 5 after the US Treasury’s proposals had been announced the day before, the share price of Allergan started down almost 20%. As a holder, I was running out of hair to pull. However, as cumulative event risk goes, the hit to our fund’s performance could have been worse. This was because we held more Pfizer than Allergan, and bought more Allergan as the US market opened on Apr. 5. The Allergan share price finished that down day down about 15%. The managers of those merger-arbitrage funds who were long Allergan and short Pfizer probably won’t need to visit their barbers for some time.

There may not be much sympathy for them, but investment bankers relying on the chunky transaction-associated fees and bonuses were among the casualties.

It took about 24 hours between the announcement of the Treasury’s previous anti-inversion measures and the termination of the merger of AbbVie, Inc. and Shire Plc. So right about on schedule on Apr. 6 there was a similar official termination announcement by Pfizer and Allergan. There may not be much sympathy for them, but investment bankers who had been relying on the chunky transaction-associated fees and bonuses were among the casualties. However, on Apr. 6, their analysts were focused more on the silver linings than the clouds, publishing lists of biotech client companies that will be acquired by either Pfizer or Allergan. TheNASDAQ Biotech Index finished up 6% and had its best day for five years.

Thankfully cooler and more rational heads eventually prevailed as the share prices of most of those “imminent” targets slipped back from their artificial highs over the last two days of last week. A case in point was Vertex Pharmaceuticals Inc., whose share price finished the Apr. 6 balloon day up over 8% and whose failure to bring to the market a drug that could ensure its profitability over nearly 27 years of cash burn seemed to have been forgotten by those who saw it as an accretive acquisition target.

There have been more convoluted casualties of the war on inversions and the failure of the attempted inversion of Salix Pharmaceuticals Inc. into an Irish shell company (Cosmo Tech) formed from the swarf of Cosmo Pharmaceuticals SA was probably a case of acceptable collateral damage. For this example, the adage that war has no winners is especially poignant. Salix was subsequently rescued from the clutches of Cosmo Tech by the attentions of Endo Pharmaceuticals Inc. and ultimately Valeant Pharmaceuticals International Inc., both inverted companies that subsequently ran into difficulties. Most of the assets that were going to be swept from Cosmo into Cosmo Tech subsequently found their way to a spin-off IPO from the parent company called Cassiopeia SpA. It only goes to show that Cassiopeia’s investors were less discerning than the Salix board who chose to be acquired by Valeant.

Cool heads were also absent in the UK on the day the inversion guns fell silent, when the share price rises of AstraZeneca Plc, GlaxoSmithKline Plc and Shire Plc were collectively responsible for dragging up the FTSE 100 index. The investors who bought shares in those UK-listed companies in the hope of Pfizer’s continued attraction to a lower European corporate tax rate should have probably read the lips of the US Treasury – no more inversions.

With the Pfizer share price finishing the week up over 7.5% and Allergan’s down by over 10.6%, last week’s obvious loser may yet still be a winner. This is because companies like Allergan, which has been built on a series of transactions, typically end up themselves being acquired (Allergan has been bid for by Valeant, Actavis and Pfizer in the last two years). Some may counter that Allergan’s licensing of a Phase I compound from Heptares Therapeutics is a sign of its go-it-alone soup-to-nuts pharmaceutical development strategy, although this has not typically been its modus operandi. Since the Heptares transaction was going on whilst Pfizer and Allergan were merging, it suggested to me that the licensing of an early-stage asset by Allergan was only a cosmetic demonstration of a fondness for discovery-research meant to placate the powerful discovery-research SVPs within Pfizer.

The financial implications of the current US administration’s war on inversions aside, there are also the personal costs. Spare a thought for the board of the Foundation responsible for President Obama’s library in Chicago. After last week their jobs got significantly harder since Pfizer, Allergan or any funds banking on their merger will probably not now be available for donations and thus books on the shelves, if not the bricks in the building, will be a little sparser. Also come January 2017, those senior US Treasury officials who might have been banking on a job, consultancy or board position at any organization connected to or influenced by Pfizer, Allergan or their investors (long or short) might have to reassess their future prospects. But then again, isn’t that the altruistic self-sacrifice that is known to be the defining characteristic of politicians?

The Magna Biopharma Income fund holdings include Pfizer and Allergan.

