10 Approvals To Watch For

Dupixent, Austedo, brigatinib and Olumiant are among a raft of new drug approvals expected (p16)

Expert View

Advisors at Monitor Deloitte outline five design principles to create a value-based care project (p20)

Stockwatch

Most of the big companies have reported 4Q earnings and the clouds that descended after the first week, continued to roll in (p21)

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Carrots and Stick: Biopharma At The White House

Drug industry executives discuss drug pricing and tax and regulatory reform in a high-profile meeting with President Trump at the White House.

CATHY KELLY cathy.kelly@informa.com

President Donald Trump offered a deal to the biopharmaceutical industry during a high-profile meeting with several company representatives at the White House on Jan. 31.

He told them to lower drug prices and expand US jobs, and in return, his Administration will make the tax and regulatory environment in this country more favorable to business. The session served as a forum for Trump to repeat earlier threats about government price controls, which may be intended to coerce better industry behavior. At the same time, Trump was more specific than in the past about potential quid pro quos.

He also emphasized his intention to foster continued innovation in the industry, a sentiment that could play into industry's defense against government price controls. The reaction of attendees after the meeting was generally upbeat.

"We had a positive discussion with the president today. We're encouraged that he supports the need for continued biomedical innovation in the United States, including the need to make our tax code more competitive," Merck & Co. Inc. said in an email.

Amgen Inc. said: "The President and the Administration made it clear that they wish to be Amgen's ally on two critical fronts: first, in the war we wage against serious illness through biotechnological innovation; and, second, in ensuring that jobs – good, highly-skilled and high-paying jobs – are created in the United States."

Merck & Co Chair and CEO Ken Frazier and Amgen Chair and CEO Robert Bradway were two of six biopharmaceutical executives attending the meeting. The others were Celgene Corp. executive chair Bob Hugin, Eli Lilly & Co. president and CEO Dave Ricks, Novartis AG CEO Joseph Jimenez and Johnson & Johnson Pharmaceuticals chair Worldwide Juaquin Duato.

Also attending was Pharmaceutical Research and Manufacturers of America President and CEO Stephen Ubl. vice president Mike Pence was also present, as was House Energy & Commerce Committee chair Greg Walden, R-Ore., who could oversee some of the legislative changes that were raised out at the session.

Trump set the stage for the meeting with a few minutes of on-the-record remarks and then he dismissed the press for what was presumably a more in-depth discussion with attendees. He opened by criticizing industry pricing practices but also implied he was in deal-making mode.

"The US drug companies have produced extraordinary results for our country but the pricing has been astronomical for our country. We have to do better," Trump said.

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IN THIS ISSUE

from the editor

eleanor.malone@informa.com

This week biotech leaders put their signatures to a letter to *Nature Biotechnology* to collectively voice their concern and opposition to President Trump's immigration order. They underline the magnitude and dominance of the US biopharma industry, and how that industry depends on talent from all over the world.

One of the ironies about Trump's belief that other countries have been "freeloading" on the US, and that segregating the US from the rest of the world and bringing corporate activity within US borders will Make America Great Again, is that on close inspection the major engines of the US drug industry look quite – erm – foreign. America's AbbVie didn't develop the world's best-selling drug Humira in-house: it owes its existence to technology developed in the Cambridge on the wrong side of the Atlantic and a partnership with a German-owned company. As for Gilead's HCV blockbuster, Harvoni, second on the list of global best-sellers, we have scientist and entrepreneur Raymond Schinazi to thank. Mr Schinazi was a refugee from the Middle East and his entry to the US would likely have been given short shrift under the current regime.

exclusive online content

Video: Tocagen Aims Double Barrels At Glioma
Gene therapy technology company Tocagen has glioma in its sights. Marty Duvall, newly appointed CEO of the San Diego-based firm, tells Mike Ward how his company's approach has potential to double survival in one of the deadliest diseases, for which little to no effective treatments exist.
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Video: ProNAI Defects From Oligos to DDR As Sierra Oncology
Sierra Oncology president and CEO Dr Nick Glover tells Mike Ward how the company is rebranding itself from its former incarnation ProNAI Therapeutics, armed with two in-licensed assets focused of DNA damage repair (DDR) and $100m in the bank.
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Pfizer Sees Ways To Work With Trump

Pfizer CEO Ian Read said during the company's quarterly call that there are 'lots of ways' to work with the new Trump administration, his comments coming on the same day several industry leaders met with the new US president.

JESSICA MERRILL jessica.merrill@informa.com

Already scheduled to report Pfizer Inc.'s year-end financial results Jan. 31, CEO Ian Read missed the high-profile, face-to-face meeting with President Donald Trump that several other pharma and biotech CEOs attended. But he reassured investors there appear to be opportunities for the industry to work with the new president.

As far as whether or not Pfizer will review its pricing strategy, Read said no. "We are not changing our philosophy vis-à-vis how we price our medications and how we take price increases," he insisted.

