Valeant: Another Fine Mess

Michael Pearson’s "Leap Day" return to Valeant Pharmaceuticals International Inc. was supposed to be a victory for the CEO and his firm after he’d spent the past few months on sick leave recovering from a severe bout of pneumonia. But before Pearson could get his footing, Valeant got shoved off a cliff on Feb. 29 – tumbling 21% after the company confirmed a new investigation and subpoena from the Securities and Exchange Commission (SEC), whose details are yet to be known, but it’s believed it’s related to the firm’s previous relationship with Philidor Rx Services Inc.

Valeant was hit again when Moody’s Investors Service placed the firm’s ratings under review for a downgrade, declaring that action reflected its concerns that the company’s underlying operating performance was “weaker” than previously expected, potentially impeding its deleveraging plans.

Shares of Valeant closed at $65.80 on Feb. 29, down $14.85, or 18.4%. The stock continued its decline through much of the trading day on March 1 – losing 9%, although the shares slightly touched green, before ending the day at $65.45, down 35 cents, less than 1%.

Part of the March 1 stock drop may have been related to a new political ad by former Secretary of State and presidential candidate Hillary Clinton, who said she was “going after” Valeant, accusing it of “absolutely gouging American consumers and patients” through its “predatory pricing.”

The Clinton ad actually came from a Jan. 28 town hall rally, where the candidate

AstraZeneca Offloads More Mature Drugs

China Medical System has agreed to pay a total of $500m for selected rights to two mature AstraZeneca PLC cardiovascular products, with the divestments set to provide new growth prospects for the Chinese firm while helping the UK-based multinational focus on innovative products in its second-largest global market.

The deal marks a step by AstraZeneca to concentrate effort on its newer drugs in China, which is now not only its largest emerging market but also the second-biggest globally for the UK-based firm.

Under the deal, announced Feb. 29, CMS will pay $310m ($155m upfront and $155m a year later) for the commercial rights in mainland China to the once-daily calcium antagonist Plendil (felodipine), which was first approved in the country in 1995 for hypertension and is also used in the prophylaxis of chronic stable angina pectoris.

The product had China sales of $189m last year and was incorporated into Shanghai’s essential drugs list in 2011.

HINTING AT A ROYALTY COMPONENT, THE UK’S SECOND-BIGGEST DRUG MAKER SAID IT WOULD ALSO “MAINTAIN A SIGNIFICANT, LONG-TERM INTEREST IN”

Valeant: Another Fine Mess

DOWNWARD SPIRAL: Before Pearson could get his footing, Valeant was shoved off a cliff with shares down by 18.4%
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Scrip
Editor: eleanor.malone@informa.com
Managing Editor: alex.shimmings@informa.com
News Editor: sukaina.vaigi@informa.com
South Asia Editor: anju.changarde@informa.com
Washington Editor: donna.poueg@informa.com
US West Coast Editor: mandy.jackson@informaua.com
Features Editor: joanne.shorthouse@informa.com
Senior Reporter: francesca.bruce@informa.com
Principal Analysts: ian.schofield@informa.com; peter.charlish@informa.com; ashley.yoo@informa.com
Reporters: lisa.lamotta@informa.com; lucie.elliott@informa.com; lucia.ahmed@informa.com; paul.wilkinson@informa.com; john.hodgson@informa.com
Global Content Director: mike.ward@informa.com
Global Content Director: mike.ward@informa.com
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A couple of weeks ago I asked in this column whether orphan drugs might get too big for their boots. A new development in the reimbursement pathway for Alexion’s orphan drug Soliris suggests that in future companies in the space are going to need to know their shoe size when they’re asked.

The aim of orphan drug legislation introduced in many countries including the US and the EU towards the end of the last century was to incentivize the development of new therapies for rare diseases. With global sales of $83bn, orphan drugs now make up a sizeable portion of the pharmaceutical market, so it would seem that the legislation was a success.

But who benefits? Granted, some patients have benefited hugely from new treatments. Nevertheless, 95% of orphan diseases remain without a therapy, even while pharma are seen to reap their rewards.

Meanwhile, payers in Europe wrestle with the ethical, political and practical issues of funding treatment for patients with very rare diseases from finite health budgets. On page 11, we see the early signs of pushback, albeit very cautious, with NICE calling for information from Alexion on its R&D costs for Soliris, which it estimates would benefit around 200 patients at an annual cost starting at £58m in the first year. It doesn’t say that it won’t pay, but it declares an interest in what is a “reasonable cost.”

Companies can still draw some comfort from the fact that public sentiment has yet to turn against the drug makers: a new survey of UK members of parliament commissioned by the UK Biotechnology Association shows most believe there should be no maximum price per patient for treating people with very rare and complex diseases, and that access to treatments for such diseases should be based on clinical need and not the NHS’s ability to pay.

Nevertheless, 95% of orphan diseases remain without a therapy, even while pharma are seen to reap their rewards.

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However, bodies like NICE are starting to ask the ‘shoe size question’ and it shouldn’t be assumed that the public won’t too. It is up to companies to remind them that for every successful drug approved for use, there are many more that failed to make it to market. Nevertheless, 95% of orphan diseases remain without a therapy, even while pharma are seen to reap their rewards.

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Five Questions For Boehringer Ingelheim’s Data Boss

The end of 2015 saw Boehringer Ingelheim follow a number of its pharmaceutical peers by bringing in an external service provider – in this case Medidata Solutions – to meet its cloud technology and data analysis needs. Scrip spoke with Klaus Stern, global head of biostatistics and data sciences at Boehringer, to find out why fortifying the company’s internal R&D efforts with external cutting-edge technology was so vital.

Scrip: How has the concept of innovation changed in recent years to make new information technology so critical?

Klaus Stern: There are several factors, but the overarching one is that the pharmaceutical industry has to change its business model. We are under new pressures: financial pressures, technical pressures, regulatory pressures, pressures from payers, from the insurance companies. That is a lot to cope with. To be successful we have to bring innovative therapies on to the market otherwise we will not succeed. Technology is very important to enable us to get new and important products to market in the most time efficient manner as possible.

Scrip: What areas of clinical development have been impacted by new technology?

KS: We have a lot more data sources in our current trial settings then we had in the past, e.g. laboratory data analyzed by specialized laboratories, images, biomarkers, e-COA, more attributes, more committees, and so on. This makes trials much more complicated just from a pure technical point of view, and additionally trial designs become much more complex, e.g. adaptive trial designs. This could, from a technical point of view, become a nightmare – and for this you need flexible tools to be able to cope with all these different challenges.

Scrip: What are the key drivers for adopting technology?

KS: We have a lot more electronic devices getting increasingly more data directly from the patients via a central vendor. Direct access to health records will be a goal. We are looking to minimize the interfaces, and to have them working automatically. We work towards metadata-driven end-to-end processes, which are automatically steered by metadata with no human intervention, meaning it is less error prone, guarantees consistency between documents and data, and is also of course faster.

The other thing is that we use the data itself to steer the trial, known as risk-based monitoring. We need the data in real time or almost in real time to be able to steer the trial, to look into any potential issues, so we can react immediately. We never had this before. That’s very important because all the regulators are asking us to have oversight of the trial at any time and to deal with the risks in a controlled manner.

Scrip: What technology have you implemented in your development processes?

KS: We have lots of more cutting-edge technology in place. Top-line data from the two identical placebo-controlled LAVOLTA studies show that LAVOLTA II missed the primary endpoint of a significant reduction in the rate of asthma exacerbations at 52 weeks in people with higher levels of serum periostin or blood eosinophils (both biomarkers of airway inflammation). LAVOLTA I did meet this endpoint and also demonstrated a significant improvement in lung function as measured by forced expiratory volume in one second (FEV1). However, the observed effect in the primary and secondary endpoints was less than seen in the lebrikizumab Phase II trials, Genentech said.

Scrip: Are there further efficiencies to be had in the development process through the use of more technology?

KS: Yes I think so. Medidata has a whole suite of products which fit together, which is essential for us. So we don’t have to build the interfaces by ourselves. With regard to metadata-driven processes it becomes very important that the different systems are able to talk to each other smoothly. And if you have a whole suite of systems which can talk to each other then of course it facilitates the process a lot and reduces maintenance cost.

Scrip: Why don’t pharmaceutical companies develop these systems in-house?

KS: The times when BI developed a system by itself are long gone because we are not an IT company, we are a pharmaceutical company. I trust that with a specialized company, dealing with other pharmaceutical companies in addition to us, that we will get better systems by buying them than if we do this by ourselves.

Of course we have had to adapt some of our processes, but overall that’s much more efficient than doing development ourselves. You have to understand that the outside world is changing, and having to maintain all the interfaces by ourselves would be very labor intensive. It is not value adding for a pharmaceutical company and confers no competitive advantage.

What Future For Genentech’s Lebrikizumab

Roche/Genentech’s IL-13 inhibiting investigational severe asthma product lebrikizumab has failed in one of its two pivotal trials, adding to reservations about its future. Lebrikizumab is already trailing other biological competitors to the market and the lack of robust data at Phase III could well spell the end in this indication.

Top-line data from the two identical placebo-controlled LAVOLTA studies show that LAVOLTA II missed the primary endpoint of a significant reduction in the rate of asthma exacerbations at 52 weeks in people with higher levels of serum periostin or blood eosinophils (both biomarkers of airway inflammation). LAVOLTA I did meet this endpoint and also demonstrated a significant improvement in lung function as measured by forced expiratory volume in one second (FEV1). However, the observed effect in the primary and secondary endpoints was less than seen in the lebrikizumab Phase II trials, Genentech said.

Together the studies enrolled more than 2,100 patients with severe asthma that is uncontrolled despite standard-of-care treatment with an inhaled corticosteroid and a second controller medication. The evaluation of the primary and secondary endpoints was based on a subgroup of people with higher levels of serum periostin or blood eosinophils. No new safety signals were seen in either study, and the full data will be presented at a future medical meeting.

Dr Sandra Horning, chief medical officer and head of Global Product Development, said that Genentech had been hopeful that the studies would confirm the Phase II data because of the remaining unmet need in severe asthma. In the event, she said, “These data require further interpretation and analyses are ongoing to better understand the results and determine next steps.” Other clinical studies with the product in asthma, chronic obstructive pulmonary disease, atopic dermatitis and idiopathic pulmonary fibrosis are under way.

Other observers were already less than confident about the product. Christina Vasiliiou of Datamonitor Healthcare said that lebrikizumab’s Phase III results came as no surprise. “[They] validate our assumptions that, if approved and launched, the anti-IL-13 monoclonal antibody would see the lowest uptake among the late-phase biologics in asthma, and GlaxoSmithKline’s recently approved Nucala (mepolizumab).”

She added that key opinion leaders have previously highlighted that they were unconvinced about the benefits lebrikizumab can offer, even in patients with higher levels of serum periostin or blood eosinophils, and are therefore unlikely to prescribe the drug, should it reach the market.

Lebrikizumab is one of a number of biological products targeting this severe form of asthma.
EMA: Minimize Risks With SGLT2 And Tysabri

The European Medicines Agency has confirmed the recommendations of its Pharmacovigilance Risk Assessment Committee (PRAC) to update the product information for the sodium-glucose co-transporter-2 (SGLT2) inhibitors, used to treat type 2 diabetes, to include diabetic ketoacidosis as a rare adverse reaction. The EMA has also recommended temporarily stopping SGLT2-inhibitor use in patients who are in hospital because of serious illness or are undergoing major surgery.

The products affected (including combinations) are: AstraZeneca’s Forxiga (dapagliflozin), Boehinger Ingelheim’s Jardiance (empagliflozin), Janssen’s Invokana (canagliflozin), Ebymect (dapagliflozin/metformin), Synjardy (empagliflozin/metformin), Vokanamet (canagliflozin/metformin) and Xigduo (dapagliflozin/metformin).

Diabetic ketoacidosis can occur in diabetes sufferers, with life threatening cases having been documented in patients taking SGLT2 inhibitors for type 2 diabetes. SGLT2 inhibitors work by blocking a protein that absorbs glucose from the urine back into the blood as it is filtered in the kidneys. If the SGLT2 protein is blocked, more glucose is filtered out through the urine, as a result lowering glucose levels in the blood.

Meanwhile, the EMA has also completed its review of the risk of progressive multifocal leukoencephalopathy (PML) with the multiple sclerosis (MS) medicine Tysabri (Biogen’s Natalizumab). Based on an initial review by PRAC, the EMA has recommended that patients at a higher risk of PML should undergo more frequent MRI scans, every three to six months. Studies have shown that early detection and treatment of PML, when it is in early stages with no symptoms, can improve patient outcomes.

Tysabri was approved in the EU in June 2006 and is used in relapsing–remitting MS, usually when the disease does not respond to other treatments. The medicine is a monoclonal antibody that recognizes and attaches to a protein called α4β1 integrin found on white blood cells. It prevents the blood cells passing from the blood into the brain, as a result reducing inflammation and nerve damage caused by MS.

Califf Admits Hard To Navigate Biosimilars Without Guides

Robert Califf, the new commissioner of the FDA, admitted during a March 2 Senate hearing that if the agency doesn’t get its pending biosimilars guidance out soon, “it’s going to be difficult for people to navigate and know what they need to do.”

The FDA already is a couple of weeks behind in providing an estimated timeline to Congress outlining the agency’s plans for finalizing all pending draft biosimilars guidance documents and regulations.

FDA has ~60 proposed biosimilar products to 18 reference innovator drugs enrolled in its program

Regulators were supposed to submit that timeline to Congress within 60 days under a directive included in the massive $1.1tn “Omnibus” spending bill signed by President Barack Obama on Dec. 18, 2015.

“What’s the status?” demanded Sen. Jerry Moran (R-KS), chair of the Senate Appropriations Subcommittee on Agriculture, Food and Drug Administration and Related Agencies, who said there’s a lot of industry folks who would like to provide input on issues like naming, labeling, interchangeability and indication extrapolation.

While Califf, who was testifying for the first time before a congressional panel after being sworn-in as commissioner on Feb. 25, said it “sounds lame to say I’m going to get back with you on the details of the timing” on reporting the biosimilars guidance timeline, he vowed “we’re going to get this out as quickly as we can.”

“After all,” Califf said, the FDA has about 60 proposed biosimilar products to 18 different reference innovator drugs enrolled in its Biosimilar Product Development program – the mechanism and structure for collecting the development-phase user fees to support the review activities.

