MannKind Is Ok…Or So It Says

In a not-so-surprising move, Sanofi finally ended its distribution agreement with MannKind for the inhaled insulin Afrezza – a move that could mean a slow death for the biotech, despite its claims to the contrary.

The French pharma’s move to return rights to the drug should come as no shock to investors or anyone who watches the diabetes market – the product has only brought in about $5.6m over the first nine months of 2015.

The biotech announced Sanofi’s decision before the market opened on Jan. 5, prompting the stock to drop 48.4%, or 70 cents, to close at 75 cents per share. According to the statement from MannKind, Sanofi will work to transition the drug back over the next six months or by July 4 at the latest. MannKind said during a conference call with analysts on Jan. 5 that it “is still optimistic about the prospects of Afrezza… despite the troubles it experienced in 2015.”

The company intends to pursue “a new approach” and try new pricing strategies for the product. MannKind CFO Matthew Pfeffer explained that this is “not the end of Afrezza or MannKind.” He noted that the company still has $60m in cash on hand.

The company’s CEO did not join the conference call and did not take questions from analysts and social media quickly began to buzz with skepticism about prospects for the company’s future. The firm subsequently revealed that its new CEO Duane Sisto would no longer join because of a non-compete clause with his previous

Volatile Valeant Substitutes Schiller For Ailing CEO

With investors growing increasingly edgy over the lingering absence of Valeant Pharmaceuticals International Inc’s ailing chair and CEO Michael Pearson – whose hospitalization late last month due to severe pneumonia came in the midst of the company’s struggle to rebuild its image after being mired in a scandal over its business practices – the firm’s board on Jan. 6 appointed former chief financial officer Howard Schiller to take the helm in the interim.

Investors were initially skittish on the news about Valeant’s move to substitute Schiller for Pearson – pushing shares of the company down 3.4% in morning trading on Jan. 6. But once they had a chance to mull it over, investors grew more comfortable with the idea – driving shares up about 5%, with the stock ending the day at $102.40, a gain of $1.54, or 1.53%.

Robert Ingram, lead independent director at Valeant, who also was appointed interim chair, said the timing of Pearson’s recovery and return “remains uncertain.”

The company has declined to provide any updates on Pearson’s condition – declaring
R&D Highlights Of 2015 – The Five Big Drug Stories Of The Year

2015 may have been the year when immune-oncology dominated the R&D headlines, but there were other products that caught Scrip's readers' interest during the 12 months for reasons both good and bad – here are five of the most-read topics.

**A Rare Alzheimer’s Success**

Something unusual happened in 2015: there was some good news for an Alzheimer’s drug in Phase III. Long-awaited results of Lilly’s solanezumab appeared to support the company’s hypothesis that it is effective in treating patients with mild Alzheimer’s disease and provided evidence that the biologic might be able to slow disease progression rather than just reduce Alzheimer’s symptoms. Solanezumab acts by clearing amyloid-beta proteins before amyloid plaques associated with Alzheimer’s disease build up in the brain.

The data were from a delayed-start analysis of patients in Lilly’s Phase III EXPEDITION and EXPEDITION2 clinical trials who were enrolled in the EXPEDITION-EXT extension trial and were presented in July at the Alzheimer’s Association International Conference (AAIC) in Washington, DC. People with mild Alzheimer’s disease who were treated with solanezumab in the company’s first two Phase III studies and in the extension study had a 34% slowing in the rate of disease progression compared with patients who received a placebo in EXPEDITION and EXPEDITION2 and were treated with Lilly’s biologic in EXPEDITION-EXT.

Despite the initial mixed data from the original trials, Lilly moved forward with the ongoing Phase III EXPEDITION3 trial after the company noted a significant difference between mild and moderate patients in terms of cognitive effects of Alzheimer’s disease. A delayed-start analysis similar to the one used in the EXPEDITION-EXT extension study will be used in EXPEDITION3, which is expected to yield data late this year or in early 2017.

Industry is far more familiar with failure when it comes to Alzheimer’s disease, and the year did not disappoint in this respect. In September, another candidate hit a road block when the FDA instituted a clinical hold on Forum Pharmaceuticals Inc’s (formerly EnVivo) Phase III drug encenicline due to a number of reported adverse events. Forum would only reveal that there was “a small number of serious gastrointestinal events reported in the AD studies” that prompted the clinical hold. This product is an orally-active nicotinic acetylcholine alpha-7 receptor agonist, and is also in development for cognitive impairment in schizophrenia.

As is the way with an unmet medical need such as Alzheimer’s, potential breakthroughs even in mice make the headlines. In one such case, a drug that AstraZeneca had pursued as a treatment for cancer – only to see it fail in mid-stage development – provided new hope as a potential Alzheimer’s therapy. Yale University researchers, supported by a program from the National Institutes of Health (NIH), reported data for the Src tyrosine kinase inhibitor known as saracatinib (AZD0530), showing that it restored memory loss and reversed brain problems in mouse models of Alzheimer’s – results NIH Director Dr Francis Collins called “substantial.”

The EGA is hosting its 12th Legal Affairs Conference in Brussels which will encompass interactive discussion between leading industry experts, in-house counsels and European Commission officials on the latest legal and IP developments regarding generic and biosimilar medicines in Europe and worldwide.

Topics will include:

- High level discussion: today’s environment, the opportunities & challenges of tomorrow
- IP & Competition: how to stimulate growth
- Legal and IP considerations for regulatory and market dynamics
- Developments in IP for Biosimilars
- The industry’s international IP & legal perspective
- In-depth discussion on UPC

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Sprout Gets Flibanserin To Market

The progress of Sprout Pharmaceuticals Inc’s (now part of Valeant Pharmaceuticals International Inc) female sex pill Addyi (flibanserin) was keenly followed last year all the way to the US market. Rebounding from two previous knock-backs (once when it was submitted by the originator Boehringer Ingelheim in 2000, and again in 2013 when filed by Sprout after it bought the product from the German firm), it finally gained FDA approval in August. But the nod did not come without any restrictions, in deference to its previous regulatory difficulties, particularly surrounding its use with alcohol.

Specifically, Addyi is indicated as a once-daily treatment for premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not a co-existing medical or psychiatric condition, problems within the relationship or the effects of a medication or other drug substance.

Because of the drug’s serious risks of hypotension, or low blood pressure, and fainting, which get severely worse with alcohol use, the FDA imposed a strict risk evaluation and mitigation strategy (REMS) plan on Addyi, which includes elements to assure safe use – something a panel of the agency’s outside advisers insisted must be in place for the drug to be marketed in the US.

Addyi was launched in October, at a price comparable to male erectile dysfunction drugs, but with little fanfare and no DTC campaign (as yet), and attention has now turned to its market success: so far, sales have been disappointing, with only a couple of hundred prescriptions written.

Cardiovascular Firsts And Failures

The summer of 2015 saw the arrival of the first two PCSK9 inhibitors to market, as well as the first novel product for heart failure in decades, proving that the cardiovascular sector can still innovate.

Amgen’s Repatha (evolocumab) and Sanofi/ Regeneron’s Praluent (alirocumab) both reached the US and EU markets after a dizzying race. Then the action turned to both reached the US and EU markets after Sanofi/ Regeneron’s sector can still innovate.

In December Regeneron and Sanofi managed Medicaid plans – with the payer snubbing Repatha. But the previous month, the PBM CVS Health Corp. chose Repatha over Praluent for its commercial formularies.

Previously in October, the US’s largest PBM, Express Scripts Holding Co., announced it was putting both PCSK9s on its national preferred formulary and locking in reduced prices on Praluent.

Meanwhile, Novartis’s angiotensin receptor neprilysin inhibitor Entresto (valsartan/sacubitril) was approved first in July and gained an EU positive opinion in September to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure and reduced ejection fraction (HFrEF). The approvals were based on the results from the 8,442-patient PARADIGM-HF study, which was stopped early when it was shown sacubitril/valsartan significantly reduced the risk of cardiovascular death versus ACE-inhibitor enalapril.

Once again, its fate with payers is impacting the drug’s success. Early signs were disappointing: its US sales start was sluggish but Entresto is still widely tipped to become a multi-blockbuster.

There were major disappointments in the field; two in particular caught Scrip’s readers’ attention although neither was a major surprise.

Lilly’s CETP inhibitor evacetrapib was discontinued in October after an independent data safety monitoring board recommended that Lilly stop the Phase III ACCELERATE trial due to futility – meaning the 13,000-patient outcomes trial was not showing signs of efficacy at the interim analysis and was not worth continuing.

ACCELERATE was meant to have a final read out in mid-2016 and was trying to show that evacetrapib could decrease the likelihood of major cardiovascular events by raising good HDL cholesterol and decreasing the bad LDL cholesterol.

While trials of evacetrapib have been largely positive, the industry has been particularly wary of the HDL hypothesis because of the limited evidence in support, coupled with several high-profile failures, namely Prizer’s torcetrapib and Roche’s dalcetrapib. Once considered the next big thing in cholesterol, the CETP mantle now rests on Merck & Co’s anacetrapib, the Phase III REVEAL trial of which did at least pass a futility test in November.

GlaxoSmithKline also failed in its bet on the novel anti-inflammatory losapimod, which in October failed to reduce major cardiac adverse events in heart attack patients in a Phase III study. An interim review of data from the first part of the LATITUDE-TIMI 60 study in 3,503 patients gave no sign of efficacy for the primary endpoint and so did not support investment in the larger part B of the study as currently designed, GSK said.

MS Advance And Retreat

Much excitement surrounded Roche AG’s ocrelizumab at the ECTRIMS conference in Barcelona in October when detailed clinical data were presented from three Phase III trials: OPERA I and II in relapsing-remitting multiple sclerosis (RRMS) patients and ORATORIO in primary progressive multiple sclerosis (PPMS) patients.

The CD20 antibody showed impressive efficacy across the entire pivotal clinical trial program, with the PPMS data most notable considering the absence of any approved treatment options in this patient population. With no safety signal yet emerging that might jeopardize its regulatory approval, ocrelizumab is expected to be a very competitive drug for RRMS patients, where it will predominantly target the 2bn market segment currently occupied by Biogen’s Tysabri (natalizumab). Furthermore, as the first effective drug for PPMS patients, ocrelizumab will provide true growth to the wider market and reinvigorate drug development for this underserved population.

New Migraine Battle Ground

Finally, Scrip readers were intrigued about a new front opening up in migraine prevention, with the advent of the calcitonin gene-related peptide (CGRP) antagonists.

New biologicals targeting the CGRP pathway could prove to be the biggest thing to hit the migraine market since the triptans in the 1990s, experts said, upon presentation of highly promising mid-stage data in June. Four antibody products from Amgen, Lilly, Teva and Alder Therapeutics are all either just entering or shortly to enter Phase III in episodic and chronic migraine patients.

CGRP is a potent neuropeptide thought to play a prominent role in the underlying pathophysiology of migraine and, by blocking CGRP, the products are thought to inhibit the transmission of the pain signals that lead to migraine headaches.

Further back, competition is also heating up in the small-molecule CGRP antagonist field, where delivery routes could be less invasive. In November, Teva teamed up with Heptares Therapeutics for its small-molecule product, while Allergan licensed two oral CGRP antagonists from Merck & Co earlier in the year.
Surprisingly, Fewer ‘Expedited’ Approvals In 2015

Even though the FDA’s Richard Pazdur and his Office of Hematology and Oncology Products appeared to be on fire in 2015 – approving many medicines well ahead of their Prescription Drug User Fee Act (PDUFA) action date – there were fewer applications for novel drugs and biologics overall cleared for marketing under the agency’s expedited pathways than a year earlier.

The FDA reported that of the new molecular entities (NMEs) and novel biologics approved by the Center for Drug Evaluation and Research (CDER) in 2015, only 31% had achieved fast-track status – a designation reserved for medicines aimed at treating unmet medical needs – versus 41% in 2014.

Products that received an accelerated approval – those based on markers that predict a reasonable benefit, with more testing required to confirm clinical benefit after entering the US market – fell from 20% in 2014 to 13% in 2015. And the number of applications approved last year for NMEs or novel biologics that gained a priority review – products deemed to potentially provide a significant advance over existing medical care – also dropped, falling from 61% in 2014 to 53% in 2015.

The FDA pointed out that new drugs OK’d in 2015 assigned priority review under CDER’s rare pediatric and neglected tropical diseases voucher programs were not included in last year’s figures. But the number of FDA breakthrough therapy designated NMEs or novel biologics that won approvals in 2015 remained steady at 22%, the same as in 2014. Nonetheless, the overall approvals of NMEs and new biologics under the expedited development and review methods were down from 66% in 2014 to 60% in 2015.

The FDA reported that it only missed its PDUFA goal dates in 2015 for two products out of the 45 NMEs and novel biologics CDER cleared – Alkermes PLC’s schizophrenia drug Aristada (aripiprazole lauroxil) and Retrophin Inc’s Cholbam (cholic acid), which was approved for bile acid synthesis disorders due to single enzyme defects, a group of highly symptomatic conditions that prevent the liver from properly producing bile acids that help the intestines absorb essential fats, vitamins and nutrients, and as an adjunct to standard care for peroxisomal disorders, including Zellweger spectrum disorders in patients with evidence of liver disease, based on improvements in liver function.

CDER also reported that 16 of the 45 NME and novel biologic approvals, or 36%, were considered first-in-class medicines – products whose mechanisms of action is different from those of existing therapies.

“This first-in-class approval rate is one factor that suggests the 2015 group of novel new approvals is a field comprised of many innovative products,” Janet Woodcock, CDER director, said in a memo posted on the FDA’s website.

Woodcock also pointed out that for the second consecutive year, CDER approved more orphan drugs for rare diseases – 21 of the 45 NMEs or novel biologics – than any previous year in the agency’s history.

John Jenkins, director of the FDA’s Office of New Drugs, emphasized in a blog on the agency’s website that 64% of CDER’s NME and novel biologic approvals were cleared in the US before any other country. The 45 CDER new drug and biologic approvals was the highest number since 1996, when 53 were approved.

Teva’s CNS Strategy Snagged By Safety Concerns

Teva Pharmaceutical Industries Ltd has placed many of its hopes for a future in the CNS space in the multiple sclerosis drug laquinimod, but recent setbacks due to safety issues raise questions about how realistic this future really is.

The Israeli company and its partner, Active Biotech, announced Jan. 4 that based on the recommendation of a data safety monitoring board (DSMB), the companies will discontinue the use of two higher doses of the multiple sclerosis drug laquinimod. The decision will affect two ongoing Phase III clinical trials.