Trump has been critical of the industry's high drug prices and even called the industry out for "getting away with murder" during his first press conference Jan. 11 after being elected president. The rhetoric has made executives and investors nervous about the kinds of pricing restrictions the president might try to implement, but in a public statement following the meeting, the Pharmaceutical Research & Manufacturers of America said the meeting went well and discussion revolved around reforming the tax code to spur job creation in the US.

Despite Read's firm stance on pricing, the chief executive noted, "there's lots of ways we can work with the administration to ensure that patients have more affordable drugs in the US."

Trump's number one message to pharma's leadership was to create manufacturing jobs in the US. "That falls squarely inside of getting tax reform, which allow us to reinvest in the US and create jobs, so I think we could be a very big part of the story of creating jobs in the US if we get the tax reform," Read said.

Another option to lower the cost of developing drugs and thus lower the cost to the consumer is around deregulation, Read suggested. Streamlining the approval process would make it easier for generic drugs to be approved, he said.

Other opportunities exist around balancing the out-of-pocket expenses consumers pay for hospital and drug costs, he said, as well as easing regulations that could improve value-based reimbursement contracting. Read was also asked about potential tax risk if the administration pursues a border tax. To that, Read responded only, "I think the Republican leadership has overall tax changes that are overall favorable for the pharmaceutical industry."

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Some analysts questioned how the opportunity to return cash to the US through a tax holiday or other tax reform policy would change Pfizer's business development strategy. Read insisted it won't. The most impactful change resulting from tax reform as it relates to business development is that foreign companies would not have an advantage over domestic ones, he said, which might make assets more affordable.

"But the lens we look at is from a point of view of creating value for shareholders, so I don't see tax reform alters our approach," he said. There will be no "pause" on the M&A front while the company waits to see new tax policy, he added.

The company has completed $40bn in deals since September 2015, chief financial officer Frank D'Amelio added. "If we get dealt a new set of cards, a new hand, then obviously we will play that hand," he said. Pfizer's largest buyout during that time was Medivation Inc., and the addition of the prostate cancer drug *Xtandi* (enzalutamide) helped drive growth in Pfizer's Innovative Health division, which was up 1% to $7.73bn in the fourth quarter and 9% to $29.2bn in 2016, the company reported. Growth was also spurred by sales of the breast cancer drug *Ibrance* (palbociclib) and the blood thinner *Eliquis* (apixaban). Ibrance surpassed $2bn in sales for the year.

Essential Health sales fell 8% to $5.9bn in the fourth quarter, but grew 7% to $23.6bn for the year. The unit was impacted in the fourth quarter from a 20% operational decline from products that have lost exclusivity, but offset by 3% operational growth from the sterile injectable pharmaceutical portfolio and 48% operational growth from biosimilars.

Pfizer saw strong growth off a small base in biosimilars. The first biosimilar to launch in the US, Inflectra, generated $4m in the US in the fourth quarter, the company reported. Pfizer launched the first biosimilar version of Johnson & Johnson's *Remicade* (infliximab) in the US Nov. 21 under partnership with Celltrion Inc. Worldwide Pfizer's biosimilars business, including assets gained from its 2015 acquisition of Hospira, brought in $319m for the full year.

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Lilly CEO 'Encouraged' By Trump Meeting As Volume Drives 4Q Revenue Growth

Lilly's new CEO David Ricks said he had confidence in the Trump Administration's ability to understand and respond to the biopharma industry's needs as well as address drug pricing concerns. The company's fourth quarter earnings could insulate it from cost criticism, since sales volume drove revenue gains, not prices.

MANDY JACKSON mandy.jackson@informa.com

Eli Lilly & Co. president and CEO David Ricks said that he left a meeting alongside other big biopharma executives with President Donald Trump on Jan. 31 with "some confidence" about working with the new administration on tax, regulation and drug pricing issues.

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'I was encouraged by the sense that there will be changes made, most of those will involve the legislative branch'

Lilly may be cushioned somewhat from criticism about its drug price increase practices, since the company's 7% revenue growth in the fourth quarter of 2016 was driven largely by sales volume rather than price hikes. Pharmaceutical product sales volume jumped 9% (15% in the US) while drug prices slipped 1% globally despite a 1% rise in the US. The sales volume gains were driven largely by newer products, which could help Lilly and the industry as they seek government support for innovation.

Lilly reported $5.76bn in fourth quarter revenue versus $5.38bn for the same period in 2015; for the year, revenue rose 6% to $21.22bn in 2016 compared with $19.96bn in the prior year. The financial report was generally in line with analyst consensus, although non-GAAP earnings per share (EPS) of $0.95 for the fourth quarter was $0.03 below consensus as revenue gains were offset by higher operating expenses, including increased sales and promotion costs for new products.

The sales growth numbers may give Lilly a reasonable defense against Trump's statement earlier this month that the industry is "getting away with murder" in terms of drug price increases. The company's double-digit US sales volume boost based on new products compared with a low single-digit pricing gain also aligns with the biopharma industry's message about medicine costs paying for innovation.