“I hear you, and we will get back with you,” he told lawmakers at the hearing.

Califf, a cardiologist and former Duke University researcher and professor, noted he was “in charge” of the clinical trial testing the first biologic in cardiology, “so I’m well aware of the issues. They are complex.”

Janet Woodcock, director of the FDA’s Center for Drug Evaluation and Research, who Califf called a “world’ authority on biologics, told lawmakers at a Feb. 4 hearing the agency “hoped” to have drafts of the guidances for interchangeability, labeling and statistical approaches to analytical similarity out by the end of this year.

Opioids Concerns

The hearing was convened to vet the FDA’s proposed fiscal year 2017 budget proposal, but was cut short – lasting only about 40 minutes – because lawmakers needed to leave for votes on the Senate floor, including two related to efforts to address the nation’s struggle with opioids addiction, which was another matter for which lawmakers grilled Califf and was one of the issues that threatened to hold up his nomination. But both of the opioids bills failed in the Senate, including one aimed at making $600m in appropriations available this fiscal year to address the heroin and opioids abuse epidemic in the US.

Califf pointed to the FDA’s new action plan and three advisory committee meetings – one of which was held a day earlier with the Science Board – to stress the agency is taking a new direction when it comes to the review and approval of opioids. The FDA also plans to hold an advisory committee hearing in May to discuss the results of an assessment of its extended-release/long-acting risk evaluation and mitigation strategy plan.

Healthy FDA IT?

Among the issues lawmakers questioned Califf about at the brief March 2 hearing was the health of the FDA’s information technology infrastructure.

The new FDA chief acknowledged the agency has had past problems concerning the protection of companies’ information “that’s under constant attack.”

Indeed, a congressional investigation into the October 2013 breach of data systems run by the FDA’s Center for Biologics Evaluation and Research, in which a hacker gained access to 14,000 accounts held by regulated companies, found the agency’s lack of security had left drug makers’ and other firms’ trade secrets and other product information open to theft – something manufacturers had no control to stop.

Califf said the agency was working to “close the gaps” with the FDA’s IT systems, acknowledging “There was a plan for IT inside the FDA, but not a marriage of the IT plan with the overall strategic plan of the organization.”

“If you don’t have those systems working, you’ve got a real deficit that’s going to hurt you. So we are very focused on it,” he said.
J&J Opens Houston Incubator With 21 Startups, 12 Biopharma Firms

Johnson & Johnson Innovation LLC, the big pharma’s early-stage company accelerator and partnership negotiator, opened its fifth US incubator to house and support startup firms with 21 tenants, including a dozen therapeutics developers, in the Houston, Texas facility.

Known as JLABS @ TMC, the incubator’s 34,000 square feet of office and lab space can house up to 50 companies near the Texas Medical Center and its TMC Innovation Institute, which teaches doctors how to be entrepreneurs and launch their own companies. JLABS tenants have access to shared equipment and various resources to help entrepreneurs, including the advice of J&J scientists, but their landlord does not have any rights to the biotech and digital health companies’ technology.

The first “no strings attached” JLABS site opened in San Diego in 2012 and based on the success of that project J&J has built additional incubators in San Francisco, Boston and South San Francisco. The first international JLABS location will open in Toronto, Canada this spring. However, the fifth US site in Houston is the first to open with a medical device prototype lab, including a 3D printer.

The existing JLABS locations are home to more than 100 early-stage biopharma, medical device, consumer and digital health companies, but all six sites – including Toronto – have the capacity to house up to 225 firms.

Altera and Resonant were two of four companies who won the JLABS Quick Fire Challenge, which gave the victorious startups free space in the Houston facility.

The JLABS incubators are separate from J&J’s Innovation Centers where the big pharma has set up shop in San Francisco, Boston, London and Shanghai with business development teams seeking potential partners and investment opportunities. However, the JLABS sites in San Francisco and Boston are adjacent to the Innovation Centers in those cities.

The 12 biopharma tenants at the Houston startup hub

<table>
<thead>
<tr>
<th>Company</th>
<th>Technology</th>
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<tbody>
<tr>
<td>Beta Cat Pharmaceuticals Inc.</td>
<td>Small molecules that target cancer stem cells and tumor activator pathways with a lead program targeting Wnt/beta catenin signaling.</td>
</tr>
<tr>
<td>Icelex Therapeutics</td>
<td>A T cell engager-armed oncolytic virus to treat solid tumors.</td>
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<tr>
<td>IDA Therapeutics</td>
<td>Immuno Diverse Antibodies to satisfy unmet demand for efficacious antibody-based therapeutic, diagnostic and research products.</td>
</tr>
<tr>
<td>ImmunoMet Therapeutics Inc.</td>
<td>Oncology drugs that aim to increase survival by disrupting cancer metabolism and enhancing anti-cancer immunity.</td>
</tr>
<tr>
<td>Medigenex BioPharma</td>
<td>Highly selective cytokines for targeted treatment of cancer, autoimmune disease and fibrosis.</td>
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<tr>
<td>Metacure Therapeutics</td>
<td>Personalized cancer immunotherapy that combines tumor membrane vesicles from the patient’s tumor with immuno-stimulatory molecules.</td>
</tr>
<tr>
<td>Panamab Inc.</td>
<td>Monoclonal antibodies for cancer, fibrosis and infectious disorders.</td>
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<tr>
<td>Viracry</td>
<td>Novel, cost-effective T cell therapies for viral infections.</td>
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<td>Wntrix</td>
<td>Antibody-drug conjugates and other targeted cancer therapies.</td>
</tr>
<tr>
<td>Alterna Therapeutics Inc.</td>
<td>Novel diabetes and obesity therapeutics.</td>
</tr>
<tr>
<td>Resonant Therapeutics Inc.</td>
<td>A high-throughput antibody discovery platform for cancer therapies targeting novel antigens in the tumor microenvironment.</td>
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‘Rapid Kill’ Antibiotic Awaits US Data

Destiny Pharma Ltd., a small UK antibiotic developer, and its lead “rapidly bactericidal” product XF-73, has placed itself firmly on the radar in the US. The National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, is sponsoring and funding a clinical trial which is expected to complete in the coming weeks. If successful, XF-73 will be filed for the prevention of post-surgical Staphylococcal infections, a completely new indication. CEO Dr Bill Love explained to Scrip why the interest in Destiny’s child. XF-73 is being developed against Staphylococcus aureus, including the multi-antibiotic resistant strain, methicillin-resistant S. aureus (MRSA).

“We have conducted 55 passages with XF-73 (exeporfinium chloride) in standard laboratory resistance tests and there has been no resistance detected to date,” said Love.

The FDA granted the product Qualified Infectious Disease Product (QIDP) status last November for the prevention of post-surgical Staphylococcal infections. “There are tens of millions of patients entering hospitals each year who are at significant risk of contracting a post-surgical infection because they ‘carry’ this bacteria,” said Love.

Data from Phase I/IIa studies in Europe has shown that XF-73 quickly reduces the number of bacteria in the nose, where Staphylococcal bacteria usually congregate. The bacteria die in hours rather than days, according to Love. Destiny has developed an intranasal gel formulation of its product to administer the product. The NIAID-funded trial is studying S. aureus decolonization (i.e. the clearance of the bacteria from the nostrils of carriers).

“There is a tendency in the US to decolonize all forms of Staph but this ‘carpet-bombing’ leads to an increase in resistance. So while there is an established benefit of decolonization prior to surgery, it’s not feasible to do that now.”

Big pharma approaches to tackling this have focused on vaccines; many have failed and others are ongoing. “The current plan is to pursue this through to regulatory filing and approval ourselves, but we continue to engage with industry with regards to getting the product onto the market,” said Love.
Rare Disease Goalposts: A Conundrum For Pharma, FDA

Having clinical trial endpoints that are pragmatic and doable and a clear understanding of what the goalsposts are for winning the FDA’s approval to get a drug on the market will help decrease the uncertainty and drive investment, said Rakesh Marwah of Palo Alto Investors LLC, a Silicon Valley healthcare investment firm.

But in the world of rare disease research and development, that’s not always so easy, acknowledged Marwah, who also is a clinical instructor in anesthesiology, perioperative and pain medicine at Stanford University.

He noted that one of the biopharmaceutical rare disease startups Palo Alto had funded had assets it wanted to develop and a program it was ready to build and was eager to “kick the ball through the goalposts.”

But, Marwah said, the young company ran into trouble getting clarity from the FDA on where the agency was placing those goalposts.

“They had all of these resources set to launch, but they didn’t know which direction to launch in,” he explained during a March 3 Capitol Hill briefing hosted by the Rare Disease Congressional Caucus, in conjunction with the nonprofit Every Life Foundation.

Janet Woodcock, director of the FDA’s Center for Drug Evaluation and Research, acknowledged drug developers need clarity from the agency on its criterion for endpoints and meeting the standards for putting medicines on the market.

“They have to understand what the pathway to the market is,” she said.

But regulators “often don’t even know” themselves because they don’t have a clear understanding of what the rare disease is, its symptoms, the population it affects or what’s causing the condition, Woodcock lamented. That’s because there’s often not been enough study of the disease and it lacks a natural history, she explained.

Woodcock noted the FDA launched a new grants program on Feb. 29 – Rare Disease Day – to fund natural history studies with the aim of bringing new diagnostics and therapeutics to patients with rare diseases.

The FDA program is offering a maximum of $400,000 in total costs per year for up to five years for prospective natural history studies involving clinical examination of affected individuals and a maximum of $150,000 in total costs per year for up to two years for retrospective natural history studies or survey studies.

Woodcock said one of the obstacles that’s impeded rare disease research is a lack of “goal-orientation,” which leads to uncertain timeframes of completing trials and obtaining results.

She also urged anyone involved in rare disease R&D to form “collaborative networks” so they are not stuck re-inventing the wheel – something Woodcock has often preached about in recent months.

With uncertainty the enemy of investment, companies need to work closer with the FDA to ensure the doubt is alleviated and the agency needs to provide more flexibility, otherwise, investors won’t stick around for long, Marwah said.

“Once the uncertainties start to increase, once the risk starts to increase, once failures start to happen, [investors] pull resources away and then either put them in other sectors of healthcare that they feel more comfortable with or just take it out of healthcare altogether,” he said. “That’s exactly what we don’t want to have happen. We want to keep this in the community. We want to keep these dollars pushing new treatments forward.”

Marwah urged companies to find ways to shift their resources and focus on avenues of less uncertainty. He pointed out that one of the firms Palo Alto funded had put together a “myriad of development possibilities” for a molecule it had developed, which showed promise in a couple of pathways.

After meeting with the FDA and having some “fruitful discussions,” the agency worked with the company on a development path for a rare disease after determining it actually had the surer pathway to the market first before the other option of treating a more common condition in a large population.

donna.young@informa.com 

Pearson Returns To Valeant, Delays Financial Update

Michael Pearson has returned from sick leave to take back the helm of Valeant Pharmaceuticals International, Inc. Howard Schiller, the company’s former CFO who has been acting CEO since Jan. 6 following Pearson’s temporary exit with severe pneumonia announced in late December, 2015, will “transition out of his current duties” but will continue as a director.

Robert Ingram, formerly lead independent director on Valeant’s board, is to become chair of the board, a role formerly filled by Pearson. The firm has now split the two roles, and is to look more closely at succession planning and building up the senior leadership team to support Perason.

Valeant also withdrew its previously issued financial guidance and said that it would delay its call to discuss Q4 results, provide a business update and forecasts for 2016, which had been planned for Feb. 29. It had already said it would delay filing its 10-K annual report with the SEC until an ad hoc committee had completed a review of accounting matters. This committee reported a restatement of EPS for 2014 and 2015 last week, which appeared to reassure investors that the scale of the problem associated with Valeant’s questionable use of specialty pharmacy distribution was not as large as had been feared. The internal investigation continues however, and the company has also been plagued by political scrutiny of its pricing practices.

In December 2015, Valeant revised downwards its financial guidance for Q4 and FY 2015 issued a forecast for 2016. This saw it knock $600-700m off expected 2015 revenues and $550-650m off Q4 revenues. It scaled back 2015 revenue expectations from $11.0-11.2bn to $10.4-10.5bn, and Q4 revenue expectations from $3.25-3.45bn to $2.7-2.8bn. It still expected considerable growth in 2016, though, with revenues of $12.5-12.7bn, and claimed it would generate “double-digit same-store organic sales growth - primarily driven through volume.” The firm has previously underscored that volume rather than price growth is a key driver for its top selling products, but it has come under strong criticism for price hikes. For its portfolio as a whole, price has at least until recently been a major driver.

Ingram said: “We are delighted that Mike is back as his vision and execution have been central to Valeant’s success over the past eight years, but his illness serves as a reminder of the importance of succession planning. Given the size and breadth of our company, succession planning and building out our senior team to provide additional resources and support for Mike are high priorities for the Board. Our hope is that the Ad Hoc Committee will be able to conclude its efforts soon with regards to financial reporting and internal control matters, so we can all focus on building the best company we can.”

Pearson said: “I realize that recent events are disappointing to everyone and it is my responsibility to set the appropriate tone for the organization.”

eleanor.malone@informa.com
called out the company on the price hike for its injectable migraine drug D.H.E. 45 (dihydroergotamine), which rose from $180 for 10 shots to about $14,730.

The day of that political event, Valeant’s shares fell as low as 9.3%. The March 1 Clinton ad pulled the scab off that wound. But in a March 1 statement, Valeant said it had “reached out” to the D.H.E. 45 patient who appeared in the Clinton ad, Ellen Mayberry, and claimed the woman informed the company her insurer covered the drug, “so it is not a significant out-of-pocket expenditure for her.”

Another SEC Probe
Valeant acknowledged on Feb. 29 there are several ongoing investigations of the company, including another at the SEC involving disclosures and accounting issues at Salix Pharmaceuticals, which the firm acquired last year, plus probes by the US attorney’s offices in Massachusetts and the Southern District of New York and Congress.

The company said it received the new subpoena from the SEC in the fourth quarter of 2015 and, “in the normal course, would have included this disclosure in its 2015 10-K.”

Valeant said it didn’t have any further details to provide “at this time.”