The companies noted in a public statement that the DSMB revealed some concerns about cardiovascular risks for the drug that could be dose related – specifically the 1.2mg and 1.5mg doses. Eight patients across the two trials – CONCERTO and ARPEGGIO – experienced nonfatal myocardial infarction, while none of the placebo patients or patients taking the 0.6mg dose of the drug showed any cardiovascular safety signals.

CONCERTO is a late-stage trial in patients with relapsing-remitting MS with the goal of delaying disability. The trial includes 2,199 patients that were randomized to either placebo, 0.6mg of laquinimod or 1.2mg of laquinimod. ARPEGGIO is a trial of 191 patients with primary-progressive MS. Patients in the trial are being given a placebo, 0.6mg of laquinimod or 1.5mg of the drug.

Clinical trial sites have all been notified to discontinue drug in patients taking either the 1.2mg or 1.5mg doses. The trials will continue with the 0.6mg dose of the drug, but the DSMB recommended that patients be closely monitored for any cardiovascular risks. Laquinimod is a once-daily oral drug that Teva licensed from Active Biotech in June 2004 with a $5m upfront payment. The Israeli company has been responsible for all development costs and agreed to another $92m in milestone payments, as well as double-digit royalties should the drug reach the market. The companies filed for the approval of the drug in Europe previously; the CHMP rejected the drug in 2014. It is also being studied in Huntington’s disease.

While Evercore ISI analyst Umer Raffat points out in a Jan. 4 note that most investors have written off laquinimod as a future revenue contributor for Teva, but some analysts and, more importantly, the company have emphasized the drug as a cornerstone of its strategy in the central nervous system (CNS) space.

Teva relies heavily on revenue from its only specialty drug, the MS treatment Copaxone (glatiramer). While the drug has brought in more than $4bn annually, it now faces generic competition from Novartis’ Gilenya. Teva has been trying to combat a loss of revenue by converting patients to the 40mg dose of Copaxone that is taken three times per week, as opposed to the daily option. And while Copaxone faces headwinds, laquinimod is obviously not a slam dunk either. In the 2011 BRAVO study, laquinimod failed to show a statistically significant reduction in the rate of annualized relapses – a major focus of MS trials. The failure prompted Teva to switch endpoints to delay in disability and launch the two new Phase III trials that are currently ongoing.

Yet, as Raffat points out in his note, reducing the rate of relapses is something that two competing MS drugs – Biogen’s Tecfidera and Novartis’ Gilenya – are both able to do. Teva had been banking on a stronger efficacy profile from the higher dose. The recent safety concerns are definitely a setback for the program, but Raffat admits he can’t count out laquinimod yet. BioMedTracker analysts haven’t written off the drug either, estimating the likelihood of approval to be about 45%, about 7% lower than average.
To ensure prescribers and patients are informed a product is a biosimilar and not a brand-name biologic, and to protect against any inadvertent substitution of the two, the labeling for the copyleft medicines should clearly state they are indeed, biosimilars, the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Biotechnology Innovation Organization (BIO) said in a new petition to the FDA.

Instituting such a requirement also would promote consistency with domestic and international precedents, PhRMA and BIO said, urging the FDA to include such measures in its forthcoming draft guidance on biosimilar labeling – a document regulators had vowed early last year to produce before the end of 2015, which ended up being a pledge not kept.

PhRMA and BIO, which recently changed its name by replacing “Industry” with “Innovation,” called on the FDA to “promptly” issue that guidance – reflecting, of course, the two lobbying groups’ demands in the document.

“Release of a formal policy document on biosimilar labeling in accordance with good guidance practices will ensure that stakeholders receive notice and an opportunity to comment on FDA’s policies on this important topic before they are applied,” the two innovator trade organizations said.

Along with a statement of biosimilarity, PhRMA and BIO said the FDA should require biosimilar labeling to include a description of the nonclinical and clinical data supporting the product’s approval, a narrative of the basis for licensure of each indication and a statement about whether the agency made a determination of interchangeability with the referenced innovator medicine, including a result of that finding.

They suggested that when it comes to describing the data, biosimilar labeling should mimic that of Sandoz Inc’s recombinant human growth hormone Omnitrope (somatropin), which is not considered a biosimilar in the US, even though it is in Europe.

The Rationale
The industry trade groups noted that in a survey conducted by the Alliance for Safe Biologic Medicines (ASBM) – whose membership includes BIO, Amgen Inc. and Roche Holdings AG unit Genentech Inc., among others – 90% of prescribers said it was important labeling clearly indicates when a product is a biosimilar.

So far, the FDA has only approved one biosimilar – Sandoz’s Zaxio (filgrastim-sndz) – and there’s no sign anywhere in its labeling that it’s a biosimilar and not an innovator biologic, which has had much of the brand-name industry up in arms.

PhRMA and BIO argued that because the FDA’s regulations provide that a medicine’s prescribing information must contain “a summary of the essential scientific information needed for the safe and effective use of the drug,” they said biosimilar labeling should include a statement of biosimilarity.

Such a statement, they said, would accord with the principles underlying the FDA’s Transparency Initiative and with the approach adopted by health authorities in the European Union and Canada.

82% of doctors say it’s important for labeling to include analytical data to demonstrate a biosimilar’s analytical similarity to a reference product

Including the relevant nonclinical and clinical data supporting the finding of biosimilarity and identifying whether those studies were conducted with the innovator or the biosimilar version would ensure healthcare providers are fully informed when evaluating prescribing options and also could avoid misimpressions about the product studied in each trial, PhMRA and BIO insisted.

They again pointed to the ASBM survey – noting 82% of responding physicians deemed it important for labeling to include the analytical data developed to demonstrate a biosimilar’s analytical similarity to the reference product, while 83% also said it was important the labeling include the clinical data, if any, submitted to FDA to demonstrate the product is highly similar to the innovator drug.

PhRMA and BIO noted the ASBM survey also showed that 80% of those who responded said it was important for biosimilar labeling to clarify which indications were studied by the biosimilar manufacturer. And 79% of the doctors said it was important for the labeling to distinguish data generated by the biosimilar maker versus the reference product sponsor.

PhRMA and BIO argued a description of the nonclinical and clinical data supporting a biosimilar’s licensure is relevant because the FDA may approve different biosimilars on the basis of different information.

They pointed to Sandoz’s Omnitrope, which gained the FDA’s nod in 1987 as a follow-on protein product referenced on Pfizer Inc’s Genotropin under the 505(b)(2) pathway long before Congress passed the Biologics Price Competition and Innovation Act (BPCIA) – the law that gave US regulators the authority to approve biosimilars.

Omnitrope’s US labeling contains Pfizer’s clinical data, plus some from Sandoz.

PhRMA and BIO contended that Sandoz’s product distinguishes itself from Pfizer’s medicine because Omnitrope’s labeling refers to “another somatropin product,” although it doesn’t state the brand name Genotropin.

“Comparable approach is appropriate for biosimilars given their similarities to follow-on protein products approved under the federal Food, Drug & Cosmetic Act,” the industry organizations said.

They said that because Omnitrope and other somatropin products are subject to the BPCIA’s transition provisions, such follow-on products will eventually be subject to approval under the 351(k) biosimilars licensure pathway, “suggesting the approach for biosimilar labeling should accord with that applied to Omnitrope.”

Unless the FDA requires that biosimilar labeling clearly declares whether the product has been deemed – or not – to be interchangeable, prescribers will be confused about the medicines’ ability to be substituted for the referenced innovator product, PhRMA and BIO asserted.

They noted that 79% of the doctors who responded to the ASBM survey said it was important for biosimilar labeling to carry a statement about the product’s status of interchangeability.

Finally, PhRMA and BIO also insisted in their petition that it was essential that brand-name and biosimilar product makers timely update their labeling to reflect new safety and effectiveness information about the medicines observed in the postmarket environment.

AbbVie Inc., whose drug Humira (adalimumab) is being pursued as a biosimilar by Amgen, submitted a similar petition to the FDA in June.

The agency notified AbbVie this past December that regulators have not yet made a decision on the firm’s labeling petition “because it raises complex issues requiring extensive review and analysis by agency officials.”

AbbVie recently submitted another petition to the FDA calling for strict standards for interchangeability and insisting the agency must hold a hearing before issuing its guidance – another document regulators said they’d have out by the end of 2015, but failed to issue.
Enterome And Takeda To Jointly Mine The Microbiome

French company Enterome Bioscience S.A. has further expanded its credentials by inking an alliance with Japan’s Takeda Pharmaceutical Company Ltd. to research and develop novel therapeutics aimed at microbiome targets thought to play crucial roles in gastrointestinal (GI) disorders.

The pact, announced Jan. 6, aims to combine Paris-based Enterome technological expertise in microbiome science and Takeda’s global therapeutic drug discovery and development capabilities, Enterome’s CEO Pierre Bélichard said in a statement.

With Enterome, Takeda can ‘bring innovative therapies forward’

The biotech will use its proprietary metagenomic platform to support the discovery of potential small molecules or biologics derived from gut bacteria and then directed to the GI targets selected by the pair aimed at conditions such as ulcerative colitis and irritable bowel syndrome. Takeda has an option to license selected agents on an exclusive global basis and will be responsible for their regulatory and clinical development and eventual commercialization, the companies said.

Microbiome Mining A Growing Interest

A growing number of scientists – and investors - believe bacteria may be the source of an entire new generation of therapeutics. They’re looking at the trillions of mostly friendly microorganisms, including over 1,000 bacterial species, found in the human gut. The collective gene sequences of these bacteria, known as the microbiome, have generated reams of data on the huge role played by these bacteria and their by-products in health, as well as across a wide range of diseases.

These conditions aren’t limited to acute bacterial infections such as hospital-acquired Clostridium difficile, and include chronic conditions such as inflammatory and autoimmune diseases, diabetes, obesity, cardiovascular disease, and even neurological disorders – a far larger, more compelling commercial opportunity for investors, Shire Plc and France’s National Institute for Agricultural Research’s (INRA).

US-based AbbVie Inc. was sufficiently lured by Enterome’s platform to partner with the biotech in November 2014. The partners uncovered a biomarker for Crohn’s that provides a non-invasive means of evaluating disease activity. Enterome hopes AbbVie – which owns the IP on the biomarker – will license it, potentially for use as a companion diagnostic with blockbuster Humira (adalimumab), which faces biosimilar competition.

One year later, in November 2015, Enterome entered a collaboration with European cancer research institute Gustave Roussy to create a new generation of drugs and non-invasive monitoring tools using the gut microbiome in immuno-oncology. That alliance is also based around Enterome’s metagenomic technology platform which the parties hope will provide new ways to determine how effective cancer immunotherapies are and in identifying personalized ways to boost immune response against cancer tumors.

“Still a largely unexplored field, the gut microbiome offers numerous promising avenues for research that may soon lead to a shift to a new treatment paradigm in oncology,” Bélichard said at the time.

Afrezza’s flop underscores the problems with inhaled insulins as a category

Afrezza, an inhaled powder insulin, has a storied history. Most people bet against the drug from the start, but not Alfred Mann, the founder of the company, who put own more than $1bn of his own cash to move the product forward. Yet, Afrezza has been overshadowed. Pfizer had a similar product that it pulled from the market after only a few short months due to a failure to gain market traction. Pfizer later discovered that its inhaled insulin was linked to lung cancer. But living in the shadow of the Exubera failure wasn’t the only thing bringing down Afrezza, MannKind has gone back and forth with FDA regarding approval of the drug for almost a decade. After several rejections, it finally gained approval in June 2014 – the drug wasn’t launched until the start of 2015.

MannKind Is Ok… Or So It Says (Continued from page 1)

employer, and Pfeffer was given the post. MannKind had to borrow money from Sanofi when they signed the collaboration and has been reporting a loss on its quarterly calls. MannKind had $100m in debt that was due in August that it was unable to repay. Some of that debt has been converted to stock and some pushed out to a new deadline of 2018, but the company has been largely mum on how much is still owed.

Afreiţa’s flop underscores the problems with inhaled insulins as a category. The products required a massive push by marketers to educate physicians and patients and concerns about safety have always plagued the drugs. This is a hit for Sanofi as well. Long a leader in the diabetes space due to its insulin Lantus, Sanofi has been scrambling to hold onto its lead now that Lantus is being threatened by a highly crowded market and potential generic options. Sanofi has been trying to shore up revenues and pad its diabetes portfolio, even as warning investors that diabetes sales are going to lag.

In what many saw as a desperate move, Sanofi inked its deal with MannKind in August 2014, laying out $150m upfront and promising $775m in milestone payments should the drug hit certain sales goals. Obviously, Sanofi wasn’t as confident in the prospects for Afrezza as it claimed to be when it inked the deal – backloading the milestone payments to keep risk down.
Allergan’s New Buy Bolsters Blockbuster Botox

Allergan PLC will pay $90m up front to acquire the topical botulinum toxin maker Anterios Inc. in a move that may protect and improve the company’s position in aesthetic and therapeutic indications in which the blockbuster wrinkle-reducer and migraine-reliever Botox (onabotulinumtoxinA) is approved. The deal gives New York-based Anterios an immediate payment that’s almost $30m more than it sought in an initial public offering that was abandoned in May, while allowing the firm to keep the rights for an injectable botulinum toxin via a new entity called Eirion Therapeutics Inc. For Allergan, which expects to complete a $16bn merger with Pfizer Inc. this year, the transaction gives the company a topical botulinum toxin called ANT-1207 for patients who are asking for less invasive treatments. Allergan will pay, in addition to the upfront cost, undisclosed milestone fees related to the development and commercialization of ANT-1207 as well as the drug delivery platform called NDS that enables local, targeted delivery of neurotoxins through the skin without the need for an injection.

BMS Taps Oncodesign For Discovery

Bristol-Myers Squibb continues to strengthen its position in cancer research, this time with an early discovery collaboration with Dijon, France-based Oncodesign. The big pharma has agreed to pay $3m upfront, as well as $80m per target for Oncodesign to use its small macrocycles platform to develop drug candidates for oncology and potentially other therapeutic areas. Oncodesign is responsible for picking drug candidates, while BMS will be in charge of pre-clinical and clinical development. BMS will pay Oncodesign royalties on any products that result. The main component of the collaboration will be Oncodesign’s Nanocyclyx platform, which can increase the binding power and potency of small molecule drugs.

J&J Starts The Year With A Bang

Johnson & Johnson revealed 22 research collaborations and partnerships on Jan. 7, running the gambit across the company’s diversified business and highlighting its emphasis on tapping external sources for innovation. The deals are ones that culminated in late 2015 and early 2016 that the company chose to highlight ahead of the JP Morgan Healthcare conference from Jan. 11 to 14 in San Francisco, chief scientific officer and worldwide chair of pharmaceuticals Paul Stoffels said in an interview. “It is our strategy to collaborate externally, and we have many objectives, first of all getting the best minds in the world to advance health care, to advance therapies and products,” Stoffels said. Collaborating also allows J&J to improve its own internal research, he added. The 22 deals highlighted in the announcement include collaborations in pharmaceuticals, medical devices and consumer health care. Within the pharma space, many are early-stage discovery or preclinical partnerships with academia or with biotech companies facilitated by J&J’s Innovation Centers in London; Menlo Park, California; Boston and Shanghai. Stoffels said investors should expect many more such deals to follow.