Andy Smith is chief investment officer of Mann Bioinvest. Mann Bioinvest is the investment adviser for the Magna BioPharma Income fund which has no position in the stocks mentioned, unless stated above. Dr Smith gives an investment fund manager’s view on public life science companies. He has been lead fund manager for four life science—specific funds, including International Biotechnology Trust and the AXA Framlington Biotech Fund, and was awarded the Technology Fund Manager of the year for 2007.
Scrip’s weekly **Pipeline Watch** tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.

### Late-stage clinical developments for the week 1-7 April 2016

<table>
<thead>
<tr>
<th>LEAD COMPANY</th>
<th>PARTNER COMPANY</th>
<th>DRUG</th>
<th>INDICATION</th>
<th>MARKET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer Inc.</td>
<td>Celltrion Inc.</td>
<td>Inflectra (infliximab-dyyb)</td>
<td>Crohn’s disease, ankylosing spondylitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis</td>
<td>US</td>
</tr>
<tr>
<td>Gilead Sciences Inc.</td>
<td>–</td>
<td>Descovy (emtricitabine, tenofovir alafenamide)</td>
<td>HIV</td>
<td>US</td>
</tr>
<tr>
<td>Bristol-Myers Squibb &amp; Co.</td>
<td>Ono Pharmaceutical Co. Ltd.</td>
<td>Opdivo (nivolumab)</td>
<td>advanced renal cell carcinoma</td>
<td>EU</td>
</tr>
<tr>
<td>Novartis AG</td>
<td>–</td>
<td>Revolade (eflotropopag)</td>
<td>pediatric chronic immune (idiopathic) thrombocytopenic purpura (ITP)</td>
<td>EU</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>–</td>
<td>Giotrif (afatinib)</td>
<td>squamous cell lung cancer</td>
<td>EU</td>
</tr>
<tr>
<td>Pharming Group NV</td>
<td>Swedish Orphan Biovitrum (Sobi)</td>
<td>Ruconest (conestat alfa)</td>
<td>hereditary angioedema attacks in adolescents</td>
<td>EU</td>
</tr>
</tbody>
</table>

**CHMP POSITIVE OPINION ON FIRST APPROVAL**

<table>
<thead>
<tr>
<th>Company</th>
<th>Partner</th>
<th>Drug</th>
<th>Indication</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>GlaxoSmithKline plc</td>
<td>–</td>
<td>Strimvelis (GSK2696273)</td>
<td>severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)</td>
<td>EU</td>
</tr>
<tr>
<td>GlaxoSmithKline plc</td>
<td>Amicus Therapeutics Inc.</td>
<td>Galafold (migalastat)</td>
<td>Fabry disease</td>
<td>EU</td>
</tr>
<tr>
<td>Johnson &amp; Johnson Inc.</td>
<td>Genmab A/S</td>
<td>Darzalex (daratumumab)</td>
<td>relapsed and refractory multiple myeloma</td>
<td>EU</td>
</tr>
<tr>
<td>Samsung Bioepis (Samsung BioLogics and Biogen jv)</td>
<td>Biogen</td>
<td>Flixabi (infliximab)</td>
<td>rheumatoid arthritis, Crohn’s disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, psoriasis</td>
<td>EU</td>
</tr>
<tr>
<td>AstraZeneca PLC</td>
<td>–</td>
<td>pandemic live attenuated influenza vaccine</td>
<td>flu prophylaxis</td>
<td>EU</td>
</tr>
<tr>
<td>Actelion Pharmaceuticals Ltd.</td>
<td>–</td>
<td>Uptravi (selexipag)</td>
<td>pulmonary arterial hypertension</td>
<td>EU</td>
</tr>
</tbody>
</table>

**CHMP POSITIVE OPINION ON SUPPLEMENTAL APPROVAL**

<table>
<thead>
<tr>
<th>Company</th>
<th>Partner</th>
<th>Drug</th>
<th>Indication</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janssen-Cilag International NV</td>
<td>–</td>
<td>Trevicta (paliperidone palmitate) three-month inj</td>
<td>schizophrenia</td>
<td>EU</td>
</tr>
<tr>
<td>Bristol-Myers Squibb &amp; Co.</td>
<td>–</td>
<td>Opdivo (nivolumab)</td>
<td>advanced melanoma</td>
<td>EU</td>
</tr>
<tr>
<td>Eisai Co. Ltd.</td>
<td>–</td>
<td>Halaven (eribulin)</td>
<td>advanced liposarcoma</td>
<td>EU</td>
</tr>
</tbody>
</table>