“It is very difficult to predict the potential range of outcomes of this SEC investigation, particularly given that we do not know its scope,” said BMO Nesbitt Burns Inc. analyst Alex Arfaei, who said he was “not entirely surprised,” given the firm already has been in hot water over its now-ended “questionable relationship” with the specialty pharmacy Philidor Rx Services Inc. – an affiliation that was kept hidden from investors until this past fall.

Valeant had scheduled a Feb. 29 call with sell-side analysts, which was supposed to take place after the markets closed, but the firm abruptly canceled it after it was leaked to the media – leaving a void that was filled in by speculation.

Indeed, the SEC’s new investigation, plus Valeant’s decision to delay its 10-K, BMO’s Arfaei said, has only increased concerns about the integrity of the company’s financial reporting.

“Almost unbelievably, there are yet even more questions than answers,” said Jeffries analyst David Steinberg, although he said a critical issue has been addressed with Pearson’s return after his medical leave.

Pearson did end up picking up the phone on March 1 and called some sell-side analysts at UBS Securities and Nomura Securities, who said in research notes they felt more comfortable with the situation and urged patience. “It will take some time,” said UBS analyst Marc Goodman, for Pearson to “get his arms back around the business.”

That Philidor Thing?
BMO’s Arfaei said he suspected that given the timing of the subpoena, the probe likely is a financial disclosure case related to Valeant’s relationship with Philidor and perhaps even other specialty pharmacies.

The SEC probe was reportedly sparked when the agency looked into short-selling firm Citron Research’s allegations of fraud by Valeant involving Philidor.

If that’s the situation, Arfaei said he didn’t expect a potential financial penalty to be “indigestible” for Valeant.

“But again, this is difficult to handicap at this point,” he emphasized.

Arfaei noted that Philidor represented only about 1% of the drug company’s sales in 2014, but grew to about 7% of total revenue in the third quarter of 2015.

Based on his estimates, the specialty pharmacy sales accounted for, at most, 13% to 19% of Valeant’s earnings in recent quarters.

Arfaei said other potential implications of the new SEC investigation could include more limited access to capital markets and continued strain on a “thin management team.”

And without knowing what the SEC’s latest probe entails, he wouldn’t rule out the possibility of individual liability for Valeant’s key officers, directors or employees – which could not only be demoralizing, but could also lead to more difficulties in retaining or attracting talent.

Arfaei warned investors, whose confidence in Valeant already is shot, to expect continued volatility.

Deutsche Bank Securities Inc. analysts suspended their rating and estimates of Valeant’s stock based on the firm’s plans to restate prior results, the delay in filing its 10-K, the removal of prior 2016 guidance and an ongoing board investigation – declaring they’ve “long been skeptical” of its business model that had “formerly depended heavily on fast-paced acquisitions, aggressive cost cutting, tax arbitrage, aggressive US price increases and a heavy debt load.”

Don’t Worry So Much
But Rodman & Renshaw analyst Raghurom Selvaraju said the downside action on Valeant’s shares in response to the latest developments was “overblown,” and that “all of these issues may not be as concerning as they may seem at first blush.”

Selvaraju said he believed Valeant would provide updated forecasts for 2016 within the coming days.

And, he said, while the SEC inquiry “may take time to resolve,” it may ultimately be limited in scope since, Valeant is no longer connected to Philidor and the fact that such distribution channels have historically been utilized by specialty pharmaceutical firms.

Selvaraju also insisted the Canadian drug company’s additional disclosure on Feb. 28 of an FDA Paragraph IV filing by Allergan PLC seeking to sell a generic version of Valeant’s big moneymaker Xifaxan (rifaximin) was “not necessarily cause for alarm,” since the challenge does not automatically ensure generic competition in the near-term, given the patents protect the brand-name medicine through 2029.

donna.young@informa.com
is a healthy sum for the first two months of the year, considering biotech firms only need to raise $500m in March to catch up with the $1.7bn raised during the first quarter of 2015.

**Opexa Slims Down Ahead Of Key MS Data**

With results from its long-awaited multiple sclerosis trial expected before the end of the year, Opexa Therapeutics is prepping for business after the big event, but the move seems like a bad omen of things to come. The Texas biotech announced March 3 that it would be cutting its workforce by 30%—about a dozen employees— including its chief financial officer, as part of company-wide restructuring. The move will cost the company about $325,000 in severance expenses during the first quarter. It also expects to pay out another $333,000 in payments associated with a retention plan, according to a filing with the Securities and Exchange Commission. Employees that stay with the company through February 2017 will be eligible for bonus pay: CEO Neil Warma has taken over the CFO role, as well as the roles of principal financial officer and principal accounting officer—both of which were held by previous CFO Kirthik Radhakrishnan.

The company has tapped the market several times in order to continue funding the trial. It’s most recent public offering was in April 2015 when it netted $12.8m. It also held two offerings in 2013, bringing in $18m and $7.5m, respectively. The staff cuts will allow Opexa to extend its cash runway through the first quarter of 2017. This will be the make-or-break moment for the biotech. The company has hung all of its hopes on Tcelna, a T-cell vaccine that is currently being tested in secondary-progressive multiple sclerosis (SPMS) patients. The Abili-T trial, which was launched in 2012 and dosed its last patient in late-February, is expected to read out in the fourth quarter of 2016. The trial includes 190 patients with the debilitating autoimmune disease. Patients received five injections a year of either the therapy or a placebo. “We have aligned the restructuring to coincide with the reduction of activities associated with nearing completion of the Abili-T trial. The restructuring should enable us to extend our current cash into the first quarter of 2017, providing us with additional runway beyond the expected Q4 2016 release of top-line data,” said Warma. Opexa inked a worldwide license agreement with Merck Serono in February 2013. The German drugmaker has the option to license the product at the end of the Abili-T trial. Merck Serono has already paid Opexa about $8m in funds to move the Phase IIb trial forward and the biotech was required to provide its big pharma partner with a pre-Phase III plan when the agreement was amended in March 2015. Should Merck Serono take its option for the drug, Opexa will be free of the R&D costs for the drug and will not be responsible for the costs associated with commercialization. The cuts to staff could mean the company thinks Abili-T and Merck’s option are a sure thing. Or maybe not. While Tcelna is a unique therapy, it doesn’t come without its share of problems. The therapy, previously called Tovaxin, failed in another Phase IIb trial in 2008 in patients with the relapsing-remitting (RRMS) form of the disease. Opexa contends that there was an imbalance in disease burden of the two study arms with sicker patients being assigned to the therapy arm instead of the placebo group. The company is also quick to point out that Tovaxin (Tcelna) did improvement the secondary endpoint of annualized relapse rates and that the therapy was found to be safe for patients.

**Horizon, Centauri Going to Avvinity And Beyond**

The UK gene-editing group Horizon Discovery and Centauri Therapeutics Ltd hope their newly formed immuno-oncology joint venture, called Avvinity Therapeutics, will create a proprietary platform able to discover novel immuno-oncology therapies for both solid tumors and leukemias and give them access to a market currently worth £25bn and growing rapidly. The duo on March 2 said their JV will be jointly managed and combine Horizon’s gene editing, immunology, oncology and research capabilities with the British biotech’s Alphamer technology of synthesized molecules to redirect antibodies to cancers. The Alphamer technology is based on “programmable immunity” in which chemically synthesized molecules redirect naturally occurring antibodies to selected pathogens to fight the infection. The molecules have two distinct parts: one end binds a cell-surface target on the pathogen using an aptamer whereas the other end presents specific epitopes that attach to the circulating antibodies. Avvinity will have exclusive rights in oncology to use the Alphamer therapeutic platform, invented by a Nobel Laureate, Kary Mullis, and developed by Centauri. The groups believe Alphamers offer key advantages over conventional antibody and antibody-drug conjugate molecules in immuno-oncology applications, including the ability to target cancers driven by both wild type gene overexpression as well as mutant gene overexpression, and by exhibiting a short half-life in the body resulting in reduced toxicity and systemic side-effects. Horizon is investing up to £5.3m, with an initial outlay of £2.5m, in Avvinity Therapeutics. Under the terms of the deal, Horizon will out-license certain background intellectual property relating to its translational genomics and drug discovery platforms. Centauri, which was founded in 2010 and focuses on antibiotic-resistant bacteria, will license background IP and expertise on its Alphamer technology to Avvinity, which will have exclusivity for the field of oncology for an initial three-year period. Horizon CEO Darrin Disley said the gene-editing group was confident its joint venture with Centauri “will break new ground” in the development of immunotherapies, and bring significant value creation to Horizon shareholders. Mike Westby, CEO of Centauri, said that “through this joint venture with Horizon, we look forward to applying our combined know-how and capabilities to develop Alphamers as important new immuno-oncology medicines, particularly for cancer indications that have proven intractable to date.”
Lawsuit: Sandoz Copycat Piggybacks Enbrel, Ducks Duties

For the second time, Novartis AG unit Sandoz Inc. is trying to “reap the commercial benefits” provided to biosimilar manufacturers under the Biologics Price Competition and Innovation Act (BPCIA), while seeking to avoid the obligations Congress established under the 2010 law “to protect innovators,” Amgen Inc. and Roche AG charged in new court documents.

Sandoz is seeking the FDA’s blessing to market a biosimilar version of Amgen’s tumor necrosis factor (TNF) alpha inhibitor Enbrel (etanercept).

But Amgen and Roche are asserting Sandoz is “piggybacking on the fruits” of the innovators’ “trailblazing efforts.”

Enbrel, which is approved in the US to treat rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, anklyosing spondylitis and plaque psoriasis, was developed by Immunex Corp., which Amgen acquired in July 2002.

Roche and Immunex were early pioneers in isolating, characterizing, cloning and sequencing p55 and p75 versions of the human TNF receptors, respectively.

Roche owns two patents involved in Enbrel’s development – ‘182 and ‘522, for which Immunex holds the exclusive license of all commercial rights, including all rights to sell Enbrel.


In their lawsuit, filed with the US District Court for the District of New Jersey, Amgen and Roche are accusing Sandoz of infringing those five Enbrel patents.

Amgen already has been in an ongoing battle with Sandoz over its biosimilar Zarxio (filgrastim-sndz) – a fight the latter firm wants the Supreme Court to settle.

In the Zarxio suit, a three-judge panel from the US Court of Appeals for the Federal Circuit ruled 2-1 last year that the disclosure and negotiation procedure requirements of the BPCIA – the so-called patent dance – was optional and biosimilar makers could choose not to disclose their application and manufacturing details.

But 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.

Amgen also has filed other BPCIA lawsuits against other companies, including Apotex Inc. involving its pegfilgrastim biosimilar – a case the Federal Circuit is scheduled to hear on April 4.

Unlike the Zarxio case, in which Sandoz didn’t dance with Amgen, Apotex got down and boogied with the California biotech giant.

But Amgen’s and Roche’s newly filed lawsuit is different, because in that case, Sandoz started to tango, but abruptly stopped the music, which is somewhat similar to another case filed by Johnson & Johnson Inc. subsidiary Janssen Biotech Inc. against Celltrion Inc. and its partner Pfizer Inc. unit Hospira Inc.

Amgen and Roche are not asking the New Jersey court to enforce provisions of the BPCIA like in the other lawsuits – at least, not yet.

Sandoz is ‘piggybacking on the fruits’ of Amgen and Roche’s ‘trailblazing efforts’

While Amgen and Roche in their complaint recited the BPCIA steps Sandoz engaged in during its brief dance, the innovators noted those moves only in connection with establishing the jurisdiction for their declaratory judgment claims, not so the court could take any actions on the law itself, explained Elaine Herrmann Blais, a partner and head of litigation in the Boston office of Goodwin Procter LLP.

“The statute says if you don’t engage in the dance, then the reference product sponsor can sue right away on all of the patents that it has identified,” Herrmann Blais told Scrip.

Dancing In The Dark?

In the case of Zarxio, Sandoz didn’t provide any access to its 351(k) application to Amgen.

But on Oct. 19, 2015, Sandoz provided Amgen “remote access” to the biosimilar firm’s hosted database of TIFF images, which the company said constituted the etanercept application, submitted to the FDA this past September, and manufacturing information.

But Amgen said it couldn’t access the database except to manually download thousands of documents, so therefore, Sandoz failed to provide complete information.

Sandoz did not provide a local copy of the database – including the necessary database load files and associated data – and an unaltered copy of the etanercept application in the same electronic format as submitted to the FDA until Oct. 28, 2015, Amgen and Roche contended.

Amgen asked for more information on Nov. 9, 2015 – declaring Sandoz had failed to provide complete description of the processes used to manufacture the etanercept biosimilar, and the latter firm responded a week later with additional documents.

Amgen said it provided Sandoz on Dec. 18, 2015 with a list of patents for which claims of infringement could be reasonably asserted. But Sandoz responded in an 86-page letter on Jan. 27 that it no longer wanted to follow the strictures of the BPCIA, although it said it agreed with Amgen’s patent list.

Amgen acknowledged it received additional documents that day from Sandoz, which the latter firm said represented more information about the etanercept biosimilar’s manufacturing process.

According to the innovator firms’ complaint, Sandoz also said it was “waiving” its right to receive a statement by Amgen and declared the BPCIA patent dance negotiations were unnecessary and insisted the innovator file an action for patent infringement within 30 days – by Feb. 26.

On Feb. 10, Amgen told Sandoz its “refusal to participate” in the BPCIA negotiations “was contrary to the text of the statute,” and requested the biosimilar maker change its mind. But on Feb. 17, Sandoz confirmed it was sticking to its guns and told Amgen it wanted the patent litigation to begin as soon as possible.

Sandoz has “repudiated its obligations under the BPCIA,” Amgen and Roche asserted.

The innovators said they would be “irreparably harmed” if Sandoz was not stopped from infringing the five patents. Herrmann Blais noted Amgen and Roche didn’t ask the court for a preliminary injunction to stop Sandoz from marketing its etanercept biosimilar.

That, she said, likely will come as it gets closer to the FDA’s decision on the etanercept biosimilar application, which is expected in May.

Right now, Herrmann Blais said, the lawsuit is like a typical patent infringement case – with one big exception: Sandoz will be required under the Federal Circuit’s earlier ruling to give the mandatory 180-days notice of commercial marketing. And if the biosimilar company refuses to do that, then the case likely will become more like the other BPCIA battles, she said.

A Sandoz spokesperson said the company could not comment on litigation.