Cell Therapy Catapult Launches New CAR-T Company

The Cell Therapy Catapult (CTC), a UK-based organization focused on growth of the UK cell and gene therapy sector, is teaming up with the University of Birmingham and Cancer Research UK to develop a new generation chimeric antigen receptor T-Cell (CAR-T) immune-oncology therapy for solid tumors. CTC will work with Cancer Research Technology, the commercialization arm of Cancer Research UK, and Dr. Steven Lee and Professor Roy Bicknell of the University of Birmingham under a newly launched company, to be called Chimeric Therapeutics Ltd. The new company will hold all future intellectual property rights to the resultant discoveries from the collaboration. CTC told Scrip the aim of the collaboration is to create an “investable proposition that will go on to attract further investment and ultimately create a commercial product.”

C4 Therapeutics In Roche Tie-Up

One of the decade’s largest series A financings for a biopharmaceutical start-up and a potentially lucrative collaboration with Roche mark the unveiling of C4 Therapeutics, which will work primarily with partners to develop what it calls Degronomids against targeted disease-causing proteins. Based in Cambridge, Mass., and working with research licensed exclusively from Dana-Farber Cancer Institute, C4 will perform initial preclinical development of Degronomids, novel chemical adapters that are conjugated with selective small-molecule therapeutics to naturally degrade targeted proteins via a cell’s ubiquitin/proteasome system. Upon completion of predefined preclinical work, Roche will hold the option to pursue further development and commercialization of the candidates. No specific financial terms were disclosed for the deal, announced Jan. 7, but C4 said it will receive an unspecified upfront payment and could earn development, regulatory, commercial and sales milestones and potential tiered sales royalties under the agreement. All told, the deal value could exceed $750m, the start-up said.

Millendo Raises $62m

Millendo Therapeutics raised $62m in a series B round led by New Enterprise Associates and the endocrine disorder-focused biotech firm licensed a polycystic ovary syndrome (PCOS) drug candidate from AstraZeneca PLC in a deal that will widen the company’s focus. Ann Arbor, Michigan-based Millendo, formerly known as Attercor, will have a broader focus on orphan and specialty endocrine diseases with the acquisition of AstraZeneca’s PCOS drug AZD4901 and funding from its series B round that was supported by Roche’s venture fund and other investors. Attercor got its start in 2012 with a $16m series A round to develop a treatment for adrenal cancer. That drug – ATR-101, a selective small molecule inhibitor of ACAT1 – is being evaluated in a Phase I dose escalation study for the treatment of adrenocortical carcinoma (ACC) and future studies are planned in the treatment of congenital adrenal hyperplasia (CAH) and endogenous Cushing’s syndrome.

Merck & Co Joins Up With Complix

Complix, a private Belgian biotech company developing novel protein therapeutics, has secured Merck & Co Inc. as its first big name pharma partner. Complix will use its “Alphabody” platform to deliver CPAbs (cell-penetrating Alphabodies) against two undisclosed intracellular cancer targets suggested by Merck. Merck will fund related research activities and has an option to the exclusive, worldwide rights for any of the resulting compounds. Complix will receive an upfront payment and potential development milestones of up to $280m, as well as tiered royalties. Dr Mark Vaeck, CEO of Complix, told Scrip the deal was a “major corporate milestone” for his company.

VC-Run Dementia Fund Plays It Safe With 1st Investment

The Dementia Discovery Fund, launched in October 2015 to much fanfare in the UK, has made its first investment in an established US biotech company – not quite the move UK scientists were hoping for. The DDF is joining a syndicate of venture capital investors in a $29.5m series D financing in Alector LLC which is using antibodies to target neurodegeneration. Six pharma companies (Biogen, GlaxoSmithKline plc, Johnson & Johnson, Eli Lilly & Co, Pfizer Inc. and Takeda Pharmaceutical Company), the UK government and the charity Alzheimer’s Research UK worked together to raise $100m in total in the first closing of the DDF. This “new” investment model would see pharma pool its expertise, experience, resources and knowledge of the space, but the fund itself would be managed by an experienced venture capital firm.

Almirall Aesthetics Takeover

Dermatology focused Almirall has announced that it will be exercising a call option to acquire 100% of aesthetics technology company ThermiGen LLC. Almirall plans to complete the acquisition by Jan. 31st 2016, with hopes to create a profile in the aesthetics market to strengthen its presence in derma. ThermiGen is a privately held company and a developer and manufacturer of thermistor-regulated energy systems for plastic surgery and aesthetics dermatology applications. In September last year, Almirall acquired a minority stake in ThermiGen for $5m and paid $2.5m in exchange for a call option right to acquire up to 100% of the company.
New Data Could Boost ‘Switching’ To Biosimilar Infliximab

New data that could help boost biosimilar infliximab uptake has been presented from “the largest real-world study to date” showing the effectiveness of the biosimilar infliximab Remsima in patients with inflammatory bowel diseases who have been switched from the reference product infliximab.

In Europe the uptake of biosimilar infliximab (versions of Janssen’s blockbuster Remicade) has been patchy to date. In some countries of northern Europe, notably Norway, Denmark and the Netherlands, the biosimilar has been embraced and is capturing a large part of the infliximab market.

However in other parts of Europe, such as the UK, biosimilar developers report frustration at the lack of movement from the branded product.

Biosimilar companies hope that as more switching data, and other types of data, become available, prescription habits in countries with poor uptake will change.

The latest data is from the PROSIT-BIO study conducted at 49 centers in Italy in patients with ulcerative colitis (UC) and Crohn’s disease (CD) and were presented at the Italian National Congress, Palermo, Italy.

The study of 397 patients (174 UC and 223 CD) demonstrated that those who were switched from reference infliximab to biosimilar infliximab (93 patients) demonstrated comparable efficacy to those patients receiving a biosimilar who had previously been naïve to anti-TNFα (217 patients) and to those receiving a biosimilar who had previously been exposed to one or more biologics (87 patients; response rate 95% vs. 92% vs. 91%, respectively). Safety was also found to be comparable across the patient groups.

Mundipharma (which did not sponsor the Italian study), via its network of independent associated companies, distributes Remsima on behalf of developer Celltrion Healthcare in Germany, Italy, UK, Netherlands, Belgium and Luxembourg. Hospira also distributes a biosimilar infliximab on behalf of Celltrion, called Inflectra. Pfizer and Samsung Bioepis are among other companies with advanced biosimilar infliximab programs in development.

Meanwhile, further switch data on Remsima are expected from the ‘Nor-Switch’ study funded by the Norwegian government, with data expected to be reported in 2016. Five hundred patients across all indications will be switched to Remsima from reference infliximab in this study, with occurrence of disease worsening as the primary endpoint.

In an exclusive interview with Scrip recently, Celltrion president and CEO Dr Stanley Hong said that the most important factor in encouraging biosimilar uptake is to “generate extrapolation data and switching data.” Extrapolation data are additional clinical data to support extrapolation to other indications.

Remsima has yet to be approved in the US, but Hong said, “My prediction is that market uptake in the US is going to be faster than any other territory.”

Volatile Valeant Substitutes Schiller For Ailing CEO (Continued from page 1)

it was being kept private per his family’s request. But there’s been some speculation Pearson may have experienced complications, given his extended hospitalization.

Valeant revealed Pearson’s medical leave of absence on Dec. 28, 2015. At that time, the company’s board, in an unusual move, had created an “Office of the Chief Executive Officer” consisting of three people – Robert Chai-Onn, general counsel; Ari Kellen, company group chair; and Robert Rosiello, chief financial officer – to serve in an interim capacity while Pearson was out. It also established a committee to oversee and support those executives.

Now, though, the board has decided it’s better to have one person in charge – calling on Schiller to fill Pearson’s shoes for the time being. Schiller had actually left the Canadian specialty pharma this past June after being CFO for more than three years, although he has continued to serve on the board. But analysts said Schiller’s tightness with Pearson and his 24 years of experience at investment banking company Goldman Sachs, where he previously served as the chief operating officer and also was responsible for the global healthcare, consumer products, retail, industrial and natural resource businesses, made him a good pick to lead Valeant.

Indeed, said UBS Securities analyst Marc Goodman, Schiller is the “best choice in a tough situation. From our many discussions with him, it was clear that he learned a great deal about running the operations’ from Pearson, Goodman said in a research note – pointing out that Schiller was at Valeant when it was going through its “significant growth period,” which was a result of many acquisitions, and he “understands the business very well.”

But while Schiller’s “certainly a capable executive,” Valeant currently is in an “all-hands-on-deck situation” following the scandal involving its sketchy relationship with specialty pharmacy Philidor Rx Services Inc, so the prolonged absence of Pearson – a very “hands-on CEO” – will make the firm’s recovery and ability to rebuild confidence with investors more difficult, insisted BMO Nesbitt Burns Inc. analyst Alex Arfaei.

Philidor has been accused of using “phantom” pharmacy accounts to mask the drug company’s price increases and circumvent the traditional insurance reimbursement process. Valeant also has been at the center of the current firestorm over high drug prices and is among the companies being investigated by lawmakers on Capitol Hill and federal prosecutors.

Aside from the current issues plaguing the company, Pearson also is viewed by investors as the “chief architect of Valeant’s strategy since he became CEO in 2008, and they attribute much of the company’s success since then to him personally,” BMO’s Arfaei argued.

But Bill Ackman, founder and CEO of hedge fund Pershing Square Capital Management, which holds an 8.5% stake in Valeant, said in a statement provided to Scrip he had “enormous confidence” in Schiller. “We think Howard will do an outstanding job,” Ackman said, adding that Ingram was a “superb choice” to fill in as chair because of his “deep industry knowledge, enormous integrity and credibility.”

This past October, Pearson said the “tumour” over Valeant’s practices of buying up companies with older drugs and raising their prices had driven the company to change its strategy to seek fewer transactions focused on what he called “mispriced products.”

Valeant officials then said the company expected to have low single-digit price increases for 2016 and beyond. They said while Valeant’s focus would remain on high-growth markets – therapeutics areas and geographies, durable assets, concentrated specialist populations, segments where physician education matters, consumer pay and commercial insurance reimbursement – pricing would become a less important part of the firm’s growth, while research and development activities, specifically with its dermatology, eye care and gastrointestinal businesses, would be broadened.
Amgen’s Biosimilar Injunction ‘Abuse Of Discretion’

A Florida district judge’s decision to grant a preliminary injunction (PI) to Amgen Inc. against Apotex Inc. preventing it from marketing its biosimilar of Neulasta (pegfilgrastim) was an “abuse of discretion” and amounts to a de facto 180-day extension of the 12-year exclusivity protection for innovator drugs provided by the Biologics Price Competition and Innovation Act (BPCIA), the latter company said in newly filed court documents.

In its opening brief filed with the US Court of Appeals to the Federal Circuit, Canada-based Apotex insisted the district court had no basis “in law or fact” to support its interpretation of the BPCIA and argued the decision to impose the PI should therefore be reversed.

The dispute centers on whether Apotex, which complied with the disclosure and negotiation procedures of the BPCIA – known commonly as the patent dance – and provided Amgen with the pegfilgrastim biosimilar application and manufacturing information, must also provide the innovator firm with at least 180 days notice before the date of first commercial marketing of the copycat product after the FDA licenses it.

The FDA has yet to approve Apotex’s 351(k) application for its pegfilgrastim biosimilar – a decision that was expected this past October and the status of which the company has kept mum.

But Apotex argued in earlier documents that no matter when the FDA acts on the application, the company would “suffer immediate harm” because it could not launch the product until 180 days later unless the Federal Circuit overturns the PI on the 351(k) application for the pegfilgrastim biosimilar, which is referenced on Amgen’s Neulasta, a long-acting human granulocyte colony-stimulating factor.

Judge James Cohn of the US District Court for the Southern District of Florida granted Amgen’s motion for the PI on Dec. 9, 2015.

Aptex immediately appealed – setting up a second fight over the BPCIA at the Federal Circuit.

In the first case that went before the Federal Circuit, which also was brought by Amgen – that time against Novartis AG unit Sandoz Inc. involving its biosimilar Zarxio (filgrastim-sndz), referenced on the California innovator’s Neupogen – a three-judge panel in July 2015 ruled 2-1 the patent dance was optional and biosimilar makers could choose not to disclose their application and manufacturing details. But 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 and Sandoz both had sought a rehearing of their arguments by the full Federal Circuit en banc, but on Oct. 16, 2015, the court denied the companies’ petitions. Late last month, Sandoz requested and obtained from the US Supreme Court an extension of the deadline from Jan. 14 to Feb. 16 to file a writ for certiorari, although the company is under no obligation to actually file it.

In the meantime, the Federal Circuit’s decision in Amgen v. Sandoz left open several questions – particularly, whether the 180-day notice of commercial marketing is mandatory when firms engage in the patent dance.

“This issue of first impression is of great importance not only to the parties here, but to the biopharmaceutical industry as a whole,” Apotex said in its brief, which was filed on Dec. 30, 2015, but was locked until Jan. 4.

Aptex received notice from FDA in December 2014 the agency had accepted the company’s pegfilgrastim biosimilar 351(k) and the firm provided Amgen the application two weeks later.

Under the BPCIA’s patent dispute-resolution provisions, Amgen in February 2015 provided Apotex a list of patents purporting a claim of infringement the innovator said could reasonably be asserted against the pegfilgrastim biosimilar. Then this past April, Apotex provided what it called a detailed statement to Amgen about each patent included in its list.

After some back-and-forth over two of Amgen’s patents – 784, which actually expired this past October, and ‘138, which Apotex asserted was “invalid” – the California biotech giant sued in August 2015.

Aptex sought an expedited review of its appeal of the Florida court’s PI, which the Federal Circuit granted, but only in part – setting deadlines a little later than the company had sought, but still faster than a normal schedule.

Aptex is arguing that the district court erred in its interpretation of the BPCIA and that its “plain text” indicates the 180-day notice of commercial marketing “is not always mandatory” and that the law anticipates the biosimilar applicant would not always follow that path, so the statute provides an exclusive remedy for the biologic innovator. And, Apotex said, if the notice was always mandatory, the remedy provided to the reference product sponsor would be “superfluous.”