**PRIORITY REVIEW**

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Indication</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xbiotech Inc.</td>
<td>Xilonix (CA-18C, MABp1)</td>
<td>colorectal cancer</td>
<td>EU</td>
</tr>
</tbody>
</table>

**REGULATORY REVIEW EXTENSION**

<table>
<thead>
<tr>
<th>Company</th>
<th>Partner</th>
<th>Drug</th>
<th>Indication</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valeant Pharmaceuticals</td>
<td>Progenics Pharmaceuticals</td>
<td>Relistor (Oral) (methylaltrexone bromide)</td>
<td>opioid-induced constipation</td>
<td>US</td>
</tr>
</tbody>
</table>

**PRODUCT LAUNCH**

<table>
<thead>
<tr>
<th>Company</th>
<th>Partner</th>
<th>Drug</th>
<th>Indication</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zambon SpA</td>
<td>Newron Pharmaceuticals SpA</td>
<td>Xadago (safinamide)</td>
<td>Parkinson’s disease</td>
<td>Belgium</td>
</tr>
<tr>
<td>BTG plc</td>
<td>–</td>
<td>LC Bead LUMI</td>
<td>liver cancer</td>
<td>US</td>
</tr>
</tbody>
</table>

*Source: Sagient Research’s BioMedTracker*
PhaseBio Pharmaceuticals Inc. has appointed John S. Lee chief medical officer and John P. Sharp to the role of chief financial officer (CFO). Lee joins PhaseBio, a clinical-stage biopharma company specialising in biopolymer-based drugs, from Quintiles, where he served as vice president and global head, Cardiovascular Center of Excellence. Prior to this, Lee has held senior positions at Bristol-Myers Squibb and Merck & Co. Sharp has previously served as CFO at HUYA BioScience International and Ligand Pharmaceuticals, and will be based in San Diego in his new role at BioPhase.

Avion Pharmaceuticals LLC. has appointed Harold A. Deas, Jr. CEO. Deas will retain his role as chief operating officer at the company, which specializes in women’s health and dermatology.

Lambda Therapeutic Research, a leading clinical research organisation, has appointed Tausif Monif president, global operations. Monif brings over 24 years’ of experience within the clinical research industry to LAMBDA, which offers clinical research and drug development solutions to pharma companies worldwide.

Adapt Pharma has appointed Mike Kelly president of US operations and joins the company from Covis Pharmaceuticals Inc., where he was CEO and board member. Prior to Covis, Mika was a member of the founding management team of Azur Pharma and later, following a strategic merger, he was senior vice president of sales and marketing for Jazz Pharmaceuticals PLC.

Ovid Therapeutics has appointed Amit Rakhit chief medical and portfolio management officer and Daniel H. Geschwind to the company’s scientific advisory board. Prior to Ovid, Rakhit was senior vice president, head of worldwide medical at Biogen and he was also vice president, program leadership and management at Biogen. Previously he held leadership roles at Bristol-Myers Squibb including director, cardiovascular R&D and executive medical director, cardiovascular/metabolics. Recently Geschwind was appointed senior associate dean and associate vice chancellor of precision medicine in the UCLA Health System and David Geffen School of Medicine. He is a professor of neurology and psychiatry and biobehavioral sciences at the UCLA School of Medicine and director of the Center for Autism Research and Treatment (CART) and co-director of the center for neurobehavioral genetics at UCLA.

Aurinia Pharmaceuticals Inc. has appointed Charles Rowland CEO, replacing Stephen Zaruby who will be resigning as the company’s CEO and from its board of directors. Rowland was vice president and chief financial officer (CFO) of ViroPharma Inc. until it was acquired by Shire PLC. in 2014. Prior to this, he held various leadership positions at biotech and pharma companies and most recently was interim co-CEO, executive vice president, CFO for Endo Pharmaceuticals Inc. Previously Rowland held positions at Biovail Corp., Breakaway Technologies Inc., Pharmacia Corp., Novartis AG and Bristol-Myers Squibb.

Skypharma PLC. has appointed David Lescuyer executive vice president, oral business. Lescuyer joins Skypharma from Patheon Pharmaceuticals where he was executive director and general manager, Patheon France and more recently global vice president, operational excellence.
RESERVE A TABLE

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