“We continue to work with the FDA on the proposed biosimilar etanercept and look forward to bringing this medicine to the US market as soon as possible,” the spokesperson said.
AstraZeneca Ditches A Second I/O Monotherapy

Monotherapies have not been lucky for AstraZeneca; just months after abandoning the pursuit of its PD-L1 inhibitor durvalumab as a monotherapy due to an overcrowded marketplace and unclear regulatory pathway, the British pharma announced the failure of its other immunotherapy tremelimumab as a solo treatment.

AstraZeneca told investors on Feb. 29 that its cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor tremelimumab failed to meet its primary endpoint of overall survival in the DETERMINE trial. The Phase IIb study of 571 patients tested the 10 mg/kg dose of the drug as a second- or third-line treatment in patients with unresectable malignant mesothelioma.

“We are disappointed that tremelimumab monotherapy did not demonstrate a survival benefit in this patient population with no approved medicines beyond first-line treatment,” said AstraZeneca’s Head of Immunoncology and global medicines development Robert Iannone.

The company did not elucidate on the results of the DETERMINE trial, but said it would announce further data at an upcoming medical meeting later in the year.

The trial failure was a hit to the British pharma, but is certainly not the end of tremelimumab. AstraZeneca is studying the drug in combination with its PD-L1 inhibitor durvalumab in multiple tumor types, including non-small cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck, bladder, pancreatic, gastric and liver cancers.

Recent results announced from the combination study of the two announced earlier in the month showed that the combo therapy had anti-tumor activity in NSCLC patients. The combination of durvalumab and tremelimumab is being further investigated in a series of Phase III trials in NSCLC, including the MYSTIC and NEPTUNE studies. These studies will not report out until 2017.

Last year, AstraZeneca chose to stop pursuing durvalumab as a monotherapy treatment for NSCLC — not because the drug wasn’t effective, but because the competition in the space had gotten too great.

AstraZeneca Offloads More Mature Drugs

The future value derived from Plendil sales in China, and would manufacture and supply the drug to CMS.

The deal does not involve the transfer of any employees or facilities from AstraZeneca and will have no impact on its 2016 financial guidance. In a stock market disclosure on the deal, CMS noted that the agreement includes certain “pre-agreed sales targets” over the first three years, which if not met will give AstraZeneca the right to terminate it.

Mutual Benefits

CMS said that the product, although mature for AstraZeneca, still presents “a significant commercial opportunity” in China, and will allow the company to expand its reach into lower-tier markets in China.

According to official figures, around 300 million people in the country suffer from hypertension, with around 10 million new cases diagnosed annually.

Although growth in AstraZeneca’s total China sales slowed last year, it remained strong at 13% to $2.53bn, and the firm’s stated intention there and across other emerging markets is to accelerate investment to commercialize its innovative pipeline.

In addition, among older portfolio products in China, Crestor (rosuvastatin) now dominates cardiovascular sales, while therapeutically the main focus is on the respiratory sector, where there was very strong growth last year on the back of disease awareness and education initiatives.

CMS, which floated on the London Alternative Investment Market in mid-2007 and moved to Hong Kong’s main bourse in 2010, brings to the table a well-developed distribution and marketing infrastructure across China, acting as a third-party promotion service for mainly smaller and mid-sized firms without independent capabilities.

It has a direct network that covers around 18,000 hospitals nationwide and its third-party agency network includes 6,000 hospitals in the country.

CMS’s total turnover rose 23% to CNY1.68bn ($257m) in the first half of last year.

Imdur Ex-US Divestment

The second part of the AstraZeneca agreement involves another older cardiovascular drug, the vasodilator Imdur (oral extended release isosorbide mononitrate).

CMS and its affiliate, Shanghai-listed Tibet Rhodiola Pharmaceutical Holding, will pay $190m ($100m upfront and $90m a year later) for global rights outside the US to the product — an active metabolite of isosorbide dinitrate — that is used for prevention of angina pectoris caused by coronary artery disease.

Imdur’s ex-US worldwide sales were $57m in 2015, and the product provides a route into global markets for Rhodiola, the first “high-tech” pharma firm in Tibet that also has interests in traditional medicines.

Deal marks a step by AstraZeneca to concentrate on its drugs in China, its largest emerging market and second-biggest globally

CMS noted that China is the single most important market for Imdur, which it said is “highly recognized” by physicians in the country and covered by the National Reimbursement Drug List, and is fully reimbursed in some areas.

Rhodiola, now 26.6%-owned by CMS, intends to raise around $230m in a new share issue to support the deal, after which CMS’s stake will rise to around 35.7%.

European Moventig Rights Sold To ProStrakan

In another example of its intent to offload non-core drugs, AstraZeneca on March 1 said it was selling the rights to opioid-induced constipation drug Moventig (naloxegol) in the EU, as well as Iceland, Norway, Switzerland and Lichtenstein to Kyowa Hakko Kirin subsidiary ProStrakan Group.

Under the terms of the agreement, AstraZeneca will receive an upfront payment of $70m, sales-based milestones and tiered double-digit royalties on net sales. It will also be eligible for additional payments contingent on market access decisions in certain European markets. Moventig is currently available in the UK, Ireland, Germany, the Nordics, Austria and Switzerland.

AstraZeneca’s Luke Miels, executive vice president of global product and portfolio strategy, said the Moventig deal “is in line with our strategy to focus our resources within our three main therapy areas while unlocking value from the important medicines in our portfolio.”

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ian.haydock@informa.com, sten.stovall@informa.com
R&D Bites

Aveo’s Tivozanib Lives to Fight Another Day

Aveo Pharma’s targeted anticancer, tivozanib, is a few steps closer to the market after two of its licensees, EUSA Pharma and Pharmstandard Group, filed the drug for approval in advanced renal cell cancer in the EU and Russia respectively. The tyrosine kinase inhibitor was dealt a body blow back in 2013 when the US FDA rejected it for the indication, after declaring the results of the firm’s Phase III TIVO-1 study which compared it with Bayer’s Nexavar (sorafenib) “uninterpretable” and “inconclusive.” But its fortunes reversed last May when the FDA indicated that there might be a path forward for the product in the third-line setting. Momentum continued when the product was licensed to Pharmstandard for Russia, Ukraine and the CIS in August, and then to EUSA Pharma in December in Europe and in a number of other territories outside North America, including South America and South Africa. EUSA’s filing via the centralized procedure is based on tivozanib’s existing dataset and follows positive interactions with the rapporteur and co-rapporteur during 2015 which indicated support for a filing using the TIVO-1 trial as the pivotal study. Under the agreement, EUSA Pharma will undertake and fund the commercialization of the product in its territories, if approved. Pharmstandard’s Russian filing was accepted last week by the Ministry of Health following its filing in December, also based on TIVO-1. In the US, Aveo now has plans for a further US Phase III clinical study in renal cancer potentially to enable registration in the first- and third-lines in the US, as well as a possible combination study with a checkpoint inhibitor. “Both studies may provide important strategic datasets in a rapidly evolving treatment landscape in RCC,” the company said. There are now eight targeted therapies available for the treatment of renal cell cancer (RCC), and although the approval of Bristol-Myers Squibb’s PD-1 inhibitor Opdivo (nivolumab) was based on clinical data that showed a significant increase in overall survival there still remains a need for developing effective treatment options capable of sustaining a more durable response, say analysts at Datamonitor Healthcare. Additionally there continues to be an unmet need for drugs that are more tolerable, as current therapies are associated with a number of toxicities.

BioMarin’s Cerliponase Alfa Data Support Mid-Year Submissions

BioMarin Pharmaceutical Inc’s cerliponase alfa (BMN 190) significantly slowed the rate of neurodegenerative decline for young patients with CLN2, a form of Batten disease, compared with historical controls in a Phase II/I clinical trial, supporting plans to seek US and EU regulatory approvals within the next few months. San Rafael, California-based BioMarin said a week ago when it reported 2015 earnings that the company expected to submit applications for cerliponase alfa to the US FDA and European Medicines Agency (EMA) by mid-2016 if results from its first clinical trial for the recombinant human tripeptidyl peptidase 1 (rhTPP1) were positive. The enzyme replacement therapy’s efficacy, which could lead to approvals during the first half of 2017, was a welcome boost for BioMarin after the FDA rejected the company’s Duchenne muscular dystrophy (DMD) drug Kyndrisa (drisapersen) in January. BioMarin gained 2.4% to close at $89.57 per share on March 3 following the company’s disclosure of the cerliponase alfa data after the stock market closed on March 2. Its share price has been on the rise since BioMarin said in its 2015 earnings report on Feb. 25, which showed a $14.62m loss for the year, that the company should achieve break-even status in 2017. Cerliponase alfa’s contribution to BioMarin’s profitability in 2017 became more important after the FDA issued a complete response letter (CRL) rejecting Kyndrisa in January. Jefferies analyst Eun Yang forecasts $214m in peak annual sales of cerliponase alfa in 2026, but doesn’t expect BioMarin to launch until 2018. However, Yang noted that consensus among peer analysts is for $32m in 2017 cerliponase alfa sales. Evercore ISI analyst Mark Schoenebaum predicts peak sales of about $500m. The cerliponase alfa data presented on March 2 during the WORLD (We’re Organizing Research for Lysosomal Diseases) Symposium gave BioMarin investors some assurance that the company’s break-even prediction could happen even without Kyndrisa approval in the US. “We believe an unprecedented approval trajectory [less than three years from investigational new drug (IND) application to approval] would allow investors to move beyond the Kyndrisa mishap and return BioMarin to its prominence in the rare disease space,” Leerink analyst Joseph Schwartz wrote in a March 3 report. CLN2 affects about 1,200 to 1,600 children worldwide, according to BioMarin’s estimates. Most patients lose the ability to walk and talk around the age of 6 and die by age 12, so slowing the disease’s progression could add years to what already are short lives. The average rate of motor and language function decline for patients treated with cerliponase alfa in BioMarin’s Phase II/I trial was about 80% less than the expected rate of decline for patients with CLN2 based on the natural history of the disease (p<0.0001). The disease stabilization rate at 48 weeks of treatment was 65% with 15 out of 23 patients seeing no decline based on the Hamburg Motor + Language CLN2 rating. The study could have enrolled children between the ages of 3 and 16, but the mean age of trial participants was 4.3 years old. They received 300mg of cerliponase alfa every two weeks via intracerebroventricular (ICV) infusion. The highest score for the rating scale used to determine motor and language function status is 6 and a natural history study of CLN2 patients shows that the average decline would be 2.1 units during a 48-week period. However, the mean decline for 21 out of 24 patients who were treated with cerliponase alfa was 0.43 units at 48 weeks (p<0.0001). One patient dropped out of the study due to an inability to comply with treatment after one dose of the therapy and two patients were excluded from the data analysis, because their motor and language function were not in decline at the start of the trial and their CLN2 rating remained at 6.

Novo’s LEADER Trial Move GLP-1 To Diabetes Front Line?

Novo Nordisk AS has an impressive victory with a benefit demonstrated in the LEADER cardiovascular outcomes study of its GLP-1 agonist Victozza (lixisenatide) in high-risk type 2 diabetes, but the real test could be whether the magnitude of benefit is big enough to shift practice and expand use beyond the class’s tiny base. The company reported that Victozza reduced the cardiovascular event rate compared to standard of care in diabetes patients in LEADER in a release of top-line results on March 4. Safety was consistent with multiple previous clinical trials. The study of long-term outcomes in type 2 diabetes at high risk of cardiovascular events was started in September 2010, at the request of US and European regulators. Per protocol, the trial randomized 9,340 patients with an average baseline HbA1c of 8.7% with the goal of accruing 633 cardiovascular events. The primary endpoint related to a composite of major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal myocardial infarction and non-fatal strokes. Safety was assessed over 3.5 to 5 years. It’s not exactly clear what mechanism explains the beneficial effects, but it could relate partly to improvements in glucose control and partly to improvements in other parameters related to CV risk, Chief Scientific Officer Mads Krogsgaard Thomsen said in an investor call. However, the company did not disclose any details, like the magnitude of benefit for the primary endpoint or performance for the components. Full results will be presented at the American Diabetes Association annual meeting in June.
FDA OK’s Gilead’s ‘TAF’ Combo HIV Drug Odefsey

Gilead Sciences Inc. on March 1 gained the FDA’s approval to market Odefsey as a treatment for HIV-1 infection – the second so-called TAF-based regimen to win the agency’s OK.

The drug is a single tablet containing 200mg of emtricitabine, 25mg of rilpirivine, which is sold as a single agent by Johnson & Johnson Inc. as Edurant, and 25mg of tenofovir alafenamide, or TAF, which is a prodrug of tenofovir, a product Gilead markets as Viread.

Odefsey, approved by FDA, will carry a ‘blackbox’ warning label for risks of lactic acidosis or severe hepatomegaly

TAF is one of the components in Gilead’s recently approved HIV drug Genvoya (elvitegravir 150mg/cobicistat 150mg/emtricitabine 200mg/TAF 10 mg) – a medicine currently at the center of a lawsuit brought by the AIDS Healthcare Foundation, which is alleging the company manipulated the US patent system and engaged in anticompetitive practices to prevent economical access to a newer form of tenofovir.

The FDA approved Odefsey as a complete regimen to treat HIV-1 infection in patients 12 years or older who have no antiretroviral treatment history and HIV-1 RNA levels less than or equal to 100,000 copies per mL.

Odefsey also is indicated as replacement for a stable antiretroviral regimen in patients who are virologically-suppressed for at least six months with no history of treatment failure and no known substitutions associated with resistance to the individual components of the medicine.

The product, however, comes with a black-box warning on its labeling alerting prescribers and patients about the risks of lactic acidosis or severe hepatomegaly with steatosis and post-treatment acute exacerbation of hepatitis B.

donna.young@informa.com

FDA: Generics Rule ‘Complicated,’ But Not About Litigation

The FDA’s reasons for proposing a rule that would permit generic drug makers to independently revise their product labeling to add new safety updates before regulators review or approve such changes – just like brand-name manufacturers already do – are “complicated,” declared Stephen Ostroff, who up until last week had been serving as the agency’s acting commissioner for much of the past year.

“It’s related to being able to assure that the labels contain information that’s important regarding the safety of products, whether it’s the reference drug or whether it’s the generic,” Ostroff told the House Appropriations Subcommittee on Agriculture, Rural Development, Food and Drug Administration and Related Agencies on Feb. 25.