“Basic canons of statutory construction urge strongly against construing a statute in a way that makes some of its provisions superfluous,” Apotex insisted. The company also noted that Amgen has had more than 11 months to assert its patent rights and argued that "there can be no statutory purpose served by delaying the launch" of a biosimilar by 180 days so that an innovator has additional time to “evaluate information that has been in its possession” since the FDA first accepted the 351(k) application.

A "compulsory" notice of commercial marketing, Apotex contended, would provide Amgen with a de facto six months of additional exclusivity on top of the 12 years that the company already has enjoyed, even though it “has no additional patents to assert and so can make no legitimate use of the 180-day waiting period.”

“Granting of a windfall extra six months of monopoly sales for the reference product sponsor was not Congress’ intent” in the BPCIA and could not be "squared" with lawmakers’ “explicit choice or a 12-year period" of exclusivity, Apotex declared.

Plus, the company said, "Imposing an additional six-month delay would delay the availability of more affordable biosimilar products for no good reason.”

While the Florida judge expressed “hope” that by making the 180-day notice mandatory would result in some patents expiring before that six-month period was up, “there is no logical connection between patents expiring and the 180-day notice period,” Apotex contended.

“The longer any litigation goes on, the better the chances that some patents will expire and some issues will become moot. That truism, however, provides no legitimate basis for requiring all biosimilar applicants, now and in the future, to delay the launch of their biosimilar products for six months," the company argued, calling the district court "mistaken" in its beliefs.

Finally, Apotex said, the district court failed to “respect the exclusive remedy provided by Congress” for circumstances in which an applicant does not provide the notice of commercial marketing (see p11).

“Instead, the district court created a new extra statutory injunctive remedy not contemplated by Congress, in derogation of the longstanding principle that when a statute creates a right and expressly provides a remedy for violation of that right, then the aggrieved party’s relief is limited to that statutory remedy,” the Canadian firm said.
Apotex Allies: Amgen’s Views Distort Congress’ Biosimilars Goals

If a Florida district court’s ruling is upheld granting Amgen Inc.’s motion for a preliminary injunction (PI) blocking Apotex Inc. from marketing its pegfilgrastim biosimilar for 180 days after US approval, it would distort Congress’ intent in enacting the Biologics Price Competition and Innovation Act (BPCIA), supporters of the latter company’s views said in friend-of-the-court briefs.

The lawsuit, Amgen v. Apotex, which currently is before the US Court of Appeals for the Federal Circuit (see p10), presents “critical issues” about the interpretation of the BPCIA, said the Biosimilars Council, a division of the Generic Pharmaceutical Association, which said it has a “strong interest” in seeing the court construe the statutory language as Congress intended and in a manner consistent with the law’s overarching goals.

The council said it also wants to see the court ensure the BPCIA’s “notice provisions” are not used by the brand-name industry to improperly delay competition from biosimilars.

The case, said Mylan Inc., which filed a separate amicus brief, boils down to one issue: Whether the notice of commercial marketing provision in the BPCIA is “mandatory” in all instances, including when a biosimilar maker follows the law’s disclosure and negotiation procedures – known commonly as the patent dance – and provides a copy of its 351(k) application to the innovator whose product acts as the reference, like Apotex did with Amgen.

Apotex is seeking approval from the FDA to market a biosimilar in the US of Amgen’s long-acting human granulocyte colony-stimulating factor Neulasta (pegfilgrastim).

The FDA accepted the application in December 2014. The status of the application, however, is unclear and Apotex, which had anticipated a decision this past October, has remained mum.

Apotex and Amgen engaged in the patent dance. Apotex provided Amgen a statement of the biosimilar maker’s intentions about marketing its product in April 2015. But Amgen called that a violation of the BPCIA – arguing that companies that want to copy an innovator’s biologic must provide the referenced product sponsor (RPS) with a 180-day notice before first commercial marketing, with that notice coming after the FDA licenses the biosimilar.

Judge James Cohn of the US District Court for the Southern District of Florida agreed with Amgen and imposed the PI on Dec. 9, 2015.

But, said Hospira Inc. and Celltrion Healthcare Co. Ltd., which filed a joint amicus brief supporting Apotex, if the district court’s ruling is upheld, branded biologic firms would essentially be handed an additional 180-day exclusivity windfall, which the biosimilar makers said would cause “billions of dollars in harm to consumers” by delaying the entrance of the lower-cost medicines into the US market.

And, they said, imposing a “new form of marketing exclusivity” unrelated to patent rights would “distort” the BPCIA’s “text and clear purpose” and provides innovators an “unwarranted monopoly.”

If the Federal Circuit sides with Amgen and the lower court, the “careful balance” Congress struck in the law to encourage price competition in the biologics markets and promote the development of innovative new medicines also would be out of whack, the Biosimilars Council contended.

Congress provided innovators with 12 years of exclusivity in exchange for agreement on an expedited biosimilars pathway.

But providing those innovators with an extra injunctive remedy to address a lack of notice would “effectively add six additional months of exclusivity to the express 12-year statutory exclusivity period for each and every biosimilar application,” the Biosimilars Council said.

“Congress could not possibly have intended to extend the RPS exclusivity, and thereby to further delay patients’ access to affordable medicines, by six additional months through the backdoor mechanism of the BPCIA’s notice provisions,” the group argued.

Neither the BPCIA nor the Federal Circuit’s ruling in the first biosimilars case that came before it, Amgen v. Sandoz Inc., supports the automatic 180-day marketing exclusivity imposed by the district court, asserted Hospira and Celltrion, which are caught in court battles of their own – one case at the US District Court for the District of Delaware brought by Amgen against Hospira involving its biosimilar of Epo gén (epoetin alfa), and the other brought by Janssen Biotech Inc. at the US District Court for the District of Massachusetts against Celltrion, which is partnered with Hospira on a biosimilar of Remicade (infliximab).

In Amgen v. Sandz, a three-judge panel from the Federal Circuit in July 2015 ruled 2-1 that the 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.

The full Federal Circuit declined to rehear the case en banc – an appeal that came from both Sandoz and Amgen. But the court left open several questions, like what would happen when companies participated in the patent dance.

Like Apotex, which filed its opening brief in the case on Dec. 30, 2015, Hospira, Celltrion, Mylan and the Biosimilars Council are insisting the notice of commercial marketing is not mandatory when firms do the dance.

In their briefs, Hospira, Celltrion and Mylan also said that reading into the BPCIA an “automatic injunction” would flout the Supreme Court’s 2006 ruling in eBay Inc. v. MercExchange LLC., in which the justices said that an injunction should not automatically be issued based on a finding of patent infringement and that a federal court must weigh the so-called “four-factor test” for determining whether to impose an injunction.

In eBay, the Supreme Court held that patent owners must demonstrate entitlement to a permanent injunction by it has suffered an irreparable injury; that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and that the public interest would not be disserved by a permanent injunction.

The Federal Circuit’s ruling in Amgen v. Sandz “does not impose an automatic 180-day injunction if an applicant fails to provide a mandatory notice of commercial marketing,” Hospira and Celltrion said, adding that nor should the court in the Apotex case.

“Under eBay, the four-factor injunction test still must be satisfied,” the companies said.

They insisted it would not make legal or logical sense to award automatic injunctions that do not satisfy the requirements of eBay – “especially in cases like this, where all patents are being litigated and the plaintiff is free to move for a preliminary injunction to enforce relevant patent rights.”

If Amgen and Janssen had their way, every biosimilar launch would be delayed by at least 180 days after the FDA has approved the product for marketing – costing the health care system billions of dollars and potentially harming sick patients,” Hospira and Celltrion asserted.

Amgen has until Feb. 4 to file its brief in the case.

donna.young@informa.com
Gilead Sciences Inc. is to file for US and EU approval this quarter of its once-daily treatment for hepatitis B, tenofovir alafenamide (TAF) 25 mg, on the basis of two newly reported Phase III studies.

The top-line data show that TAF was non-inferior to Gilead’s older nucleotide reverse transcriptase inhibitor Viread (tenofovir disoproxil fumarate, TDF) and that TAF had improved renal and bone laboratory safety parameters. Gilead is hoping to switch patients onto the new product ahead of loss of patent protection for Viread in hepatitis B, on the basis of its safety profile, although experts are skeptical as to the true extent of the benefit seen.

The two 96-week trials (Studies 108 and 110) enrolled a total of 1,298 treatment-naive and treatment-experienced patients with chronic HBV, with the primary efficacy endpoint as the proportion of subjects with plasma HBV DNA levels below 29 IU/mL. In Study 108 in HBeAg-negative patients, 94.0% of TAF patients and 92.9% of Viread patients achieved HBV DNA below 29 IU/mL at week 48. In Study 110 in HBeAg-positive patients, 63.9% of TAF patients and 66.8% of Viread patients achieved this endpoint.

Key secondary endpoints included change from baseline in bone mineral density at the hip and spine at week 48, and change from baseline in serum creatinine at week 48. Here, Gilead says, the changes favored the TAF regimen. In both studies, patients receiving TAF experienced a significantly smaller mean percentage decrease from baseline in hip and spine bone mineral density at week 48 (p<0.001). Gilead added that smaller increases in serum creatinine were seen in patients receiving TAF in Study 110 (p=0.02), and that the median change in estimated glomerular filtration rate (eGFR) from baseline to week 48 favored TAF in both studies (p<0.01).

**Lifecycle Management**

TAF is already approved as part of Gilead’s combination HIV treatment Genvoya (emtricitabine/cobicistat/elvitegravir/tenofovir alafenamide) – its first approval came in the US in November – making the data less of a surprise and more important in terms of lifecycle management.

“The takeaway point from the HBV and HIV trials is that TAF has only non-inferior efficacy to TDF but improved renal and bone safety, and Gilead is trying to plug this benefit because the HBV and HIV populations are ageing and so renal and bone safety is becoming increasingly important,” said Michael Haydock, an analyst at Datamonitor Healthcare.

He added that that the renal and bone safety benefits look to be marginal, and only apparent to date on surrogate lab markers rather than any actual real-world reduction in renal or bone adverse events (e.g. bone fractures), “which is probably what payers will be demanding evidence of when its TDF predecessor (Viread) goes off patent in 2018.”

Gilead will have about a year to try to swap patients from TDF to TAF in the HBV market, but after the patent expiry Haydock does not believe that widespread use of TAF will be considered cost-effective compared with generic TDF. “Instead TAF will probably be limited to patients with baseline renal/bone risk factors or patients who experience TDF-toxicity, but clinically significant renal and bone adverse events on TDF are already very rare in HBV patients.”

Overall, Datamonitor Healthcare does not expect TAF to replicate Viread’s current success in hepatitis B: it forecasts HBV sales in the seven major markets to reach $214m in 2023 compared to Viread’s estimated HBV revenues of $323m in 2015.

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**Baxalta, Symphogen In Potential $1.4bn I-O Deal**

Baxalta has agreed to pay €160m upfront to Danish antibody company Symphogen for exclusive option rights to an early stage immuno-oncology program.

Under the agreement, Symphogen will develop monoclonal antibody therapeutics to six checkpoint targets proposed by Baxalta, Symphogen CEO Kirsten Drejer told Scrip.

“We were familiar with some of these targets, but some were new to us,” Drejer said. She expects the first program to enter clinical testing this year, she added.

Symphogen is responsible for conducting R&D through to the end of Phase I at its own expense. “We expect the majority of the upfront payment to be spent on developing these six checkpoint programs,” she revealed.

On a product-by-product basis, if Phase I trials are successful, Baxalta will have exclusive option rights to complete late-stage development and worldwide commercialization.

The total potential value of the deal is up to $1.4bn, with option fees and milestones available, in addition to royalties on worldwide sales. Other terms, including therapeutic targets, are not being disclosed.

“This exciting partnership aligns well to Baxalta’s strategy to invest in immuno-oncology and build an innovative portfolio of immunotherapies,” said David Meek, executive vice president and president, Oncology, Baxalta. “This is just the beginning of our focus in building world-class capabilities in immuno-oncology.”

Symphogen has “obviously been following the news” with regards to Shire’s interest in Baxalta, said Drejer, but a potential acquisition “has never been part of our discussions with Baxalta,” she said. Negotiations had been ongoing with a number of companies “in parallel” regarding a partnership in the immuno-oncology space, “but this was the most strategic deal on the table, the others were more focused.”

“The interest in Symphogen is driven by “our effectiveness in generating quality antibodies quickly and getting them ready for clinical testing quickly.”

Symphogen’s lead program is Sym004 – a mixture of two antibodies (futuximab and modotuximab) that is in Phase Ib in metastatic colorectal cancer patients. Sym004 had been the subject of a licensing agreement with Merck Serono, but full rights were returned to Symphogen a year ago. Drejer said that the Phase Ib trial had recently completed enrollment of 250 patients with “read out of overall survival expected in late autumn.”

Two preclinical programs are expected to enter clinical testing this year, she added. In October 2015, the company raised €67.5m via a convertible debt facility from existing investors, bringing the total financing raised to date to €316.5m.

**Shire Takeover**

On 11 Jan. Shire plc and Baxalta confirmed they will merge. The combined company, which will be 34% owned by Baxalta shareholders, will be “the partner of choice in rare diseases,” claimed Shire CEO Flemming Ornskov in a press conference. Under the agreement, Baxalta shareholders will receive $180.00 in cash and 0.482 Shire ADS per Baxalta share. Based on Shire’s closing ADS price on January 8, 2016, this values each Baxalta share at $45.57, and a deal value of $32bn.

(Shire takeover is not expected to replicate Viread’s current success in hepatitis B: it forecasts HBV sales in the seven major markets to reach $214m in 2023 compared to Viread’s estimated HBV revenues of $323m in 2015.)

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@scripnews, linkedin.com/scripintelligence.com
Biotechs Benefit From Pharma Deals And Dollars

Big pharma companies may be under pressure to buy like-sized peers with late-stage clinical programs and marketed products, but several collaborations with and investments in biotechnology firms announced during the first few days of 2016 show that the world’s largest drug makers also are focused on long-term prospects for their research and development pipelines.

Quartet Medicine, with just $17m in previous venture capital investment, entered into a partnership with Merck & Co. Inc. to develop novel medicines for pain and inflammation that gives the bigger company an option to buy the biotech firm in a deal worth up to $595m and maybe more. In other transactions, Rodin Therapeutics raised $17.3m in a Biogen-backed financing and inked an R&D collaboration with the big biotech that’s worth up to $485m.

Meanwhile Millendo Therapeutics raised $62m in a series B round supported by Roche’s venture fund and other investors, and the endocrine disorder-focused biotech firm licensed a polycystic ovary syndrome (PCOS) drug candidate from AstraZeneca PLC.

Also, the new Pharmaceutical Product Development LLC (PPD) spinout X-Chem signed drug discovery deals with Sanofi and the University of Texas MD Anderson Cancer Center; Accelerator Corp’s first New York startup Petra Pharma Corp. raised $48m in series A cash from Accelerator’s big pharma and other investors; and Cortexyme Inc. in South San Francisco raised $15m in a series A round led by Pfizer Inc.

The pending $160bn merger of Pfizer and Allergan PLC, which will create the biggest pharmaceutical and largest healthcare company in the world, raised the bar for mergers and acquisitions among big pharma firms and major biotech players.

Large biotech companies, such as Celgene Corp. and Biogen, have built up a lot of firepower from blockbuster biologic sales to justify significant acquisitions on top of active licensing deals and small purchases. But neither blockbuster M&A deals nor small transactions alone will fill the gaps in pharma and biotech R&D pipelines, so big drug makers may dabble in both mega-mergers and mini-deals throughout 2016.

Rodin Rolling In New Money

Rodin, a biotech – like Quartet – that was founded by Atlas Ventures, has $17.3m in preferred stock financing commitments from the VC firm and Biogen to fund development of novel therapeutics for neurological disorders. In a separate multi-year R&D collaboration between Cambridge, Massachusetts-based Rodin and Biogen, the companies will focus on neuronal epigenetics.

Large biotechs have built up firepower from blockbuster sales to justify significant acquisitions on top of active licensing deals and small purchases.

Atlas and Johnson & Johnson Development Corp. funded Rodin’s $12.9m series A round in May 2014 after J&J announced an early-stage investment in the startup, which was spun out of the German firm Proteros Biostructures, back in 2013. Rodin hired repeat entrepreneur Adam Rosenberg as the company’s president and CEO in October.

Rodin is developing epigenetic modulators with a lead program that’s focused on HDAC2 inhibition, which will be advanced into the clinic via the Biogen partnership. Biogen has an option to acquire Rodin under the companies’ collaboration agreement for up to $485m in upfront and milestone fees.

Pharmas Back Accelerator Startup Petra

Accelerator raised $51.1m from Alexandria Venture Investments, ARCH Venture Partners, WRF Capital, Eli Lilly & Co., Harris & Harris Group, The Partnership Fund for New York City, Pfizer Venture Investments and Johnson & Johnson Development Corp. in Aug. 2014 to fund startups that will be headquartered in the company’s Manhattan incubator, and in Oct. 2015 AbbVie, WuXi PharmaTech and Watson Fund contributed another $11.7m for Accelerator’s incubators in Seattle, Washington and New York.

Petra Pharma is the first startup to emerge from the Manhattan location with $48m in series A funding provided by all of the investors in the syndicate, which also include ARCH Venture Partners and Innovate NY Fund. Petra will work with Weill Cornell Medicine to develop small molecule inhibitors for the treatment of cancer and metabolic diseases in collaboration with researchers who discovered PI3K as a therapeutic target and who pioneered development of therapies that target other kinases.

X-Chem Spins Out, Adds Partners

X-Chem in Waltham, Massachusetts offered few financial details about its formal separation from PPD, but the spinout company also will be a privately-held firm. X-Chem mines its DNA-Encoded X-Chem (DEX) library of 100bn compounds to discover small molecules against high-value therapeutic targets, and attracted an investment from PPD in 2010 and then was acquired by the firm in 2014.

X-Chem has several drug discovery partnerships, which involve more than 70 therapeutic programs and 16 licensed compounds, including deals with AstraZeneca, Bayer, Johnson & Johnson’s Janssen Biotech and Navitor Pharmaceuticals.

The company did not release any financial details under its new agreement with Sanofi, but X-Chem will do drug discovery on the French pharma’s behalf for multiple targets in oncology, rare diseases, diabetes and other areas. However, X-Chem will receive research funding and retain an ownership stake in compounds discovered in partnership with MD Anderson to treat various cancers.

Cortexyme Targets Neurodegenerative Infections

Cortexyme’s $15m series A round was led by Pfizer with participation from Takeda Pharmaceutical Co. Ltd’s venture capital arm and unnamed private investors, including prior backers, such as Dolby Family Ventures. The company is developing therapies, along with diagnostics, that may alter the course of Alzheimer’s disease and other degenerative disorders by targeting a specific, undisclosed pathogen that’s been associated with neurodegeneration.

Prior to the series A round, Cortexyme raised $1.025m, including an award from Breakout Labs. The company is a tenant in J&J’s biotech incubator in San Francisco.
Tailwinds Drive Lilly Growth, But Headwinds Remain

Eli Lilly & Co. investors were somewhat enthusiastic on Jan. 5 about the big pharma company’s forecast for growth in 2016 even though Lilly’s guidance for $20.2bn to $20.7bn in revenue and $3.45 to $3.55 in earnings per share (EPS) fell below Wall Street analysts’ expectations, due to well-known challenges that could moderate tailwinds driving revenue and earnings gains this year.

Analysts, including Evercore ISI’s Mark Schoenebaum, noted that Lilly tends to issue conservative predictions from year to year, so there may be hope that returns on research and development investments will be better than expected. The company made it clear, however, that R&D will be the main route to revenue growth as Lilly will continue to buy and license certain assets, but it will not chase major mergers and acquisitions just to build a bigger organization or cut its tax rate.

“From an M&A or business development perspective, what you should expect to see from Lilly going forward is behavior that’s consistent with what you’ve seen from us historically,” Lilly chief financial officer Derica Rice said during the company’s conference call with investors and analysts to discuss the 2016 financial guidance.

Rice noted that Lilly’s business development activities will be focused on early-stage programs to fill its R&D pipeline as well as later-stage assets that fit in with the company’s three main therapeutic areas: diabetes, oncology and biomedicines.

“We’re not looking for this ‘transformative’ deal or to make the mega merger deal,” he said. Lilly CEO John Lechleiter later said “we have no intention of entering into one of these deals that would change our tax rate.” If the company is at a disadvantage relative to its competitors, “we’re disadvantaged by the current US tax system,” which Lechleiter said is in need of reform.

So if R&D is the main force behind Lilly’s sales and earnings growth in 2016 and beyond, what assets currently in the pipeline will account for increased revenue over the near to mid-term?

Foundation For Growth
First, it should be noted that the company expects some of its established products as well as sales from recently approved products to contribute to the 2016 revenue forecast of $20.2bn to $20.7bn versus Lilly’s expectation of $19.7bn to $20bn in 2015. Last year’s non-GAAP EPS is expected to come in at $3.40 to $3.45 versus the $3.45 to $3.55 guidance for this year.

Established products Humalog (insulin lispro), Cialis (tadalafil) for erectile dysfunction, and the osteoporosis drug Forteo (teriparatide) will continue to grow this year, Lilly said. Newer medicines also will continue to gain market share: Cyramza (ramucirumab) for advanced gastric, colorectal and non-small cell lung cancer (NSCLC); the diabetes drugs Jardiance (empagliflozin), Trulicity (dulaglutide) and Basaglar (insulin glargine); and Portrazza (necitumumab) for squamous NSCLC.

Credit Suisse includes Lilly among its top pharma stocks in the US, because of “progress we expect them to continue to make in 2016, but – more importantly – the strong foundation they have in place to drive growth for the next several years” analyst Vamil Divan wrote in a Jan. 5 report.

Portrazza was approved in the US in November about a month before and Basaglar was approved in December, while last year included additional approvals in the US and Japan for Cyramza, for Trulicity in Japan, Humalog Kwikpen in the US, and fixed-dose combinations (FDCs) of Jardiance with metformin in the US and EU (trade name Synjardy) and with Tradjenta (linagliptin) in the US (trade name Glyxambi).

This year could add Portrazza approval in the EU, Cyramza lung and colorectal cancer approvals in the EU and Japan, an extended-release Tradjenta/metformin FDC in the US, Glyxambi approval in the EU, and the addition of long-term cardiovascular outcomes data to the Jardiance label in the US based on unprecedented results for the sodium-glucose cotransporter-2 (SGLT-2) inhibitor in September. Even without the cardiovascular outcomes data on its label and prior to expected revisions of diabetes treatment recommendations in the US and EU, Lilly Diabetes president Enrique Conterno said during the company’s 2016 earnings guidance conference call that Jardiance’s share of patients who are new to brand-name diabetes treatments has jumped from 15% to 25% for the oral drug.

Lilly product candidates that could win their first approvals in 2016 are the interleukin-17 (IL-17) inhibitor ixekizumab for psoriasis in the US and EU, and for psoriatic arthritis in Japan, as well as olaratumab in the US for soft tissue sarcoma – an indication with a breakthrough therapy designation from the US FDA. The company also may submit applications for US approval of an extended-release Jardiance/metformin FDC, and for approval in the US, EU and Japan for the JAK1/JAK2 inhibitor baricitinib to treat rheumatoid arthritis – a drug developed in partnership with Incyte Corp.

However, the most closely watched R&D program in Lilly’s late-stage pipeline at the moment is solanezumab for Alzheimer’s disease. The company revealed during its 2016 guidance conference call that it may report top-line Phase III results from mild Alzheimer’s patients late this year with more detailed data presented at a conference or published in a medical journal in 2017. Lilly considers this a high-risk/high-reward program.

Bernstein analyst Tim Anderson described Lilly as “a pipeline-driven return-to-growth story … with a major potential turbo charger in the form of solanezumab” in a Jan. 5 report. A Phase III solanezumab failure could cut the company’s stock value by about 15%, but success could boost Lilly’s share price by multiples of 15%, Anderson wrote.

Other late-stage programs from which Lilly may report top-line results in 2016 include: the CDK4/6 inhibitor abemaciclib, which is in Phase II as a breast cancer monotherapy (a potential competitor for Pfizer Inc’s Ibrance [palbociclib]); a long-term extension study for baricitinib in RA; and the Phase III MARLINA study of Tradjenta in type 2 diabetes with albuminuria.

Headwinds Blowing Through
Headwinds keeping Lilly from generating revenue growth above a mid- to high-single-digit range include patent challenges to the lung cancer drug Alimta (pemetrexed) in Europe, where one or more generic competitors could hit the market in 2016; competition for the company’s lung cancer portfolio from immuno-oncology drugs, i.e. Opdivo (nivolumab) from Bristol-Myers Squibb Co. and Keytruda (pembrolizumab) from Merck & Co. Inc.; and the loss of patent exclusivity for multiple products in various emerging markets.

Chito Zulueta, Lilly’s president of emerging markets, noted during the company’s earnings guidance conference call that more than 75% of Lilly therapeutics sold in emerging markets have lost patent exclusivity in those regions. Zulueta also said there is a year to a year and a half time lag between launches in the US, EU and Japan versus emerging market launches for newer products. That means 2016 will bring more patent losses and a $150m to $180m decline in sales in emerging markets before newer Lilly medicines are approved and launched in those countries.

Lilly attributed the difference in its 2016 guidance versus analyst consensus of $21.5bn in revenue and $3.65 in EPS to Alimta generics that may hit some markets in Europe, including Germany; lower Elanco animal health sales; and a difference of opinion on foreign currency exchange rates based on the strength of the US dollar.

mandy.jackson@informausa.com
**Pfizer/Merck KGaA And IPO Hopeful Syndax To Study Ovarian Cancer Combo**

Pfizer Inc. and Merck KGaA, through their 2014 partnership agreement, will evaluate whether the immuno-oncology agent avelumab has the potential to improve treatment options for women with advanced ovarian cancer under a new collaboration with Syndax Pharmaceuticals Inc., a privately-held firm with newly revealed public company aspirations.

Avelumab, a monoclonal antibody that inhibits the immune checkpoint known as programmed cell death ligand 1 (PD-L1), will be tested in combination with Syndax’s oral small molecule entinostat, which targets immune regulatory cells. With multiple partnerships to test its lead drug candidate in combination with other companies’ immunotherapies, Waltham, Massachusetts-based Syndax – hoping to raise up to $86.25m – was one of six biopharma firms that filed paperwork with the US Securities and Exchange Commission (SEC) on Jan. 4 to register for prospective initial public offerings.

The IPO hopeful, whose CEO is former AstraZeneca PLC chief medical officer Briggs Morrison, will be responsible for conducting a planned Phase Ib/II clinical trial evaluating entinostat in combination with avelumab in the treatment of heavily pre-treated, recurrent ovarian cancer.

Entinostat specifically targets myeloid-derived suppressor cells and regulatory T-cells. The Syndax drug is being tested in Phase Ib/II clinical trials with Merck & Co. Inc’s PD-1 inhibitor Keytruda (pembrolizumab) for the treatment of non-small cell lung cancer (NSCLC) and melanoma. Syndax also revealed an agreement in August to test entinostat in a Phase Ib/III triple-negative breast cancer clinical trial in combination with the PD-L1 inhibitor atezolizumab from Genentech, a Roche company.

Entinostat in combination with Aromasin (exemestane) won a breakthrough therapy designation from the US FDA in 2013 for in the treatment of locally recurrent or metastatic estrogen receptor-positive (ER+) breast cancer in postmenopausal women. A Phase III clinical trial in that setting is ongoing. Merck KGaAs head of global research and development for the Darmstadt, Germany-based company’s biopharma business, Luciano Rossetti, noted in a joint statement regarding its collaboration with Pfizer and Syndax that avelumab alone has shown positive results in a Phase Ib ovarian cancer trial, but dosed in combination with entinostat the PD-L1 may be able to further benefit women with the deadly cancer.

Rossetti said combination therapies are “the next frontier in immuno-oncology and a key strategy for the alliance” with Pfizer.

A range of biotech companies registered prospective IPOs with the SEC on Jan. 4, including other immunotherapy companies. In addition to Syndax, rare disease-focused Reata Pharmaceuticals is seeking up to $80m in an IPO; the gene therapy developer Audentes Therapeutics and Bavarian Nordic, a Danish firm developing cancer immunotherapies and vaccines for infectious diseases, each want to raise as much as $86.25m; the preclinical gene editing firm Editas Medicine wants up to $100m; and the immunotherapy developer Corvus Pharmaceuticals is seeking $115m.

— mandy.jackson@informausa.com
Policy & Regulation Briefs

Brazilian Government Owes Pharma R$1bn

In a situation that is “close to unbearable” for companies, Brazil’s national and state governments owe the pharmaceutical industry R$927m (US$229m), Interfarma, the Brazilian pharmaceutical industry association has told Scrip. Almost a third of the debt has been outstanding for more than six months. “Companies have faced small delays before, but nothing like this amount for so long,” says Interfarma. It adds that the companies worst affected are those that sell to the state and federal government. Among the products in question are HIV drugs and anticancers. The debt could even be higher as the figure does not include money owed by municipal authorities. The association is in talks with the government to find a solution. “Interfarma understands that the government is facing a difficult moment, with less resources than it needs. Therefore, to avoid any risk of shortage, we have been in contact with the authorities to help them find a solution,” said the association.