The interplay between brand-name medicines and generics and the safety information contained in their labeling is so complicated “because of the way the regulations and the statutes are written,” he said.

Ostroff, who was on Capitol Hill to talk about President Barack Obama’s proposed fiscal year 2017 budget, acknowledged the FDA has received a “fair amount of feedback” on the generics rule, which was proposed by the agency in November 2013, but its finalization has been postponed – most recently until this July. But Rep. Robert Aderholt (R-AL), chair of the House appropriations subcommittee, barked that the agency, which he said had actually received 23,000 comments on the proposed rule, has “never met with industry to discuss the rule or efforts to provide an estimate of costs and access,” yet had met with a group of trial lawyers.

Ostroff, who was filling in at the hearing for new FDA Commissioner Robert Califf, who was at the White House on Feb. 25 for a summit where Obama unveiled new actions to further advance his Precision Medicine Initiative, insisted that “without question,” regulators’ primary consideration for imposing the generics rule was “not related to litigation.”

The generics labeling rule is one of the few times the Pharmaceutical Research and Manufacturers of America and the Generics Pharmaceutical Association have been on the same page in opposing an FDA action.

Even though all drug makers must inform the FDA about all adverse event reports the firms receive, currently only brand-name companies are permitted to independently revise their safety information in drug labeling on their own by submitting a so-called changes being effected (CBE) supplement to the agency.

The FDA insists its proposed rule is intended to “remove obstacles” to the prompt communication of safety-related labeling changes that meet the regulatory criteria for a CBE supplement.

The consumer watchdog group Public Citizen sought to change that – petitioning the FDA in August 2011 to make generic drug makers responsible for adding safety updates in their labeling. But generic drug makers objected to that idea – citing concerns the rule could expose the companies to liability when patients have adverse reactions to those firms’ copycat medicines.

Generic manufacturers currently are protected against such liability under two US Supreme Court rulings – Pliva v Mensing and Mutual Pharmaceutical v Bartlett.

In Pliva, the high court ruled 5-4 in June 2011 that generic drug makers do not have the same obligations as brand-name manufacturers to update product labeling when new risks come to light.

In Mutual, the Supreme Court in June 2013, also in a 5-4 ruling, said state law design-defect claims that turn on the adequacy of a drug’s warnings are preempted by federal law under the Pliva decision. But the FDA said the regulatory difference in which individuals can bring a product liability action for “failure to warn” against innovators, but generally not generic firms “may alter the incentives” for the copycat manufacturers to comply with current requirements to conduct robust postmarketing surveillance, evaluation and reporting, and to ensure that their product labeling is accurate and up-to-date.

Therefore, regulators said, there’s a need for generic makers to be able to independently update product labeling to reflect certain newly acquired safety information as part of those firms’ “independent responsibility to ensure that its product labeling is accurate and up-to-date.”

The FDA insisted its proposed rule is intended to remove obstacles to the prompt communication of safety-related labeling changes that meet the regulatory criteria for a CBE supplement. But Aderholt said implementing the FDA’s rule would add $4bn to the annual costs of generics — something he argued was out of sync with Americans’ concerns over what they are paying for their medicines.

He also pressed Ostroff on whether the FDA would stick to the most recent July timeline set by the agency of finalizing the rule – citing Califf’s November 2015 Senate testimony, where he said putting getting it done was a “top priority” for him, but Ostroff would not commit to that deadline.

donna.young@informa.com
BEST COMPANY IN AN EMERGING MARKET

WINNER: HIKMA PHARMACEUTICALS

Hikma, which focuses on a wide range of generic, branded generic and in-licensed pharmaceutical products, delivered an excellent performance in 2014 with strong underlying growth, particularly from its global injectables business. This was supported by acquisitions which positioned Hikma for growth from continued new product launches and from its strong market presence in the US, MENA and Europe.

"Hikma is delighted to have received the award for Best Company in an Emerging Market. This award is a testament to the work we have done over the last 30 years to turn Hikma into a world class company and leader in the MENA region, addressing our patients’ needs and increasing their access to high quality affordable medicines."
Ipsen Pays Exelixis $200M Up Front For Ex-US Cometriq Rights

Exelixis Inc. will bring in $260m in up front and milestone payments in 2016 alone under its new partnership with Ipsen for ex-US development and commercialization of Cometriq (cabozantinib), while the company awaits both US and EU approvals of the drug for a form of kidney cancer.

Ipsen agreed to pay $200m up front for the rights to Cometriq outside of the US, Canada and Japan plus various milestone fees, including $60m upon EU approval expected later this year to treat advanced renal cell carcinoma (RCC), and double-digit royalties. The transaction allows Exelixis to concentrate on finding a Japanese partner for Cometriq and commercialization of the drug in the US, where FDA approval to treat advanced RCC is expected by June 22.

Exelixis jumped 11.8% in after-hours trading on Feb. 29 to $4.07 per share. The South San Francisco-based company closed as high as $6.62 in August based on positive progression-free survival (PFS) in advanced RCC from the Phase III METEOR clinical trial in July.

However, Bristol-Myers Squibb Co. stopped a Phase III trial in RCC due to favorable efficacy for its immuno-oncology drug Opdivo (nivolumab) in July and the programmed cell death-1 (PD-1) inhibitor won US approval in the kidney cancer in November. Opdivo was recommended for EU approval to treat RCC on Feb. 26.

While the tough competitor quickly made its way to RCC patients, Exelixis noted in its fourth quarter 2015 earnings report on Feb. 29 that Cometriq is the first therapy to show positive results versus Novartis AG’s Afinitor (everolimus) in terms of PFS, overall survival (OS) and objective response rate (ORR) in the treatment of advanced RCC. The company is saving OS results from a second interim analysis of the METEOR trial for presentation during a medical meeting later this year.

Given the METEOR results to date, Exelixis President and CEO Mike Morrissey told Scrip that financial terms “in line with the quality of data we have in RCC” was one of the three requirements that the company had for its ex-US partner. The other two requirements were for a collaborator that has an experienced oncology sales teams and a partner that will be as enthusiastic as Exelixis about the opportunity for Cometriq in multiple types of cancer.

One, Two, Three … You’re It!

On the first point, in addition to the upfront payment and $60m fee for EU approval to treat RCC, Ipsen agreed to pay $50m upon submission of a marketing authorization application (MAA) and European Commission approval for hepatocellular carcinoma (HCC) plus other undisclosed regulatory milestones for additional indications.

“‘We have a similar vision on how to collaborate and to be transparent’

The companies also agreed to commercial milestone fees of up to $545m and Exelixis will earn royalties during the initial launch period of 2% on the first $50m in sales and 12% from the next $100m in sales, after which the royalty rate will range from 22% to 26%.

On the second deal point, Exelixis noted during its earnings conference call that Ipsen has 150 genitourinary sales representatives that target 5,000 oncologists and 6,000 urologists in the EU.

Thirdly, Morrissey said Ipsen has shown optimism mirroring Exelixis’s own for Cometriq in RCC and other indications. “They’re great partners, very passionate, and there is good chemistry between the scientific teams and at the management level,” he said.

“We have a similar vision on how to collaborate, to work together, and to be transparent.”

A good working relationship will be important as the partners pursue new indications for Cometriq. Exelixis is responsible for all development cost for its ongoing clinical trials, but Ipsen will pick up 35% of the trial expenses for indications that they agree to pursue together.

A partner in Japan would pick up some of the other 65% of future study costs from Exelixis, but the company has not given specific guidance about when it expects to close a deal for Cometriq in Japan.

“We have a number of discussions ongoing,” Morrissey said.

Big Cash Position Grows

Exelixis had $253.3m in cash and investments plus $126.4m in working capital as of Dec. 31 and it expects to burn through $240m to $270m in 2016. But with its cash on hand, upfront and milestone fees from Ipsen, revenue from Cometriq’s approved indications, and royalties from the Roche-partnered Cotellic (cobimetinib), the company expects to end the year with “a healthy cash position,” but specific revenue and cash guidance was not provided.

Roche’s Genentech unit and Exelixis won FDA approval for the MEK inhibitor Cotellic to treat certain advanced melanoma patients in November after the drug won a recommendation for European Commission approval in September. The companies are pursuing additional indications with ongoing Phase Ib and II clinical trials in melanoma, colorectal and breast cancer.

Cometriq is a small molecule inhibitor of tyrosine kinases, including VEGF receptors, MET, AXL and RET. The drug is approved in capsule form to treat progressive, metastatic medullary thyroid cancer (MTC) in the US and progressive, unresectable locally advanced or metastatic MTC in the EU. The new drug application (NDA) submitted to the FDA and the MAA that’s under consideration by the EMA for the treatment of RCC pertain to a tablet formulation of the drug.

Exelixis reported $34.2m in 2015 product revenue, most of which was for the approved Cometriq indications. The drug is marketed in the EU currently by Swedish Orphan Biovitrum AB (Sobi), but Ipsen will take over Sobi’s Cometriq territories.

The Cometriq development program targets even more indications via more than 45 ongoing or planned clinical trials, including the Phase III Celestrial trial in advanced HCC with top-line results in the liver cancer expected in 2017. Several earlier-stage studies also are ongoing in partnership with the National Cancer Institute’s Cancer Therapy Evaluation Program (NCI-CTEP). The company-sponsored and CTEP study indications include kidney, bladder, colorectal, lung and endometrial cancer.

mandy.jackson@informausa.com
Precision BioSciences Says Baxalta's IO Focus Made It Preferred Partner

Genome-editing specialist Precision BioSciences says Baxalta Inc's increasing commitment to, and expertise in, immuno-oncology made it the obvious choice for the Duke University spinout to partner with on developing a broad series of allogeneic chimeric antigen receptor (CAR) T cell therapies directed against multiple cancers.

Baxalta and Precision earlier this month inked a collaboration – worth up to $1.7bn – which will use Precision's ARCUS platform to make CAR-T therapies for up to six unique cancer targets by re-engineering T cells from healthy donors and turning them into personalized cancer-cell-killing vehicles.

"We looked at a number of potential partners. Baxalta are very strong on the regulatory side and on the commercial side. And they really bring a lot of downstream product focus and expertise that we don't have," explained Derek Jantz, chief science officer at Precision BioSciences.

He said Baxalta's commitment in the immuno-oncology space is also seen in its recent deal with Symphogen AS, whereby Symphogen granted Baxalta options to exclusively license global rights to six immuno-oncology projects against undisclosed checkpoint targets.

"These are two significant deals for Baxalta in the immune-oncology space and they're continuing to build. We really like the direction that the company is taking strategically," Jantz said.

Asserting Allogeneic ARCUS

Precision's ARCUS is a genome editing platform derived from a natural genome editing enzyme called a homing endonuclease.

"ARCUS allows us to make very precise modifications to genomic DNA in a living cell and modify the function of that cell. So we are basically reprogramming T-cells to re-direct them towards cancer targets so that they recognize an attack and kill tumours," Jantz said in an interview.

That approach is very different from that currently being pursued by the leading CAR-T sponsors – Juno Therapeutics Inc, Novartis AG and Kite Pharma Inc. – which have developed autologous CAR-T therapies that are engineered for individual patients using their own T-cells and given in specialized transplantation centers.

Against An Autologous Approach

Jantz believes Precision's allogeneic "off the shelf" approach using ARCUS has many advantages over the autologous strategy which uses patients' own T-cells.

"The most obvious is the manufacturing process, which for allogeneic product is much more cost effective and scalable than autologous ones because we can derive multiple doses and treat multiple patients from a single batch of cells derived from a single donor," he said.

"The autologous approach which is being used by a lot of other groups is a highly personalized therapeutic, in which you need to go through this expensive, difficult, time-consuming cell reprogramming process on a patient-by-patient basis. So from a manufacturing standpoint it's really nice and day in terms of what we're going to be able to with the allogeneic approach."

Another advantage for the allogeneic approach, according to Precision's CSO, is that there's less of a time lag between when a patient is diagnosed and when a patient can be treated.

"That's because in our allogeneic world the product is essentially available off the shelf, so as soon as a patient is diagnosed, we can find some cells and administer those to the patient, whereas with an autologous approach, there is a time lag involved in manufacturing these cells before they can be re-introduced into a patient and that can be days or a weeks, during which time the patient is just waiting to be treated and is generally getting sicker."

Backers of an autologous approach would argue that because they are administering a product derived from a patient's own cells, the likelihood of graft rejection is much lower, so the likelihood that the patient's immune system is going to see those cells as foreign and reject them before they can kill the tumour is significantly lower.

"So the primary technical hurdle that we see to the allogeneic approach is when we introduce foreign cells into a patient. But those cells are going to be cleared eventually by the patient's immune system. What we don't know at this point is how quickly and whether or not they will have enough time to get their job done and eliminate the tumor. We think that they will," Jantz said.

Off-The-Shelf Appeal

That's also the view of Cellectis SA, which recently made headlines by saying those manufacturing advantages will allow it to price its allogeneic chimeric antigen receptor T-cell therapies on a par with the latest cancer antibodies.

Cellectis is also developing off-the-shelf therapies derived from cells of healthy donors and that could be produced by contract manufacturing organizations, potentially at a lower cost compared to autologous treatments, but its technology is different from Precision Biosciences. Last November, Pfizer Inc licensed Cellectis' TALEN gene-edited allogeneic UCART19 candidate.

"Their TALEN gene-editing platform is conceptually similar to our ARCUS in that it is also an enzyme that recognizes DNA sequences in a cell and cuts them and allows Cellectis to modify the genetics of the cell that way. So we are both using gene editing for CAR-T," Jantz said.

But Juno and Novartis seem to be hedging their bets a bit by entering collaborations that take the allogeneic CAR-T approach. Juno last May announced a partnership with gene-editing company Editas Medicine Inc, whose platform is based on CRISPR/Cas9 (clustered, regularly interspaced short palindromic repeats) which uses a protein-RNA complex of the Cas9 enzyme bound to a guide RNA molecule to recognize a particular DNA sequence.

Novartis in January 2015 entered a five-year collaboration with Intellia Therapeutics Inc to apply CRISPR/Cas9 gene editing and repair technologies ex vivo to CAR-T cells and hematopoietic stem cells for the treatment of cancers and hematological disorders.

"Novartis has an announced gene-editing partnership with Intellia. We don't know what they are doing, but it is possible that they are working on allogeneic CAR-T products, Jantz said.