Brazil operates a publicly funded universal healthcare system, the SUS, which is free to everyone and enshrined in the constitution. The government is increasingly adding expensive medicines, like new hepatitis C treatments and anticancers its list of essential medicines. The economic sustainability of the SUS has been a cause for concern for some time, especially amid the country’s deepening economic crisis. The economy is set to contract further in 2016, while inflation remains high.

Indian Nexium Generics Back

Dr Reddy’s Laboratories Ltd has re-introduced its generic version of AstraZeneca’s Nexium (esomeprazole magnesium) in the US, amid indications that the two companies may be headed towards settling the legal tussle over the product’s purple color. Dr Reddy’s, which announced the re-launch Dec. 30, told Scrip that its generic Nexium capsule was now blue in color and the color change was “annual reportable” to the FDA. Dr Reddy’s had on Sept. 2015 commenced sales in the US of its generic Nexium as purple capsules—albeit two shades of purple—following a site transfer. Camber Pharmaceuticals Inc, part of India’s Hetero group, which was also hauled to court by AZ over its purple coloured Nexium generic, is also believed to have re-launched its version [again in blue colour] in the US, though no official confirmation could immediately be got. Camber probably re-launched its version ahead of Dr Reddy’s, according to some industry watchers. Some analysts tracking the development said that they were unsure if

Dr Reddy’s had been hit materially in the period when its generic version was off the market. “I don’t think any meaningful [revenue] loss would have occurred, though Hetero may have had some edge,” said one analyst, adding that he expects annual revenues of around $40m from the product for Dr Reddy’s. Meanwhile, another Indian firm, Aurobindo Pharma, received tentative FDA approval for its Nexium generic on Dec. 24.

Califf: What Can FDA Do To Enable Innovators?

Robert Califf, who is on the verge of an expected confirmation as commissioner of the FDA, wants to make one thing perfectly clear: he has “never stated, implied or argued” the “barrier” of US regulation over medical products should be lowered or removed. “In fact, I do not believe that we should be putting inferior medical products on the market, nor do the American people want inferior products to be used in medical practice,” Califf told the leaders of the Senate Health, Education, Labor and Pensions (HELP) Committee, chair Lamar Alexander (R-TN) and ranking member Patty Murray (D-WA). “The belief that we should have evidence of benefits and risks before marketing in health care has been a driving force in my career and a motivation to develop more effective, efficient and unbiased ways of conducting generalizable clinical trials and implementing quality systems for learning in health care as a focus of my academic and practical work.” But with the appropriate requirements and “barriers” in place, Califf argued it was “reasonable” to ask “what can FDA do to enable innovators” to develop new approaches and technologies, while maintaining the same standards, but reducing the cost and time, so Americans can get access to new safe and effective medical products and investors will continue to invest. Califf’s written remarks came in response to questions from Alexander and Murray as a follow-up to the HELP Committee’s Nov. 17 hearing, at which lawmakers grilled the FDA contender about his relationship with industry, the agency’s role in controlling drug costs and why regulators have turned more to issuing what are often vague guidelines over regulations.

Canadian Pricing Body Sharpens Its Teeth

Companies doing business in Canada are likely to see new action to drive down medicine prices. Concerned by spiraling drug prices and its place in an increasingly complex pricing and reimbursement environment, the Patented Medicine Prices Review Board (PMPRB) has published a new three-year strategic plan which will address how it can better contribute to lower prices and sustainable healthcare, although nearer-term measures could be on the cards too. “The strategic plan aspires to lower Canadian prices in line with European and OECD countries and establish a greater level of cohesion and collaboration with Canadian HTA agencies and payers,” says Arvind Mani, director of market access and policy research at PDCI Market Access, a Canadian pricing and reimbursement consultancy. Unsurprisingly, the innovative pharmaceutical industry is not pleased about the prospect of more pricing constraints. Mani says the industry disagrees with the plan’s underlying assumptions, particularly the idea that Canada’s prices are higher than those in Europe. “Indeed, the prevailing view within the industry is that the PMPRB has been more than effective in regulating drug prices and that greater regulation is unwarranted,” he said. The plan will take three years to implement and the process to consult and introduce new regulations and policies will be protracted. In light of this, Mani warns that the board may introduce nearer-term changes to lower prices by focusing on guidelines and policies that do not need action from the government.

German HTA Rejects Benefit Claim For Celgene’s Innovid

Germany’s health technology appraisal body IQWiG, the committee responsible for evaluating new medicines prior to pricing negotiations in the country, has given Celgene’s multiple myeloma therapy Innovid (pomalidomide) a rating of “no added benefit” over other available treatments. Celgene claimed a “major additional benefit” rating in its submission to IQWiG and at the time of the drug’s initial approval German regulator, the Federal Joint Committee (G-BA), also said the product had a significant additional benefit. Celgene based its evaluation of the drug on positive data from the MM-003 registration trial. It has also since provided more data from this trial to the German HTA, which showed a reduced mortality risk by 47% and a gain in overall survival by 5 months in refractory multiple myeloma patients treated with Innovid. However, IQWiG has said in its assessment this month that the drug offers no additional benefit due to “methodological reasons.” Martin Völk, director of market access and public affairs at Celgene GmbH, told Scrip this outcome is because, according to IQWiG, the dossier submitted by the company does not include appropriate data to deduce an additional benefit. He said, “The comparator determined by G-BA, an active therapy individualized on the respective patient, was not realized based on the methodological standards of IQWiG. Celgene, however, considers high-dose dexamethasone, the active comparator agreed on with US FDA and European Medicines Agency (EMA) for the registration trial MM-003, as an appropriate comparator and best standard of care.” The GB-A will provide a final decision on Innovid’s benefit rating, taking into account its HTA’s recommendations, in March this year.
France Leads Europe In Reimbursing Truvada For HIV Prophylaxis

Gilead Sciences’ HIV drug Truvada is now being reimbursed in France for pre-exposure prophylaxis (PrEP) under a “temporary use recommendation” (RTU) that came into effect on Jan. 4. This is understood to be the first European country where Truvada can be officially prescribed and reimbursed for PrEP, an indication for which it has not yet received an EU marketing authorization.

The product, which is a fixed combination of emtricitabine and tenofovir disoproxil fumarate, will be fully reimbursed for PrEP, and will be aimed mainly at men aged 18 or over who are at high risk of contracting HIV through sexual activity with other men.

Gilead will provide ANSM with quarterly reports on the drugs use in PrEP setting

The decision to make Truvada available for PrEP was announced on Dec. 1 last year by the regulatory agency ANSM, which said the RTU would come into effect “at the latest at the beginning of 2016.” The product can be prescribed only by hospital doctors experienced in HIV infection.

ANSM stressed that Truvada should be used in PrEP as part of a “diversified prevention strategy” that it has drawn up giving detailed information on HIV transmission, methods of prevention, condom use, HIV testing, other sexually transmitted diseases that could facilitate HIV infection, and awareness of partners’ HIV status.

Gilead, which confirmed last month that it plans to submit a marketing authorization application to the European Medicines Agency for PrEP in the first quarter of 2016, has set up a dedicated portal for the Truvada RTU where doctors can fill in the necessary forms to begin treatment. Truvada is currently approved in the EU for treating HIV infection.

The RTU protocol for Truvada in PrEP, which available on the Gilead portal as well as the ANSM website, says that Gilead will collect and analyze all information provided by prescribers under the RTU and will send ANSM quarterly reports on the use of the drug. These will include the characteristics of subjects taking Truvada as PrEP, the different administration schedules, data on HIV seroconversion, and pharmacovigilance information. Summaries of these reports will be published on the ANSM website. The recommended dosage of Truvada in PrEP is one tablet daily on a continual basis. In men who have sex with men (MSM), doctors may also prescribe Truvada on an as-needed basis depending on sexual activity. In such cases, two tablets should be taken in the 24 hours before the first sexual encounter (and at the latest two hours before), followed by one tablet every 24 hours during the period of sexual activity, and finally one tablet 24 hours afterwards.

The product’s use as PrEP is contraindicated in people who are already HIV positive, who are in the process of seroconversion, or whose HIV status is unknown, because of the risk of development of viral strains that are resistant to antiretrovirals. Cases of such resistance have been reported in people who began taking Truvada when they had undiagnosed HIV infection, ANSM notes.

Prescribing Protocol

Before prescribing Truvada for PrEP, the doctor must carry out an “exhaustive analysis” of the subject’s risk of contracting HIV, and the results must be included in the treatment initiation form. “This initiation form constitutes a guide to the factors to be taken into account when evaluating situations at high risk of contracting HIV through sex,” the protocol says.

Doctors should carry out an HIV test (ELISA, fourth generation) and prescribe Truvada only if the serological results are negative. They should also look out for signs or symptoms suggesting a possible HIV infection based on at-risk sexual behaviour in the past few months. If there are any such signs, PrEP initiation should be delayed by a month after negative test results on account of the serological window (the time between infection and the appearance of HIV antibodies), which is usually about 20 days.

The protocol also contains sections on reporting any adverse effects of Truvada treatment. A national pharmacovigilance program has been established for the Truvada RTU, which will be run by the regional pharmacovigilance center in Besançon.

Truvada has been available for PrEP in the US since 2012, and filings have been made in other countries including Canada and Australia. Gilead said the planned 1Q 2016 EU filing was “timely given a growing body of evidence on the efficacy and safety profile of Truvada for PrEP, support from the EMA, as well as interest from the clinical and HIV communities.”

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Zydus Ups Animal Health Play With Zoetis Deal

Zydus Cadila has acquired certain animal health brands and the Indian manufacturing operations in Haridwar of Zoetis, it as it aims to build its local and export business.

But the deal, which covers brands with combined revenues of INR1.71bn ($25.6m), did not seem to enthuse investors, coming atop the recent FDA warning at two of Zydus Cadila’s Indian sites.

Shares of Cadila Healthcare ended at INR313.55 (-2.31%) on the Bombay Stock Exchange on Jan. 5.

Zydus said that the acquisition would bring with it a wide range of nutrition as well as therapeutic products, including certain livestock farmcare products which are “well accepted in the market.”

Access to the WHO GMP-approved manufacturing facility is expected to boost exports and institutional business, a company statement added. The Haridwar site manufactures tablets, liquid orals and injectables.

It is not immediately clear why Zoetis divested its products, although recently industry experts have in suggested that foreign firms could increasingly divest their older, less strategic portfolio in emerging markets like India.

Financial details of the deal were not disclosed.

Some analysts said that at best they’d be “neutral” to the transaction and believe that, in general, the opportunities in the pharmaceutical space outweigh those in animal health.

“It’s no big deal. In fact one can argue that Cadila may be stretching itself in terms of management bandwidth, when there are more pressing issues on hand,” one analyst told Scrip.

Zydus Cadila, is among the leading Indian animal healthcare players with a range of drugs, feed supplements and vaccines for livestock, pets and poultry. It has a presence in key markets across Europe, South America, Asia and Africa through Bremer Pharma, Germany, which it acquired in 2011.

Zydus animal health business reported sales INR3.08bn in 2014-15, its annual report said.
Editas IPO Will Test Investment Crispness For CRISPR Gene Editing

By filing for an initial public offering on NASDAQ the genomics company Editas Medicine Inc. hopes to cash in on rising awareness of gene editing’s power and the simplicity promised from the so-called CRISPR technique.

US-based Editas filed for an IPO on Jan. 4, the first such move from within a growing band of privately held biotechs aiming to harness the therapeutic potential of the gene-editing technology known as Crispr-Cas9.

The investment idea behind Editas’ share offering is plans to develop therapies that home in on a specific gene causing a disease then snip it out and, if necessary, replace it with a healthy segment of DNA. The group will focus on therapies designed to turn off, turn on or edit disease-causing genes based on the research of its five founders regarding clustered, regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) as well as transcription activator-like effector nucleases (TALENs).

But while the drugs industry and academia are abuzz about the CRISPR approach, the jury remains out on how investors will respond to the inherent risks of this nascent science, and thus Editas’ share offering.

Investor Nerves Might Be Tested By CRISPR Journey

In its filing with the Securities and Exchange Commission Editas said: “we have incurred significant losses since inception. We expect to incur losses for the foreseeable future and may never achieve or maintain profitability.”

Its filing notes Editas’ net loss was $1.8m and $13.7m for the 2013 and 2014 calendar years, respectively, and $60.3m for the nine months to end-September 2015.

“As of September 30, 2015, we had an accumulated deficit of $75.7 million,” the filing says. The group said it has so far raised $163m in private offerings and is initially proposing to raising another $100m through the IPO, but added that the amount could change. The proposed date for the IPO was stated “as soon as practicable” and that the company would be listed as EDIT.

Editions operations have so far been financed through private placements of preferred stock and through its collaboration with Juno Therapeutics. In August 2015 Editas raised $120m in what the company called a highly oversubscribed Series B round through which a raft of new investors joined, including Deerfield Management, Viking Global Investors, Fidelity Management & Research Co., funds and accounts managed by T. Rowe Price Associates, Google Ventures, Jennison Associates, Khosla Ventures, EcoR1 Capital, Casdin Capital, Omega Funds, Cowen Private Investments, and Alexandria Venture Investments, which were joined by returning backers Flagship Ventures, Polaris Partners, Third Rock Ventures, and Partners Innovation Fund. Previous investors who supported Editas’ $43m Series A round in November 2013 – Flagship Ventures, Polaris Partners, Third Rock Ventures and Partners Innovation Fund – also backed the Series B financing.

In May 2015 Editas entered an exclusive collaboration with Juno Therapeutics Inc. combine the former’s disruptive genome editing technologies with Juno’s chimeric antigen receptor (CAR) and T-cell receptor (TCR) immunotherapies to work on three new research programs in cancer. Under that deal Juno paid $25m up front and will contribute up to $22m in research support over five years. Through that alliance, Editas could also see up to $230m per project in development, regulatory, and commercialization milestones, plus tiered royalties from that arrangement.

One of the first genetic diseases for which Editas is developing a CRISPR therapy is a form of leber’s congenital amaurosis (LCA).editas and通过Caribou Dr Doudna, in the meantime, had distanced herself from Editas, and through Caribou Biosciences. Emmanuelle Charpentier’s IP rights eventually ended up with CRISPR Therapeutics. Dr Doudna was joined at Editas by Broad Institute scientist Feng Zhang. But in April 2014, the Broad Institute was granted a broad patent for use of the CRISPR technology in eukaryotes – essentially, everything other than bacteria. Editas promptly announced its license of this patent. Dr Doudna, in the meantime, had distanced herself from Editas, and through Caribou Biosciences decided to set up yet another company – Intellia Therapeutics, whose investors include pharma giant Novartis. Editas has strongly voiced confidence in its intellectual property position. Like many of its rivals, Editas has licensed broad patent portfolios from academic and research institutions: the Broad Institute at Massachusetts Institute of Technology (MIT) and Harvard University, Massachusetts General Hospital, and Duke University. Editas also will seek patents for CRISPR work done in its own labs.

CRISPR Candidates Have Yet To Enter Clinic

Several other companies are also rushing ahead with CRISPR platforms, but none have so far taken a therapeutic candidate into the clinic.

That could soon change, however.

A big pharma – Bayer AG - just entered the fray, teaming up with a biotech to create the first long-term stand-alone joint venture exploring Crispr-Cas9. Germany’s Bayer and Switzerland-based CRISPR Therapeutics last month created a joint venture that will explore the technology in three therapeutic areas.

Scientists note gene editing technologies could pose a challenge to gene therapy, bringing new capabilities such as correction of genes or insertion of novel genes at precise genome locations.

Still, various technical barriers remain to maximizing the technique’s efficiency, but long-term in vivo applications could transform treatment of a wide range of diseases.

Enthusiasm over the approach’s potential for treating genetic disease is now accompanied by concern about its potential for misuse. But Editas has stressed that it will use CRISPR to edit disease-specific genes in humans, and not be used to edit the human germline – genetic information passed on during reproduction – an area of gene-editing research that recently came under fire for ethical reasons.

And Patent Clouds Remain

Another issue that might inject investor uncertainty for the coming Editas flotation is the ongoing patent disputes in the CRISPR/Cas9 field.

Co-researchers Jennifer Doudna and Emmanuelle Charpentier were initially jointly credited with the recent discovery of the CRISPR-Cas9 technology. Jennifer Doudna took her share of the IP rights and went on to co-found Editas Medicines and Caribou Biosciences. Emmanuelle Charpentier’s IP rights eventually ended up with CRISPR Therapeutics. Dr Doudna was joined at Editas by Broad Institute scientist Feng Zhang.

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sten.stovall@informa.com
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FDA Slams Zydus For Flawed Investigation

The FDA's warning letter against Zydus Cadila's Indian sites has some sharp references to the firm's flawed investigations into warfarin tablet failures, controls over computerized systems and poor documentation practices. The warning letter said that the recurrence of product quality failures at the Moraiya site with respect to warfarin following the completion of the firm's investigation indicates that its corrective actions and preventive actions (CAPA) were ineffective. "The recurrence of these failures is apparently due to inadequate identification of root causes and lack of action to resolve this manufacturing problem. These persistent failures indicate that your manufacturing process is not in a state of control," details in the letter stated. Cadila Healthcare announced on Dec. 31 that it had received a warning letter against its Moraiya formulation facility and its oncology active pharmaceutical ingredients site (API) in Ahmedabad (Zyfine). Among a string of observations, the Moraiya unit also received flak for failing to establish and follow adequate written procedures describing the handling of written and oral complaints concerning a drug. The agency noted that while Zydus planned to conduct a retrospective review of product complaints, deviations, and product failures from January 2013 to August 2014, the review appeared to focus on solid oral dosage products and is conducted over a limited period. The FDA termed the retrospective review period as "insufficient" and said that it does not appear to address whether other dosage forms made at the site may also be "vulnerable to mix-ups or other major defects." The FDA has sought a series of corrective actions and details of the specific changes made to ensure prompt identification, correction, and follow-up for problems associated with the firm's products. The Moraiya site accounts for about 60% of Zydus Cadila's US formulation revenues and roughly 40% of the firm's oral solid dosage filings for the US.

Another Simgtuzumab Failure For Gilead

Gilead Sciences Inc. has chalked up its second failure for its lysyl oxidase-like-2 (LOXL2) inhibitor simgtuzumab, virtually killing its prospects, despite continuing trials in other indications. The big biotech reported Jan. 6 that a Data Safety Monitoring Board (DSMB) recommended that it stop a Phase II clinical trial in patients with idiopathic pulmonary fibrosis (IPF) due to lack of efficacy. Meanwhile, two other Phase II studies in patients with primary sclerosing cholangitis (PSC) and non-alcoholic steatohepatitis (NASH) will continue through their 96-week endpoint. Yet, simtuzumab has failed before. In a September 2014 study, the drug wasn't able to improve progression-free survival in combination with gemcitabine when tested in patients with pancreatic cancer. Analysts from BioMedTracker only put the likelihood of approval in NASH at about 24% and even lower in PSC, at 20%. "While we would have liked to see this work, expectations had been low for simtuzumab. With a lack of efficacy in pancreatic cancer and now in IPF (a pure fibrosis setting), we believe few will believe it can work in anything," wrote UBS analyst Matthew Roden in a Jan. 6 note. The company describes LOXL2 as an enzyme that modifies the extracellular matrix by promoting the cross-linking of collagen fibers. Gilead is the only company that has a compound in the clinic targeting LOXL2.

Dynavax Ready To Shake Up Hep B Market

The hepatitis B space struck a chord with investors on Jan. 7 as several companies contributed to news in the space, including Dynavax Technologies Corp., Arrowhead Research Corp. and multinational conglomerate Johnson & Johnson. The lead story in the space came out of Berkeley, Calif.-based biotech Dynavax, which has been developing a vaccine for hepatitis B that could turn out to be a major competitor to GlaxoSmithKline's already-marketed vaccine. Due to a better efficacy profile, analysts estimate that Heplisav-B could have peak sales upwards of $700m and could potentially double the hepatitis B vaccine market. Dynavax announced results from a third Phase III study of Heplisav-B that compared it to GSK's Engerix-B in adults ages 18 to 70 years of age. Due to the good news, Dynavax said it will re-file its biologics license application with FDA by the end of the first quarter, with the potential for a six month approval cycle. With this trial under its belt, the drug has been given to more than 10,000 patients. The HBV-23 study was part of the company's pursuit to fulfill FDA requirements after the regulatory agency rejected the drug two years ago. The agency called for further safety data that showed Heplisav-B did not contribute to a higher incidence of autoimmune diseases in patients.

June Verdict For Gilead SOF/VEL Combo

Gilead Sciences Inc. has won a priority review from the FDA for its new drug application (NDA) for its once-daily fixed-dose combination of sofosbuvir (SOF), a nucleotide analogue NS5B polymerase inhibitor, which is marketed as a single agent under the brand name Sovaldi; and velpatasvir (VEL), an investigational pan-genotypic NS5A inhibitor, as a treatment for chronic hepatitis C virus (HCV). The FDA has set June 28 as the Prescription Drug User Fee Act action date for the SOF/VEL combo pill, which had earlier received a breakthrough therapy designation — a status intended to speed the regulatory process for medicines aimed at treating life-threatening conditions. Unlike Gilead's high-profile HCV drugs Sovaldi, which is indicated for genotypes 1, 2, 3 and 4, and its follow-up Harvoni (sofosbuvir/ledipasvir), approved for genotypes 1, 4, 5 or 6 infection, the SOF/VEL combo pill would be intended to treat a much broader group of patients – genotypes 1-6. It’s unclear now, however, what impact the SOF/VEL combo may have on Harvoni’s and Sovaldi’s sales.

Potential Increases For Gene Therapy In Hemophilia B

Investors are getting excited about the promise of gene therapy in hemophilia B as uniQure announces positive results from an early-stage study in the rare blood disorder that could indicate a long-term therapy option is in the near future. Hemophilia B is a rare genetic disorder that mostly affects men and results in spontaneous bleeding that can be fatal. The disease is caused by a dysfunction or lack of expression in Factor IX, which helps with clotting. Patients currently require daily prophylactic treatment to prevent the spontaneous bleeds. There have been new developments in the space that allow patients to go several days between treatments, but patients and physicians are particularly worried about breakthrough bleeding and are searching for more convenient therapies. Gene therapy holds the potential to offer that convenience and could mean patients only have to be treated every few months or even years. The goal of the five-year uniQure study is to see if patients with a severe form of the disease can be improved so that they only have a mild case. While safety is the main goal, the company is monitoring the number of bleeds that patients experience, as well as Factor IX expression levels.

Transgene's Oncolytic Vaccine Enters Phase III

Transgene's development partner SillaJen Inc. has begun the first Phase III trial of the oncolytic immunotherapy Pexa-Vec in patients with advanced liver cancer. Also, the company unveiled a new strategic development plan as well as the securing of €30m new financing. The company has been struggling since April 2014 when Novartis decided not to exercise its option on Transgene's then lead product TG4041, a non-small cell lung cancer vaccine. September 2015 saw Transgene report positive overall survival data from a Phase IIb trial but prospects for the vaccine in a competitive lung cancer market remain questionable. Pexa-Vec (pexastimogene davacene/pexa-Vec) is an oncolytic immunotherapy armed with a GM-CSF gene that promotes an anti-tumor immune response. Amgen recently secured approval for the first oncolytic virus therapy on the market – Imlygic (talimogene laherparepvec), which is indicated as a melanoma treatment. SillaJen owns UK rights to Pexa-Vec through its 2013 acquisition of its originator Jennerex. Transgene, an investor in Jennerex, holds European rights and Lee's Pharmaceutical holds rights in China.
Five Indian Trial Regulation Changes Expected In 2016

India’s clinical trial approval numbers may still be well short of the heady years of 2010-12 but the implementation of a set of crucial trial-related regulations and potential tweaks in others are expected to help bring some momentum back to the sector in 2016.

Top officials of the Indian Society for Clinical Research (ISCR), whose members include several large multinational firms and clinical research organizations, have highlighted the responsiveness of the Indian regulator and government towards facilitating quality trials – the only way new treatments options can be made available to Indian patients at the earliest.

“There is lot of positive intent which has been communicated in all the interfaces that we had with the regulator and bureaucrats – the last such interface as recent as Dec. 23 [2015],” Dr Suresh Menon, member, executive committee and regulatory council, ISCR, told Scrip.

However, he warned that now the authorities must “walk the talk,” especially as regards fine-tuning of a number of “contentious clauses” that might impede the flow of trial-related activity.

India’s clinical research sector has witnessed a significant slow-down over the recent past amid uncertainties and delays caused by still-evolving regulations and ongoing trial-related litigation. India approved 107 trials in 2013 including 17 global clinical trials (GCT); 150 (including 87 GCT) in 2014; and 83 (41 GCT) up to August 2015. Trial approval numbers in in the previous years were: 262 (2012), 321 (2011) and 500 (2010).

Scrip outlines five important regulatory initiatives, expected to potentially play out or be fine-tuned this year, that could trigger optimism in the sector, based on interactions with experts like Menon and ISCR president Suneela Thatte.

India’s IT-enabled system for online submission of clinical trial applications:

Though put in place in Sept 2015, it is expected to get activated this year.

“This will help manage the logistics and approval flow much better and add to transparency and ethical, rational evaluation of clinical trial proposals. Industry is very supportive of this and we hope it gets activated this year,” Menon said.

Similarly, a system of formal pre-submission meetings of applicants with the Central Drugs Standard Control Organization (CDSCO) and subject experts – along the lines of similar systems in the US, EU – though announced in early 2015, is anticipated to go live sometime in 2016.

Mandate to conduct studies only in 50-bed hospitals and cap on trials per investigator:

Industry is hopeful of a review of these norms with greater empowerment of ethics committees (ECs) in such decisions and the government appears to be in sync on the need to evaluate these from a different perspective.

Menon explained how there was at times no need for a 50-bed hospital for studies, such as in areas like dermatology, among others, where just topical preparations are usually used, or in the case of ophthalmic preparations.

“Our submission is that rather than making such blanket caveats, each proposal be evaluated on a case by case basis and then certain norms set, what sort of infrastructure is required and again the ECs will have to play a major role in determining that.” Several stakeholders, including large foreign sponsors, are said to have expressed concern over the existing norms.

In the case of the cap on trials per investigator, expectations are that the government may consider putting the onus largely on ECs to make the decision, since investigators vary in their experience, capabilities, infrastructure and access to support staff.

Audio-visual recording of vulnerable patients:

Last year, India tweaked requirements around audio-visual recording of the informed consent process for clinical trials, mandating it in the case of “vulnerable” subjects in clinical trials of new chemical entities (NCEs) or new molecular entities (NMEs).

However, the absence of clear-cut definitions of the terms NCEs, NMEs and vulnerable in the context of such recording is believed to pose challenges on the ground.

Menon explained that the interpretation now available from the regulator is that NCEs/NMEs are those molecules which are not approved for marketing by any major regulator.

However, with the term vulnerable, in the context of audio-visual recording, not explicitly clear, industry has been relying on the definition as laid out in Indian GCP (Good Clinical Practice) or Schedule Y of the Drugs and Cosmetics Rules.

“Most of the categories mentioned there are fine but there are a few that are difficult to interpret/practice from an audio-visual recording perspective. One piece there is an unemployed person …would that include house wives? The definition of vulnerable existing currently is not with reference to audio-visual recording,” Menon said.

SOPs for subject experts:

A task force constituted by the Drugs Controller General of India (DCGI) under Dr Neelima Khirsagar, ex-dean of Mumbai’s KEM Hospital, set up to review the functioning of India’s subject expert committees (SECs) last year submitted detailed standard operating procedures (SOPs) and proposed an agenda for workshops. The first such workshop for current SEC members is expected in the first quarter of 2016, ISCR indicated.

“The idea is that if these experts come on a common platform and understand the regulations, the scope of review, then there is a standardized process by which protocols are reviewed. Currently, industry experience suggests that one SEC reviews a protocol distinctly differently from another. Hopefully, a lot of standardization is expected in this area moving forward in 2016,” Menon noted.

SECs advise the Indian regulator on trial-related permissions as part of a layered approval process. India currently follows a three-tier review process for clinical trials, under which applications are initially evaluated by specialized SECs. The recommendations of the SECs are then vetted by a technical review committee and finally cleared by an “apex committee.”

Academic research:

In November last year, India indicated that permission of the Drugs Controller General will not be required for trials for academic/research purposes that are “non-regulatory” in nature.

A circular dated Nov. 10, 2015, specified that the exemption applies provided that the trials are approved by the concerned ECs and are not for regulatory submission – i.e. if the trial is not for seeking permission of a “new drug for marketing” as per India’s Drugs and Cosmetics Rules. However, there, seems to be some ambiguity on the exact scope of the circular.

The government has just gazetted draft rules doing away with the need for permission for conduct of clinical trials intended for academic purposes in respect of “approved” drug formulations for any new indication or new route of administration or new dose/dosage form, subject to certain conditions.