He doesn't expect Precision will explore the area of CRISPR/Cas9 gene editing, despite growing interest in the approach. "We think ARCUS technology is really superior to CRISPR/Cas9 gene editing in many regards and that's the technology we have in house and that we invented and technology that we own. So we don't have a lot of interest in exploring other platforms."

Baxter International Inc. spinout Baxalta already has significant hematology and immunology businesses and is developing an oncology portfolio.

Baxalta's oncology president David Meek in an email told Scrip: "They offer some of the most advanced expertise in this area and promising proprietary genome editing technology that may be able to overcome many of the limitations of current autologous approaches to CAR-T."
Engineered T-Cell Company Raises $56M And Lands New CEO

The UK’s next-generation engineered T-cell immunotherapy company Autolus Ltd. has raised £40m ($56m) in a Series B financing that includes the first investment by the new UK investment firm, Perceptive Bioscience Investments Ltd., and funding from Woodford Investment Management LLP. The round brings Autolus’s total funding to a respectable £70m in less than two years.

The company also announced on March 3 that chair Christian Itin will take on the additional role of CEO, with Edward Hodgkin, the former CEO and a partner in the start-up investor Syncona LLP, moving to become a non-executive director.

Although there are well-funded biotechs and big pharma companies like Novartis AG, Kite Pharma Inc. and Juno Therapeutics Inc. already active in the chimeric antigen receptor T-cell (CAR-T) and T-cell immunotherapy field, Itin was keen to outline the opportunity that is still available to new T-cell immunotherapy companies.

“This is a field that is still in its infancy, that is currently evaluating very basic kinds of proprietary products, and now has the funds to take some of these into initial clinical trials, although Itin did not disclose timings or the specific conditions in which the company was interested. “We are very interested in hematological cancers, and could eventually become interested in solid tumors,” he commented.

Unusual Investor Group

Autolus was initially funded by the Wellcome Trust’s investment subsidiary, Syncona LLP, that put up £30m in a seed and Series A round in January 2015, and by attracting Perceptive and Woodford Investment Management LLP to invest in the latest round it has the backing of two high-profile UK investment firms, Perceptive’s CEO Joe Anderson, a former partner at Abingworth LLP, has joined the board of Autolus.

“The investor group supporting Autolus is quite unusual in not being VCs, they are evergreen funds that are not term-limited, and we believe that’s important in our line of business with extended product cycles,” Itin said. There are also no corporate VCs among its investors, also an unusual move for a European biotech where corporate VCs are increasingly playing a more prominent role in supporting such companies.

The Series B is one of the largest financings in pharma biotech in Europe this year, just behind the CHF60m ($60m) raised by high net-worth investors in Swiss biotech Cardiorenatis AG’s Series B in January, this year, but lagging behind the £60m raised by the UK’s Mission Therapeutics Ltd. in a Series A round in February.

Itin said he was excited about the opportunity to lead Autolus as CEO, thereby extending his previous experience as President and CEO of Micromet Inc., a biotech company developing T-cell engaging antibodies (BiTEs) that was acquired by Amgen Inc. in 2012 and whose lead program, Blincyto (blinatumomab), was approved for the treatment of acute lymphoblastic leukemia in the US in December 2014.

Itin was also from November 2012 to January 2016 CEO and chair of Cytos Biotechnology Ltd., a company that in January 2016 was merged with Kuros Biosurgery Holding Ltd. and renamed Kuros Biosciences Ltd, a company in which Itin is chair but where a new CEO has been appointed.

Janssen’s Imbruvica Not Cost-Effective, Says NICE

Janssen’s Imbruvica (ibrutinib) is not cost-effective for treating NHS patients with chronic lymphocytic leukemia, according to NICE, the health technology appraisal institute for England. But the company intends to challenge the decision, which it says is in "stark contrast" to recommendations in 48 other countries around the world, including Greece.

Mark Hicken, managing director of Janssen UK, said the recommendations showed that the NICE appraisal process was not fit for purpose for addressing cancer patients. “This is a worrying sign for people living in England and is, unfortunately, likely to be much more common under the new Cancer Drugs Fund process approved by the NHS England Board last week.”

In its preliminary draft guidance, NICE says it is not recommending Imbruvica within its licensed indication for chronic lymphocytic leukemia patients who have either had at least one prior therapy or for people with 17p deletion or TP53 mutation, for whom chemoimmunotherapy is unsuitable. The committee said the drug was an "important treatment in CLL, but because of the numerous uncertainties in the evidence base and economic modelling presented by the company, and because of the incremental cost-effectiveness ratios, it could not recommend ibrutinib for CLL as a cost-effective use of NHS resources."

According to the appraisal committee, the cost per quality adjusted life year gained for the drug, even when taking into account a patient access scheme, was well beyond the £30,000 cost-effectiveness threshold set by the institute.

The committee cited numerous problems with the Resonate trial, which supported the drug’s regulatory approval and NICE submission, and which was stopped early because of significant improvements in progression-free survival. It said the data were “immature and uncertain,” among other things.

Respondents have until 23 March to comment on the consultation. The committee will then meet to discuss responses and formulate final draft guidance on the drug. Some 27 European countries fund Imbruvica, while in England it is available on the Cancer Drugs Fund, a temporary measure to improve access to cancer drugs. Janssen says the drug is the most requested CLL treatment available on the fund, which, according to the firm, demonstrates a huge clinical demand. The CDF is set to close later this year to make way for a new system that will give limited interim funding for certain drugs while the manufacturers gather new evidence to prove the drug can be cost-effective. However, the measures outlined in proposals for the new system have proved unpopular with companies.
RESERVE A TABLE

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Forty Seven Raises $75M For Potential ‘Universal’ CD47 Cancer Therapy

Forty Seven Inc. has $75m in Series A venture capital and something else that’s pretty novel for a startup biotechnology company: an immuno-oncology development program that’s already in the clinic with data expected later this year.

Palo Alto, California-based Forty Seven made a big bet on lead therapeutic candidate Hu5F9-G4 and the cancer treatment’s target by licensing more than 100 issued or pending patents from California’s Stanford University, including intellectual property for antibodies against CD47 and alternative approaches to the target. The patents also cover novel immune checkpoint inhibitors and cancer-specific antibodies for which Forty Seven could submit investigational new drug (IND) applications to the US FDA in 2017.

Forty Seven’s Chief Business Officer Craig Gibbs said Hu5F9-G4 “has the potential to be a universal cancer regimen,” because the CD47 receptor is expressed in many different types of cancer.

The Stanford scientists who first identified CD47 as an important cancer therapy target are running two Phase I clinical trials with Hu5F9-G4, with one trial at the university focused on solid tumors and another trial at Oxford University in the UK that is enrolling patients with acute myeloid leukemia (AML).

Professor Irving Weissman and his Stanford colleagues’ work on Hu5F9-G4 to date has been funded by $30m in grants from the California Institute of Regenerative Medicine (CIRM), the state agency that oversees $3bn in stem cell–based research funding.

The Hu5F9-G4 studies qualified for CIRM grants based on Weissman’s research with cancer stem cells, which express the CD47 receptor. His lab received an $18.8m grant for the development of therapeutic antibodies that target AML stem cells and an $11.7m grant for clinical investigation of an anti-CD47 antibody that targets solid tumor and hematological malignancy stem cells.

Read full story at: http://bit.ly/1UvZ9nv

India Sovaldi Opposition Hearing Ends; EU Case Looms

US-based not-for-profit group Initiative for Medicines, Access and Knowledge (I-MAK) believes that China’s decision rejecting Gilead Sciences’ patent application for sofosbuvir could buttress its Indian opposition case against the patent claim for the blockbuster hepatitis C therapy.

Hearings pertaining to the opposition against the sofosbuvir patent application by I-MAK and the Delhi Network of Positive People (DNP+) recently concluded at the Indian Patent office, though Gilead faces similar challenges in markets like Argentina, Brazil, Russia, Thailand and the EU. The hearing in Europe is expected later this year.

“We think the China decision, which was on the prodrug application, will be helpful in the India case. Gilead has asked for the rejected prodrug application in China to be re-examined,” Tahir Amin, I-MAK’s co-founder and director of intellectual property, told Scrip.

China’s State Intellectual Property Office (SIPO) last year turned down Gilead’s patent application for Sovaldi; I-MAK had opposed the China application.

Amin, though, said that Gilead’s primary patent for the sofosbuvir chemical substance in China stays unaffected, and won’t expire until 2024.

On French charity Médecins du Monde’s (MdM; Doctors of the World) opposition in Europe against one of the Sovaldi patents, Amin said that Gilead has sought an extension of time to respond and a hearing date has been set for October. I-MAK had collaborated with MdM’s patent attorney to write the dossier for the European opposition; the challenge in Europe was against the granted prodrug.

Gilead’s Position

While Gilead did not respond to specific queries pertaining to the sofosbuvir patent application in China, it reiterated that the India hearing related to the metabolite patent and that the main sofosbuvir patent is still pending in the country.

“We believe that innovation should be recognized and we strongly defend our intellectual property. These proceedings do not impact agreements with our licensed Indian manufacturing partners to enable access to low cost, high quality hepatitis C medicines in developing countries throughout the world,” Gilead told Scrip.

It declined further comment since its patent application remains pending before the Indian Patent Office.

I-MAK, however, claimed that the licensing deals are a way for Gilead to “control their competitors” in India, and are an attempt to persuade the patent office they deserve a patent for a compound that is based on old science.

“Gilead wants the world to think their licensing deals have solved the global problem of access to this medicine, but today countries like Thailand, Malaysia and Brazil are being asked to pay thousands of dollars for sofosbuvir from Gilead, when Indian generic versions of the drug are now available for as little as $335 per 12-week treatment,” Amin said.

 Médécins Sans Frontières (MSF) has supported I-MAK/DNP+’s efforts to ensure open generic production of sofosbuvir.

In September 2014, Gilead entered into licensing deals with seven India-based firms including Cipla, Zydus Cadila, Hetero, Strides, Ranbaxy and Mylan Labs to develop sofosbuvir and the single tablet regimen of ledipasvir/sofosbuvir for distribution in 91 developing countries. Several of these firms have since launched sofosbuvir in India.

India Case

The Indian sofosbuvir patent case has, however, seen some twists, thus far.

Amin said that the access groups’ key arguments in the current Indian case were that the invention claimed by Gilead/Pharmasset which covers the base compound in sofosbuvir lacks novelty and was anticipated by earlier compounds in the art, and is obvious.

I-MAK also believes that sofosbuvir does not meet India’s Section 3d “efficacy standard” given the base compound is a derivative of the earlier known compounds and has no antiviral (therapeutic) activity in and of itself.

Section 3(d) of India’s patent regulation broadly deals with incremental inventions that are not patentable unless they show improved efficacy or unless a known process results in a new product or employs at least one new reactant.

The Indian hearing comes after a previously rejected sofosbuvir patent application covering its metabolites had been remanded by the Delhi High Court for a fresh decision by the Patent Office.

The court last year set aside the rejection of Gilead’s patent application and referred to some seemingly embarrassing observations on how the patent office may have been potentially “influenced” by material placed on record by pre-grant opposition applicants.
The Sting Of The Scorpion

In Aesop’s fable of the scorpion and the frog, a scorpion convinces a frog to carry it across a stream on its back with the protection that if the scorpion stings the frog, both will drown. After being stung by the scorpion half way across, as both are sinking the frog asks the scorpion, “why?” The scorpion answers, “I had no choice, it’s in my nature.”

The return from medical leave of the CEO of Valeant Pharmaceuticals International Inc. and the withdrawal of the company’s 2016 financial guidance may not have been causal but the 12% drop in its share price at the start of last week was hardly the ringing endorsement that either the company or the CEO would have hoped for. We are now three weeks into the re-basing of the expectations of analysts whose recommendations and share price targets have been left exposed as unrealistic by the reduced appetite for the sector by investors. Although the analysts from Jefferies, Canaccord, TD Securities, Wells Fargo and BMO Capital Markets last week rushed to reduce either their price targets or recommendations for Valeant after the event, while Deutsche Bank’s suspended their coverage altogether, those from JP Morgan, Nomura and Rodman & Renshaw kept their ‘buy’ or ‘outperform’ recommendations with share price targets ranging from $106 to $175. The share price of Valeant finished last week just over $61.

Among the swords still hanging over Valeant’s head is its $31bn debt pile. Will it be able to service and repay that debt, and also to keep in compliance with the legal covenants under which the money was lent? Even if Valeant does not borrow more, its interest cover ratio will go down and its debt to EBITDA ratio will go up as its profits decline. The withdrawal of its 2016 guidance should have been an indication that whatever the analysts had projected for Valeant’s profit in 2016, that figure might need to be drastically reduced. The reason why no fund that I have ever managed has invested in Valeant is because I could never understand how a company that sold unexciting branded primary care products, whose only differentiation from generic competition was the spend on sales and marketing, could show quarter-on-quarter sales increases.

As all this pricing pressure impacts Valeant’s sales and therefore earnings, it is not surprising that its previous guidance needed to be withdrawn. Furthermore, as Valeant’s earnings (denominator) in the debt covenant ratios moved closer to a breach, its debt came under review by the credit rating agencies last week and its business practices investigated by the SEC. What is surprising is that any investment bank analyst could recommend Valeant as a ‘buy’ to any client. It is, however, not in the nature of investment bank analysts to inform their clients of impending disasters at companies in which they hold shares until after well the disasters have transpired.

One analyst from Numis Securities, whom I regard very highly because, like me, he started as a scientist and still uses that training and experience in his analysis, tried to prepare the market for an impending failure last week by initiating coverage of GW Pharmaceuticals Plc, with a ‘sell’ recommendation. This is quite rare despite GW Pharma having a long history of bringing to the market commercially unsuccessful cannabis-based products that subsequently fail in label expansion studies. GW Pharma successfully completed a NASDAQ IPO and secondary fundraisings after the investment banks supporting its public stock offerings glossed over its past failures and painted a rosy picture of its likely future success. The analysts at Cowen, Piper Jaffray and Leerink Partners recommend GW Pharma to their clients at ‘outperform’ and ‘overweight’ recommendations, although the analysts at Piper Jaffray at least mention the historical placebo effect that has clouded the investment case for GW Pharma’s next product Epidiolex (cannabidiol) for the treatment of Dravet Syndrome. Those from Leerink Partners admit that a placebo effect ‘remains the wild card’ Numis’ ‘sell’ recommendation comprises a tiny proportion of all the analysts that cover GW Pharma. It is in the nature of investors to assume that every drug in every company in which they invest will be a success. It is in the nature of sell-side analysts to promote those assumptions until well after the product has failed.