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Fanfare For A Down Year

The build-up to this year’s annual JP Morgan Healthcare conference in San Francisco has been muted by recent events and portends a year that has started very differently from the last. This year’s dramatic falls and suspended trading in mainland Chinese stock markets as well as commodity weakness have cast a deep shadow over the healthcare sector, the share prices of which cannot avoid an association with one of the worst stock market starts for many years.

The sector also has its own specific and recent clouds, dominated by the amplification of the drug pricing debate in an election year. It was no surprise then, that there was more comment than usual on the price increases by pharmaceutical and biotechnology companies which came into effect on Jan. 1. I did not notice any presidential candidates jumping to attack even these “business as usual” price increases although their occurrence throughout 2016 will ensure that this remains a “hot button issue.” The analysts from Cowen amongst others, noted the 9.9% price increase enacted on the wholesale acquisition cost (WAC) of Gilead Sciences Inc’s cardiovascular drugs, but there was no mention of any price increases in its HIV antiviral franchise (which is more of a tender business where WAC pricing is less relevant), or its HCV antiviral drugs. Any company developing HCV antivirals faces potential commercial constraints in the medium term: once volume growth starts to slow in developed markets, sales growth by price increases is unlikely to be palatable for a class of drugs that kick-started the whole drug pricing debate two years ago.

In the same way, the business models of the likes of Valeant Pharmaceutical International Inc. and Endo International Plc, which were lauded at the start of 2015, are now assuming pariah status. The model built on borrowing cheaply, acquiring cast-off and uninteresting companies in which no one else was interested, significantly raising the price of these acquired drugs and savagely cutting R&D is irrevocably broken in 2016. This may extend to biotechnology companies whose products have either been out-competed or have growth only by price increases to look forward to in 2016. Even investment bank analysts seem to have grown tired of biotechnology companies’ sales growth being driven only by price increases. The analysts from Piper Jaffray expressed their dismay at Biogen Inc’s 16% end-of-year price increases for multiple sclerosis franchise products that appeared to ‘poke the drug-pricing beast with a stick.’ In addition, the analysts from Jefferies expressed concern that the 2016 consensus sales estimates for Vertex Pharmaceuticals Inc’s cystic fibrosis (CF) franchise may be too high, while those from Piper Jaffray have been concerned since December about the impact of slow reimbursement for Vertex’s CF products in Europe. Presumably, 2016 will demonstrate greater appreciation that while US payers may balk at paying for products that do work, those in the EU seem strangely unwilling to pay for those that have marginal efficacy.

While US payers may balk at paying for products that do work, those in the EU seem strangely unwilling to pay for those that have marginal efficacy

The business models of 2015 are not the only aspect of life science business that seems to have changed for 2016. The pre-announcements of acquisitions and earnings that have in previous years stoked the sector prior to the annual JP Morgan conference seem either absent or muted, at least up to lunchtime on the Sunday the registration desk opens. This time last year we had already woken up with Shire Plc’s acquisition of NPS Pharmaceuticals Inc. and while there is still time for Shire to overpay for Baxalta Inc., and anyone to make the same mistake with Relypsa Inc., the $1.3bn acquisition of Affymetrix Inc by Thermo Fisher Scientific, Inc. feels less like the banner opening M&A transaction for 2016 and more like Affymetrix is being put out of its misery. This is because Affymetrix has been dominated for many years by Illumina Inc., firstly in its DNA microarray business, and then in the relegation of the microarrays by cheaper and quicker next-generation sequencing. Interestingly, the cause of Affymetrix’s frequent profit warnings – Illumina – announced on the eve of the conference that it was launching a new start-up aimed at developing a universal blood test to detect any cancer.

There is still scope for spinning a lacklustre start for life sciences in 2016 into “another banner year.” Molecular diagnostics company Genomic Health Inc. pre-announced its fourth-quarter revenue and volume results, which were applauded with an increase in share price target by the analysts at Ladenberg Thalmann. The analysts at JP Morgan and Cowen were much more discerning in their reportage, describing Genomic Health’s pre-announcement as an ‘operational stumble’ or ‘disappointing’, respectively as its revenues for the quarter were below analysts’ consensus estimates.

Unlike previous years, the attendees at this year’s conference will not be swapping the low temperatures, high precipitation and the relative darkness of East Coast and European climates for the shorts and flip-flop weather of California, and we will have to bring our own vitamin D. I devoted some of the time on the flight over to this year’s conference to note the management of (formerly) potential investments in our funds travelling in the cabin classes above me (and at least one JP Morgan employee). It is comforting to know the propensity for largesse in creating and spending a budget at a loss-making biotech company is one thing that will probably never change.

The Magna Biopharma Income fund holdings include Gilead Sciences, Thermo Fisher Scientific and Illumina.

UPDATE: Soon after this article was written, Shire and Baxalta announced a merger agreement valuing Baxalta at $32bn.

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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Late-stage clinical developments for the week 25 December 2015–7 January 2016

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<td>Sinovac Biotech Ltd.</td>
<td>–</td>
<td>Enterovirus 71 (EV71) vaccine</td>
<td>vaccines</td>
<td>China</td>
<td>Sinovac announced that the China Food and Drug Administration (CFDA) issued the new drug certificate and production license for its Enterovirus 71 (EV71) vaccine. Sinovac expects to receive a GMP license in early 2016 and will start commercial production of EV71 vaccine immediately afterwards. It expects to deliver the vaccine to the market within four to five months after commercial production begins.</td>
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<td>Sanofi</td>
<td>–</td>
<td>Dengvaxia</td>
<td>Dengue fever vaccines</td>
<td>Brazil</td>
<td>Brazil has granted regulatory approval to Dengvaxia, tetravalent dengue vaccine, for the prevention of disease caused by all four dengue types in individuals from 9-45 years of age living in endemic areas.</td>
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<td><strong>REGULATORY FILING ACCEPTED</strong></td>
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<td>Sunesis Pharmaceuticals Inc.</td>
<td>–</td>
<td>Qinprezo (vosaroxin)</td>
<td>acute myelogenous leukemia (AML)</td>
<td>EU</td>
<td>The EMA has validated the MAA for vosaroxin as a treatment for relapsed refractory AML in patients aged 60 years and older. Validation confirms that the submission is complete and initiates the Centralized Review process by the EMA's CHIMP.</td>
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<td><strong>REGULATORY FILING</strong></td>
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<td>Salvat Biotech</td>
<td>Lee’s Pharmaceutical</td>
<td>Duoxal (ciprofloxacin hydrochloride and fluocinolone acetonide)</td>
<td>ear infections</td>
<td>US and Canada</td>
<td>Salvat and Lee’s Pharmaceutical announced that Duoxal is currently under review by the US FDA and by Health Canada. The approval of the product in the US and Canada is expected in 2016. Salvat's local commercial partners will market the product in these territories.</td>
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<tr>
<td>Vericel Corporation</td>
<td>–</td>
<td>MACI (matrix applied characterized autologous cultured chondrocytes)</td>
<td>cartilage and joint repair</td>
<td>US</td>
<td>Vericel announced that it has submitted a US BLA for MACI, its investigational autologous cellular product intended for the treatment of symptomatic cartilage defects of the knee in adult patients.</td>
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<td>Oasmia Pharmaceutical AB</td>
<td>–</td>
<td>Doxophos (doxorubicin/ XR-17 )</td>
<td>breast cancer</td>
<td>Russia</td>
<td>Oasmia Pharmaceutica announced that it has submitted an application for marketing approval of Doxophos for Russia and the Commonwealth of the Independent States (CIS). It expects to receive a decision regarding market approval of Doxophos by the end of 2016.</td>
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<td>ALK-Abello A/S</td>
<td>Torii Pharmaceuticals</td>
<td>TO-206</td>
<td>allergic rhinitis</td>
<td>Japan</td>
<td>Torii has filed a NDA for TO-206, an allergen immunotherapy tablet for Japanese cedar pollinosis to the Japanese Ministry of Health, Labour and Welfare. Torii has been pursuing clinical development of TO-206 which is expected to improve convenience of use (such as storage at room temperature) as compared to Cedartolen Sublingual Drop - Japanese Cedar Pollen, a sublingual immunotherapy drug for Japanese cedar pollinosis, launched in October 2014.</td>
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<td><strong>PRIORITY REVIEW</strong></td>
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<td>Gilead Sciences Inc.</td>
<td>–</td>
<td>sofosbuvir / velpatasvir</td>
<td>hepatitis C</td>
<td>US</td>
<td>For the treatment of chronic genotype 1-6 hepatitis C virus (HCV) infection. Gilead filed the NDA for sofosbuvir / velpatasvir on Oct. 28, 2015, and FDA has set a target action date under the PDUFA of June 28, 2016.</td>
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<td><strong>ROLLING NDA COMPLETED</strong></td>
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<td>CTI BioPharma Corporation</td>
<td>Baxalta</td>
<td>pacitinib</td>
<td>myelofibrosis</td>
<td>US</td>
<td>CTI BioPharma and Baxalta announced the completion of the rolling submission of the US NDA for pacitinib for the treatment of patients with intermediate and high-risk myelofibrosis with low platelet counts of less than 50,000 per microliter (&lt;50,000/μL) – a specific patient population for which there is an existing unmet medical need. The companies are seeking accelerated approval and have requested a Priority Review of the application.</td>
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<td><strong>PHASE III TRIAL INITIATION</strong></td>
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<td>Melinta Therapeutics Inc.</td>
<td>–</td>
<td>Bardela (delafloxacin)</td>
<td>community-acquired pneumonia</td>
<td>–</td>
<td>Melinta Therapeutics announced the initiation of an international Phase III trial (study ML-3341-306) comparing Bardela, an investigational fluoroquinolone, to moxifloxacin for the treatment of hospitalized patients with radiographic evidence of community-acquired bacterial pneumonia. The study is expected to conclude in 2017.</td>
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<td>OSE Pharma</td>
<td>Takeda</td>
<td>Tedopi (EP-2101)</td>
<td>non-small cell lung cancer</td>
<td>-</td>
<td>OSE Pharma announced the initiation of its registration clinical trial named Atalante 1 for advanced NSCLC. This trial aims at evaluating the benefits of Tedopi as compared to current standard chemotherapy (docetaxel or pemetrexed, both approved in second line therapy).</td>
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<td>Akebia Therapeutics Inc.</td>
<td>Mitsubishi Tanabe</td>
<td>vadamustat</td>
<td>anemia due to chronic renal failure</td>
<td>-</td>
<td>Akebia Therapeutics announced that the first patient was dosed in its global Phase III PRO2TECT program in December. The company expects to complete enrollment in late 2017. The PRO2TECT program is designed to support registration in major markets worldwide and to collect the data required to establish a new standard of care for chronic kidney disease (CKD) patients.</td>
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<td><strong>PRODUCT LAUNCH</strong></td>
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<td>Actelion Pharmaceuticals Ltd.</td>
<td>–</td>
<td>Uptravi (selexipag)</td>
<td>pulmonary arterial hypertension</td>
<td>US</td>
<td>Actelion announced the commercial availability of Uptravi for the treatment of pulmonary arterial hypertension (PAH) in the US. Uptravi was approved in the US on Dec. 21, 2015, is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.</td>
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</table>

Source: BioMedTracker
**APPOINTMENTS**

**Ergomed plc**, a UK-based company focused on specialized services for the pharmaceutical industry and the development of new drugs, has named current chief financial officer, Neil Clark, full time CEO of Ergomed’s trading subsidiary PrimeVigilance, a drug safety and medical information business. Clark will remain an Ergomed board member. Ergomed has also named Stephen Stamp CFO and a member of its board. Stamp brings to Ergomed more than 30 years of experience in corporate finance and general management in both public and private companies in the UK and the US. He joins the company from US-based AssureRx Health Inc, a personalized medicine and bio-informatics company where he was also CFO. He has also previously worked at Regus PLC and Shire Pharmaceuticals, where he led the company’s IPO on the London Stock Exchange as well as a number of major acquisitions and financings.

**Recipharm**, a contract development and manufacturing organization, has appointed Yves Buelens general manager for its wholly owned new subsidiary, Kaysersberg Pharmaceuticals SAS. Buelens has been the plant manager for the Kaysersberg facility since 2014. Kaysersberg employs around 260 people. The company, including its main asset a manufacturing facility in Alsace, France, was acquired by Recipharm Dec. 31, 2015. The facility was previously acquired by Alcon in 1984.

**Celgene Corporation** is promoting current president and chief operating officer, Mark Alles, to CEO of the company – effective March 1, 2016. Alles is a three-decade industry veteran and has been with Celgene since 2004, he will replace Bob Hugin as head of Celgene. Meanwhile, Hugin will become executive chair of the company, leading its board of directors. Celgene also announced that Jackie Fouse will be promoted to president and COO of the company. Fouse joined Celgene in 2010 as chief financial officer and is currently president of Celgene’s hematology and oncology franchise. Furthermore, Scott Smith, president of Celgene’s I&I (inflammation and immunology) franchise who joined the company in 2008, will be appointed to chair Celgene’s global management committee.

**E-therapeutics** has appointed Iain Ross to its board of directors as non-executive chair and acting chair Malcolm Young has stepped down, continuing his role as CEO. Ross brings more than 35 years’ experience to e-Therapeutics and is currently non-executive director Anatara LifeSciences Ltd., non-executive chair of Premier Veterinary Group plc. and Biomer Technology Ltd. Previously, Ross held roles in Sandoz, Hoffman La Roche and Celltech Group plc., where he was CEO.

**NEMUS Bioscience, Inc.** has appointed Donald I. Abrams to its scientific advisory board (SAB). Abrams is currently professor of clinical medicine at the University of California and chief of the hematology-oncology division at San Francisco General Hospital. He is also an integrative oncologist at the U.C.S.F. Osher Center for Integrative Medicine and was co-editor of the Oxford University Press textbook of Integrative Oncology. Previously, Abrams was president of the Society of Integrative Oncology and is a member of the National Cancer Institute’s (NCI) Physician Data Query: Complementary and Alternative Medicine editorial board.

Lexington, Massachusetts-based Inotek Pharmaceuticals has named Carsten Boess to its board of directors and board audit committee. Boess is currently chief business officer at Kiniksa Pharmaceuticals, a privately held biotechnology company. Previously he was senior vice president and chief financial officer at Synageva Biopharma Corporation from 2011 until the company’s acquisition by Alexion Pharmaceuticals in 2015.

**Mylan N.V** has announced that John Sheehan is retiring from his position of chief financial officer of the company, effective April 1, 2016. Sheehan, who joined the company in 2010, said in a statement: “This has been the most professionally rewarding experience of my career and I am very proud of all that Mylan has accomplished. I am confident that the talented and dedicated team here will continue to drive strong growth and shareholder value going forward.” Mylan’s board of directors has initiated a search to identify a replacement for Sheehan.

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