When Madonna wrote “So tired of broken hearts and losing at this game” in 1989 she could easily have been writing about the effect that investment bank analyst research has on its clients. It is difficult for analysts and investors to look into the future and decide on the most likely outcomes for clinical trials, but, notwithstanding the siren call of the sell-side analysts, we should fight human nature that assumes almost universal success.

Andy Smith

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.

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The European Commission may not have much of a say in drug pricing matters beyond making sure member states meet the requirements of the price transparency directive, but it certainly makes no bones about encouraging countries to act more collaboratively in dealing with the high prices of some new medicines and thereby improving access.

Its efforts to date include the 2001 high-level group on innovation and the provision of medicines, a working group on pricing and reimbursement as part of the 2005 “Pharmaceutical Forum,” and, more recently, encouragement for the joint procurement of high-priced medicines by the member states.

It has also commissioned a number of reports on the perennial question of how to guarantee patients access to safe, effective and affordable medicines while encouraging innovation and ensuring the financial sustainability of healthcare systems. One of these, produced by the consultancy CreativCeutical in 2014, looked at the use of external reference pricing (ERP), where countries use price levels in a basket of other EU member states to determine prices domestically.

Now the commission has published another lengthy tome, this time on “Enhanced cross-country coordination in the area of pharmaceutical product pricing.” Produced by a consortium of the Austrian consultancy Gesundheit Österreich Forschungs- und Planung, SOGETI Luxembourg and the Austrian University for Health Sciences, Medical Informatics and Technology (UMIT), the 260-page report examines the potential role of both EPR and differential pricing (DP) in terms of various technical, economic and legal considerations.

It looks at the benefits of greater pricing policy coordination across the EU countries in the light of increasing financial pressures and the arrival of new and costly innovative drugs, how member states could improve their EPR schemes by conducting regular price revisions and considering statutory discounts, and how DP schemes might be designed for EU member states.

However, the extent of savings depends to a great deal on the methodology applied. The report said there were “lost opportunities” due to discounts, rebates and similar arrangements in the reference countries that are not considered in EPR, and that it might be possible to achieve major impacts on price reductions by referencing to discounted prices and performing regular EPR reviews.

Moreover, EPR as currently applied is likely to have a negative impact on patient access “since it incentivises the pharmaceutical industry to first launch in higher-priced countries and delay, and refrain from entering the market in lower-priced countries, and may also inhibit them from offering medicines at lower prices in lower-priced countries.”

The report proposes four ways of improving the way that EPR operates:

Using a central price database, such as Euripid (which is run by the member states). This has proven to be “extremely supportive” for competent authorities when they carry out technical work such as price surveys, validation and comparisons, the report says. “A current limitation to a European price database is the provision of undiscounted list price data only,” it notes. “The inclusion of discounted prices could significantly improve the relevance and quality of such a database.”

Lower prices could also be secured through EPR if price comparisons were done at the level of actual (discounted) prices paid by payers rather than list prices. For example, countries applying EPR could take into account statutory manufacturer discounts and similar arrangements in the reference countries where these are published. Higher savings might also be possible if member states shared information on confidential discounts, rebates and similar financial arrangements.

A third possibility would be to carry out regular price reviews, with subsequent price revisions; industry could also benefit if prices increases due to exchange rate fluctuations were considered. As the report says, there is “room for improvement since several member states do not seem to perform regular (i.e., bi-annually, annually or at other defined time intervals) price re-evaluations even if provided for in the legislation.”

EPR, though, has both advantages and drawbacks, the report says. A literature review conducted as part of the study suggests that EPR has “proven to be effective in generating, sometimes substantial, savings for public payers.”

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Lower prices could also be secured through EPR if price comparisons were done at the level of actual (discounted) prices paid by payers rather than list prices. For example, countries applying EPR could take into account statutory manufacturer discounts and similar arrangements in the reference countries where these are published. Higher savings might also be possible if member states shared information on confidential discounts, rebates and similar financial arrangements.

A third possibility would be to carry out regular price reviews, with subsequent price revisions; industry could also benefit if prices increases due to exchange rate fluctuations were considered. As the report says, there is “room for improvement since several member states do not seem to perform regular (i.e., bi-annually, annually or at other defined time intervals) price re-evaluations even if provided for in the legislation.”
Finally, countries could unilaterally adjust prices based on the reference countries' purchasing power parities rather than nominal exchange rates when performing EPR. “If several countries consider such changes, an exchange of information and best practice on criteria and methods for adjustment, which would support capacity building, is recommended,” the report suggests. “A multi-national agreement on adjusting formulae in a particular method would be similar to the implementation of differential pricing in Europe.”

**Differential pricing**

Differential pricing, as the report observes, is a strategy of charging different customers different prices for the same product. In this case, it is taken as an international government policy defining the prices of medicines according to ability to pay and/or the economic situation of the countries concerned. However, on the face of it, DP doesn’t seem ideally suited to the European situation and there is no real experience with it in high-income countries such as those in Europe.

Some experience with DP has been gained with drugs for specific indications like HIV/AIDS, TB, malaria and some vaccines, which were procured under DP by international agencies and programs for low- and middle-income countries, including least developed countries.

“Though the results are mixed, it was found that in some cases DP might have resulted in an improved access to medicines for low-income countries,” the report says. “In addition, there was some evidence that DP helped to reduce prices and thus made medicines more affordable. However, the entry of generic medicines into the market was seen to be more effective in driving prices down than DP.”

DP might in certain cases serve as a “second-best” policy option to ensure short-term access, particularly to new patented medicines, but it would need to be supported by other options such as generic competition, joint procurement, and voluntary and compulsory licensing.

However, “there is no experience with DP, as defined above, applied for high-income countries, such as European countries,” the report says. DP schemes would require “enormous political will” as well as agreement on principles and mechanisms by all the countries included, “which is a challenge and might not be politically feasible in the short term.” These mechanisms would involve a maximum or minimum entry price, and when designing such mechanisms, economic indicators, such as gross domestic product or purchasing power parities, would have to be taken into consideration.

If the DP approach were chosen, it would be advisable to start with a pilot project for one or just a few products, defined according to specific eligibility criteria (candidate medicines could include orphan medicinal products or other high-priced medicines, for instance). Such pilots could be run in cooperation with pharmaceutical companies, and “trust and better planning” between the parties could be ensured if both supply and purchase agreements were integrated into contracts for drugs procured under DP.

But EFPIA remains sceptical about the report’s proposals. It said it regretted the fact that the authors “did not appreciate the opportunity they had” to address some of the shortcomings of EPR. “The trade-off is between further using EPR for cost-containment purposes or decreasing patient access inequalities in Europe, knowing that if you further use EPR then patients in the EU are likely to suffer.” It also raised the question of the role of value-based pricing and health technology assessments where EPR is being used. It said it believed that the solution lay elsewhere than with EPR.

ian.schofield@informa.com

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Policy & Regulation Briefs

**Califf Confronts Opioids Challenge**

At his first report as commissioner to the FDA’s Science Board on March 1, Robert Califf has decided to focus on the scourge of opioid addiction in the US and the challenges the agency is up against in that spotlight of approving new pain management medicines. In a notice posted on the FDA’s website, the agency said it was “deeply concerned” about the growing epidemic of opioid abuse, dependence and overdose in the US and plans to ask its Science Board to spend the full day discussing the matter — an unusual move, given the panel of advisers usually hears from top regulators on multiple topics at the meetings. Regulators pointed out the FDA recently unveiled a new action plan aimed at overhauling the agency’s policies on opioids with the intent of “reversing the epidemic, while still providing patients in pain access to effective relief.” But that plan fell short of what a handful of lawmakers have called for from the FDA in reforming the way it reviews and approves opioids. Sens. Ed Markey (D-MA) and Joe Manchin (D-WV), who tried, but failed, to hold up Califf’s nomination, have blamed the FDA for playing a role in the explosion in the misuse, abuse and addiction to prescription opioids in the US.

**Fight’s On For $50bn FDA/NIH ‘Innovation’ Fund**

Unwilling to wait to fight it out on the Senate floor to figure out how much to put into a Republican-proposed pot of money to help support high-priority biomedical research and development projects, like President Barack Obama’s Precision Medicine, BRAIN and Cancer Moon Shot initiatives, Democrats in the chamber’s Health, Education, Labor and Pensions (HELP) Committee on March 3 introduced their own plan — proposing that $50bn over the next 10 years be added to the budgets of the FDA and the National Institutes of Health (NIH). Sens. Patty Murray (D-WA), ranking member on the HELP Committee, and Elizabeth Warren (D-MA) introduced the National Biomedical Research Act, which would establish the “Biomedical Innovation Fund,” in which Congress would appropriate $5bn each year through 2025 to be used for “select” initiatives at the NIH and the FDA. Like the plan proposed by Sen. Lamar Alexander (R-TN), the chair of the HELP; the Democrats said their fund would help supplement the appropriated dollars for the Precision Medicine, Cancer Moon Shot and BRAIN — Brain Research through Advancing Innovative Neurotechnologies — initiatives, plus other projects. Murray and Warren, who were joined by all of the other eight Democratic members on the HELP panel in sponsoring the bill, said the funding boost would help restore the NIH’s budget back to the levels it was used to a decade ago, before its funding went flat each year. The NIH, however, did get a $2bn boost for fiscal year 2016, which has allowed it to move forward with its precision medicine projects. And indeed, the White House wasted no time in unveiling new actions under the initiative on Feb. 25.

**Priority Generic Reviews, Vouchers: Price-Hike Remedy?**

Priority reviews for certain generic medicines and a new voucher program for those drugs could help remedy the problem of extreme price hikes of some older products, two lawmakers said in introducing new legislation. Under the Increasing Competition in Pharmaceuticals Act, introduced by Sens. Susan Collins (R-ME), chair of the Senate Aging Committee, and Claire McCaskill (D-MO), the ranking member, the FDA would be required to fast-track the review of abbreviated new drug applications (ANDAs) for generics in which there is a shortage of the medicines or there’s only one supplier of a product and act on the ANDA within 150 calendar days. In addition, the FDA would be required to establish a new generic priority review voucher (PRV), which would be awarded to manufacturers with successful ANDAs involving a medicine that was on the agency’s drug shortage list or provided competition against sole-source products. The vouchers would be used to expedite the review of another ANDA.
**Late-stage clinical developments for the week 26 February–3 March 2016**

<table>
<thead>
<tr>
<th>Lead Company</th>
<th>Partner Company</th>
<th>Drug</th>
<th>Indication</th>
<th>Market</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>REGULATORY APPROVAL</strong></td>
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<tr>
<td>Gilead Sciences, Inc.</td>
<td>Johnson &amp; Johnson</td>
<td>Odefsey (emtricitabine 200 mg/rilpivirine 25 mg/ tenofovir alafenamide 25 mg or R/F/TAF)</td>
<td>HIV / AIDS</td>
<td>US</td>
<td>The FDA has approved Odefsey for the treatment of HIV-1 infection in certain patients. Emtricitabine and tenofovir alafenamide are from Gilead and rilpivirine is from Janssen.</td>
</tr>
<tr>
<td>Novartis AG</td>
<td>–</td>
<td>tetracaine hydrochloride opthalmic solution 0.5% SUSTAINED-RELENT</td>
<td>anesthesia</td>
<td>US</td>
<td>For use in procedures requiring a rapid and short-acting topical ophthalmic anesthetic.</td>
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<tr>
<td>Takeda Pharmaceutical Company Ltd</td>
<td>Otsuka</td>
<td>Vonoopin (Takecab (vonoprazan fumarate), Amolin (amoxicillin) and Fragile (metronidazole) tablet)</td>
<td>H. pylori eradication</td>
<td>Japan</td>
<td>Takeda has obtained approval from the MHLW for and Vonopion pack for H. pylori eradication. Vonopin is a triple-drug blister pack containing Takecab, Amolin and Fragile tablet (metronidazole) for secondary eradication of H. pylori.</td>
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<tr>
<td>Takeda Pharmaceutical Company Ltd</td>
<td>Otsuka</td>
<td>Vonoap (Takecab (vonoprazan fumarate), Amolin (amoxicillin) and Clarith (clarithromycin))</td>
<td>H. pylori eradication</td>
<td>Japan</td>
<td>Vonoap pack 400 and Vonoap pack 800 is a triple-drug blister pack combining the acid suppressant Takecab tablet, Amolin capsule and Clarith tablet for primary eradication of H. pylori.</td>
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<td><strong>SUPPLEMENTAL REGULATORY APPROVAL</strong></td>
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<tr>
<td>Otsuka Holdings Co., Ltd.</td>
<td>–</td>
<td>Abilify Maintena (aripiprazole once-monthly)</td>
<td>schizophrenia</td>
<td>Japan</td>
<td>For administration at the deltoid muscle site. Henceforth, it will be possible to administer treatment in an intramuscular area of the upper arm, the deltoid triangular muscle. This becomes an alternative injection site to the conventional intramuscular administration in the buttocks.</td>
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<tr>
<td>Astellas Pharma, Inc.</td>
<td>–</td>
<td>Kiklin (bexalomer)</td>
<td>hyperphosphatemia</td>
<td>Japan</td>
<td>The label has been expanded to say the treatment of hyperphosphatemia in patients with chronic kidney disease, rather than treatment of hyperphosphatemia in patients on dialysis with chronic kidney disease.</td>
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<tr>
<td>Bristol-Myers Squibb Company</td>
<td>Otsuka</td>
<td>Opdsvo (nivolubmab) Intravenous Infusion 20mg, 100mg</td>
<td>melanoma</td>
<td>Japan</td>
<td>The approval allows Opdsv to be given in patients who have not been previously treated with chemotherapy at the dosage and administration of 3 mg/kg every 2 weeks as an iv infusion.</td>
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<tr>
<td>Eisai Co., Ltd.</td>
<td>–</td>
<td>Halaven (eribulin mesylate)</td>
<td>sarcoma</td>
<td>Japan</td>
<td>Eisai has received approval in Japan as a treatment of patients with soft tissue sarcoma.</td>
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<tr>
<td>UCB SA</td>
<td>Otsuka</td>
<td>Keppra IR (levetiracetam immediate release)</td>
<td>epilepsy</td>
<td>Japan</td>
<td>For an additional indication as adjunctive therapy with other anti-epileptic drugs for generalized tonic-clonic seizures in adult patients and pediatric patients aged four years and over with epilepsy showing inadequate responses to other anti-epileptic drugs.</td>
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<tr>
<td>Bristol-Myers Squibb Company</td>
<td>Otsuka</td>
<td>Oncia (abatacept)</td>
<td>rheumatoid arthritis (RA)</td>
<td>Japan</td>
<td>Bristol-Myers and Ono Pharmaceutical have received the manufacturing and marketing approval of Oncia Subcutaneous Injection 125 mg Auto-injector 1 ml for RA. This approval allows Oncia to make the new formulation of subcutaneous auto-injector available, in addition to the existing formulation of intravenous infusion and subcutaneous injection syringe.</td>
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<tr>
<td>Gilead Sciences, Inc.</td>
<td>–</td>
<td>Truvada (emtricitabine 200mg/tenofovir disoproxil fumarate 300mg)</td>
<td>HIV prevention</td>
<td>Canada</td>
<td>Gilead Sciences Canada announced that Health Canada has issued a Notice of Compliance for once-daily oral Truvada in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 in adults at high risk, a strategy known as pre-exposure prophylaxis, or PrEP.</td>
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<tr>
<td>Novartis AG (NVS)</td>
<td>–</td>
<td>Affinitor (everolimus) tablets</td>
<td>neuroendocrine tumors</td>
<td>US</td>
<td>For the treatment of adult patients with progressive, well-differentiated, nonfunctional neuroendocrine tumors of gastrointestinal or lung origin that are unselectable, locally advanced or metastatic.</td>
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<tr>
<td>Roche Holding AG</td>
<td>–</td>
<td>Gazyva (obinutuzumab)</td>
<td>indolent non-Hodgkin’s lymphoma (NHL)</td>
<td>US</td>
<td>For Gazyva plus bendamustine chemotherapy followed by Gazyva alone for follicular lymphoma in patients who did not respond to a rituximab-containing regimen, or whose follicular lymphoma returned after such treatment.</td>
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<td><strong>REGULATORY FILING ACCEPTED</strong></td>
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<tr>
<td>Egylet Corporation</td>
<td>–</td>
<td>Arymo ER (morphine sulfate)</td>
<td>moderate to severe pain</td>
<td>US</td>
<td>For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The PDUFA goal date for a decision is Oct. 14, 2016.</td>
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<tr>
<td>AbbVie Inc.</td>
<td>–</td>
<td>venetoclax</td>
<td>chronic lymphocytic leukemia (CLL)</td>
<td>Canada</td>
<td>For the treatment of patients with CLL who have received at least one prior therapy, including patients with 17p deletion.</td>
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<td><strong>SUPPLEMENTAL REGULATORY FILING ACCEPTED</strong></td>
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<tr>
<td>Roche Holding AG</td>
<td>–</td>
<td>Xolair (omalizumab)</td>
<td>asthma</td>
<td>US</td>
<td>The FDA will review Xolair in children from six through 11 years for moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids.</td>
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<td><strong>ORPHAN DRUG DESIGNATION</strong></td>
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<td>AbbVie Inc.</td>
<td>–</td>
<td>Technivie tablets (ombitasvir, paritaprevir and ritonavir)</td>
<td>hepatitis C (HCV)</td>
<td>US</td>
<td>For the treatment of pediatric patients with chronic hepatitis C virus infection.</td>
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<tr>
<td>Company</td>
<td>Product</td>
<td>Indication</td>
<td>Region</td>
<td>Status</td>
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<tr>
<td>AbbVie Inc.</td>
<td>Venetoclax</td>
<td>Acute myelogenous leukemia</td>
<td>EU</td>
<td>For the treatment of acute myeloid leukemia.</td>
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<tr>
<td>Takeda Pharmaceutical Company Ltd</td>
<td>Nilotinib (ixazomib)</td>
<td>Multiple myeloma</td>
<td>Japan</td>
<td>For the treatment of patients with relapsed and/or refractory multiple myeloma.</td>
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<td><strong>FAST-TRACK STATUS</strong></td>
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<tr>
<td>ILJIN Group</td>
<td>Aurinia</td>
<td>Luveniq (voclosporin)</td>
<td>US</td>
<td>Aurinia Pharmaceuticals announced that the FDA has granted Fast Track designation for voclosporin, it next-generation calcineurin inhibitor, for the treatment of lupus nephritis.</td>
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<td><strong>CHMP POSITIVE OPINION ON FIRST APPROVAL</strong></td>
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<tr>
<td>AbbVie Inc.</td>
<td>Vekirex (ombitasvir/paritaprevir/ritonavir tablets) + Exviera (dasabuvir tablets)</td>
<td>Hepatitis C</td>
<td>EU</td>
<td>For the use of Vekirex + Exviera without ribavirin in chronic hepatitis C virus-infected genotype 1b patients with compensated cirrhosis (Child-Pugh A).</td>
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<tr>
<td>Biogen, Inc.</td>
<td>Alprolix (rFIXFc)</td>
<td>Hemophilia B</td>
<td>EU</td>
<td>For the use of Alprolix (rFIXFc), a recombinant Factor IX Fc fusion protein therapy, for the treatment and prophylaxis of bleeding in patients with hemophilia B (congenital Factor IX deficiency).</td>
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<tr>
<td>CSL Limited</td>
<td>Idelvion (albutreponacog alfa)</td>
<td>Hemophilia B</td>
<td>EU</td>
<td>For the treatment and prophylaxis of bleeding in patients with hemophilia B. Idelvion was designated as an orphan medicinal product on Feb. 4, 2010.</td>
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<tr>
<td>Eli Lilly &amp; Company</td>
<td>Taltz (teikizumab)</td>
<td>Psoriasis</td>
<td>EU</td>
<td>For the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy. Taltz will be available as a 80 mg solution for injection.</td>
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<tr>
<td>Gilead Sciences, Inc.</td>
<td>Descovy (emtricitabine and tenofovir alafenamide)</td>
<td>HIV / AIDS</td>
<td>EU</td>
<td>A fixed-dose combination for the treatment of HIV-1 infection in adults and adolescents (ages 12 years and older with body weight at least 35 kg) in combination with other HIV antiretroviral agents.</td>
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<tr>
<td>Otsuka Holdings Co., Ltd.</td>
<td>Lonsurf (tivozanib)</td>
<td>Rectal cancer</td>
<td>EU</td>
<td>For adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.</td>
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<td><strong>REGULATORY FILING</strong></td>
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<tr>
<td>Baxalta Incorporated</td>
<td>Adynovate (antithemophilic Factor (Recombinant), PEGylated)</td>
<td>Hemophilia A</td>
<td>EU and Canada</td>
<td>For use in pediatric, adolescent and adult patients with hemophilia A and for use during surgery.</td>
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<tr>
<td>TiGenix NV</td>
<td>Cel601</td>
<td>Crohn’s disease</td>
<td>EU</td>
<td>For the treatment of complex perianal fistulas in adult patients with Crohn’s disease.</td>
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<tr>
<td>AVEO Pharmaceuticals, Inc.</td>
<td>Tivopath (tivozanib)</td>
<td>Renal cell cancer</td>
<td>EU and Russia</td>
<td>For the first-line treatment of advanced renal cell carcinoma.</td>
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<td><strong>SUPPLEMENTAL REGULATORY FILING</strong></td>
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<tr>
<td>Amgen, Inc.</td>
<td>Blincyto (blinatumomab)</td>
<td>Acute lymphocytic leukemia (ALL)</td>
<td>US</td>
<td>To include new data supporting the treatment of pediatric and adolescent patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory B-cell precursor ALL.</td>
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<tr>
<td>Roche Holding AG</td>
<td>Xeloda (capecitabine)</td>
<td>Colorectal cancer (CRC)</td>
<td>Japan</td>
<td>For the additional indication of “adjuvant chemotherapy for rectal cancer.”</td>
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<tr>
<td>Merck &amp; Co., Inc.</td>
<td>Keytruda (pembrolizumab)</td>
<td>Non-small cell lung cancer (NSCLC)</td>
<td>Japan</td>
<td>A manufacturing and marketing approval application has been filed for pembrolizumab in the treatment of unrectsectable advanced NSCLC.</td>
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<td><strong>PRIORITY REVIEW</strong></td>
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<tr>
<td><strong>SPECIAL PROTOCOL ASSESSMENT AGREEMENT</strong></td>
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<tr>
<td>CoLucid Pharmaceuticals, Inc.</td>
<td>Lasmidtitan</td>
<td>Migraine</td>
<td>US</td>
<td>Colucid has received a Special Protocol Agreement for its second pivotal Phase III clinical trial of lasmidtitan for migraineurs called SPARTAN, with the US FDA. SPARTAN is scheduled to commence in the 1H 2016.</td>
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<tr>
<td><strong>SPECIAL PROTOCOL ASSESSMENT FILING</strong></td>
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<tr>
<td>Cellectux Corporation</td>
<td>Brilacidin</td>
<td>Skin and skin-structure infections</td>
<td>US</td>
<td>For a Phase III clinical trial of its novel single-dose antibiotic, brilacidin, for the treatment of acute bacterial skin and skin structure infection (ABSSSI) caused by Gram-positive bacteria, including meticillin-resistant Staphylococcus aureus.</td>
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<td><strong>PRODUCT LAUNCH</strong></td>
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<td>Otonomy, Inc.</td>
<td>Otiprim (ciprofloxacin otic suspension)</td>
<td>Ear infections</td>
<td>US</td>
<td>Otiprim was approved by the US FDA in December 2015 for the treatment of pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement.</td>
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<td>Neurim Pharmaceuticals Ltd.</td>
<td>Orlogin (prolonged-release melatonin)</td>
<td>Insomnia</td>
<td>Argentina</td>
<td>Neurim announced that Circadin 2 mg is now commercially available in Argentina.</td>
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<td>Newron Pharmaceuticals SpA</td>
<td>Zadago (safinamide)</td>
<td>Parkinson’s disease</td>
<td>EU</td>
<td>Zambon and its partner Neuron announced the launch and reimbursement of Xadago in Italy for the treatment of mid- to late-stage Parkinson’s disease (PD). Following the launch in Switzerland, Germany and Spain, Xadago is now available in Italy as add-on therapy to a stable dose of levodopa (l-dopa) alone or in combination with other PD therapies for mid-to late-stage fluctuating patients.</td>
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Martin Golden has been appointed Astellas Pharma Inc.’s senior vice president and head of marketing strategy and Frank Hudson has been promoted to senior vice president and head of budget and control, medical and development. In addition to this, Walt Johnston, Mark Reisenauer and Kenton Stewart have been promoted to senior vice presidents, with responsibility for commercial activities in the US in urology and hospital, oncology and hospital and health systems, respectively. Having previously held leadership roles at Novartis AG, Johnson & Johnson and Bristol-Myers Squibb, Golden has been vice president government affairs for Astellas US since 2014. Meanwhile, Hudson previously held financial leadership roles at Agensys, MannKind Corporation and GlaxoSmithKline plc. Johnston has been with Astellas since 2008 and most recently was vice president of US marketing and strategic new product planning and prior to this, he was at Pfizer Inc. Before Astellas, Reisenauer held various roles at Abbott, Pharmacia, Bristol-Myers Squibb and AstraZeneca plc. Stewart has held a range of leadership roles at Astellas and most recently was responsible for US health systems.

Regeneron Pharmaceutical, Inc. has appointed David Weinreich senior vice president late stage clinical development and medical affairs. With over 15 years’ experience, Weinreich was previously senior vice president and head of global development for specialty medicine at Bayer Pharmaceuticals. Prior to this, he held various senior roles at Amgen in the oncology and development organization.

Cypralis Ltd. has appointed as chief scientific officer Michael Peel, who joins the company from Scynexis Inc, where he was director of discovery. Peel has also led research projects in inflammation, cancer and virology at Glaxo Inc. in Research Triangle Park, North Carolina.

Arsanis, Inc. has appointed Michael P. Gray chief financial officer (CFO) and chief business officer (CBO). He joins the company from Curis, Inc. where he held various leadership positions including CFO, chief business officer and chief operating officer. Prior to Curis, Gray was controller and de Facto CFO of Reprogenesis, and an audit professional for Ernst & Young, LLP.

Paratek Pharmaceuticals, Inc. has appointed Kris Peterson to its board of directors. Peterson has over 30 years’ experience and joins Paratek from Valentera, Inc. where she was CEO. Previously she was company group chair for Johnson & Johnson’s biotech sector and during her time at the company, she was also executive vice president, global marketing and pharmaceuticals. Peterson has also held senior leadership positions at Biovial Corporation and Bristol Myers Squibb in marketing, sales and general management.

Astellas Pharma Europe Ltd., a subsidiary of Astellas Pharma Inc., has appointed current senior vice president, head of marketing strategy, Yukio Matsui, president of EMEA Operations – effective April 1, 2016.

Arvinas LLC. has named Angela Shen chief medical officer, she previously worked with Novartis Oncology as a global clinical program head and helped launch the CTL019 (CART-19) cell & gene therapy program. Shen was clinical lead at Novartis for the development of new oncology assets and also held a medical affairs role at Johnson & Johnson.

Kuros Bioscience, Ltd. has appointed Virginia Jamieson chief medical officer (CMO) and member of the executive board – effective immediately. Jamieson previously worked for the company from 2005 to 2012 as medical director.

Scholar Rock has appointed Yung H. Chyung chief medical officer; he previously held leadership roles at Dyax Corp. and Genzyme Corporation. Most recently he was vice president of medical research at Dyax Corp and prior to this, he was responsible for medical affairs globally at Genzyme Corporation.

The UK organization Cell and Gene Therapy Catapult has appointed new non-executive directors Fiona Watt, Susan Foden and Steven Chatfield to its board. Watt has spent 20 years at the CRUK London Research Institute. Foden has been a non-executive director for various life science companies and currently holds non-executive positions at companies including Evgen Pharma plc., and British Technology Group. Chatfield brings over 35 years’ experience and previously held executive positions at the Health Protection Agency and Emergent BioSolutions.