'BROAD-RANGING' TRUMP TALK

Ricks noted that he and colleagues from Merck & Co. Inc., Celgene Corp., Amgen Inc., Novartis AG and the Pharmaceutical Research and Manufacturers of America (PhRMA) had a "good meeting" and "broad-ranging discussion" with Trump, who was "very interested in understanding how our business works and what the opportunities are to further grow the American innovative engine in the biopharmaceutical industry."

Ricks said the executives spoke with the president about "taxes and how that could be a positive catalyst for more investment and growth in the US industry" as well as "finding ways to reduce and streamline regulation both at the FDA side, but also in health care markets that the government plays a role in. And then, of course, we did speak about pricing."

The Lilly CEO said the industry executives understand Trump's concerns about drug costs and price increases as well as the issue of rising out of pocket costs that patients pay for medicines "and how we can do a better job as an industry of getting discounts through to consumers, particularly those in high-deductible plans and government programs."

"We did not get into elaborate policy detail in terms of the US pricing environment," he continued, "but I think there'll be time for that later, and I left the meeting with some confidence that the people who we'll be working with closely as legislation moves forward have a good grasp of those facts."

As for the timing of any legislation pertaining to taxes, regulations or other biopharma industry-related matters, Ricks said he was not at liberty to share details about when Congress might act.

"But I was encouraged, overall, by the sense that there will be changes made, likely rapidly; most of those will involve the legislative branch; and that there will be follow-up with the White House to make sure we're making progress as we go along," Ricks said. "I think it was productive to engage the President – educational for both sides – and I think we can go forward and really look at enacting policies that can both help the industry, but also health care in the United States."

He said in response to a question about whether the role of pharmaceutical benefit managers (PBMs) could become a bigger part of the drug pricing discussion that PBMs were not a centerpiece of the executives' talk with Trump about the cost of medicines. However, the group shared PhRMA's recent report with the president, which found that only 39% of gross medicine expenditures in 2015 were captured by branded drug manufacturers, while 42% went to payers and others.

Ricks, who led his first quarterly earnings call since taking over Lilly's CEO role from John Lechleiter, may prove to be a good choice for the company – and for the industry – to work with the Trump

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Administration on drug pricing issues, including the role of PBMs. He was involved in the management of PBM relationships for Lilly in his previous role as President of Lilly Bio-Medicines. He advocated for pre-approval drug pricing discussions with payers to avoid sticker shock when new products launch.

NEW PRODUCTS

A change in that area could be especially important for Lilly since the company is sticking with its goal of launching more than 20 new molecules between 2014 and 2023, including more than two new products or label extensions per year. Lilly also maintained its forecast of 5% revenue growth annually between 2015 and 2020.

Key launches and label extensions in 2016 included:

- Line extensions to include cardiovascular outcomes data for *Jardiance* (empagliflozin) and empagliflozin-containing fixed-dose combinations in the US (Jardiance sales totaled $76.1m in the fourth quarter and $201.9m for the year versus $60.2m in 2015)
- *Taltz* (ixekizumab) for psoriasis in the US and EU, and for psoriasis and psoriatic arthritis in Japan ($61.3m in the fourth quarter and $113.1m for the year)
- US and EU approvals for *Lartruvo* (olaratumab) in soft tissue sarcoma ($11.9m in the fourth quarter)
- A first-line squamous NSCLC label for *Portrazza* (necitumumab) in the EU ($3.8m in the fourth quarter).

This year's potential approvals include baricitinib for rheumatoid arthritis (RA) in partnership with Incyte Corp., although the FDA decision regarding the JAK inhibitor has been delayed by three months and is now expected in April. It's already recommended for approval in the EU.

Jefferies analyst Brian Abrahams said in a Jan. 31 research note on Incyte that "comments from partner Lilly on their earnings call this afternoon in our view provide incremental reassurance that despite the PDUFA delay, there are no major issues with the baricitinib data package (and NDA), and that the drug remains likely to be approved near-term. Though RA payer contracting could make adoption gradual, we believe the highly competitive profile will enable meaningful long-term revenue contributions to Incyte."

Another potentially important approval could come in the US in May if the FDA endorses Merck's PD-1 inhibitor *Keytruda* (pembrolizumab) in combination with chemotherapy using carboplatin and Lilly's *Alimta* (pemetrexed). Data for the three drugs showed a significant improvement in overall survival last year compared with Alimta and carboplatin alone in lung cancer.

A US District Court recently upheld the Alimta vitamin regimen patent, keeping generic competition from impacting US sales for a while longer, but the blockbuster's sales fell 14% in the fourth quarter to $541.6m and declined 8% for the year to $2.28bn globally based on ex-US patent decisions and competition from immunotherapies.

SEARCH FOR EFFICACY ENDS

One potential blockbuster that won't move forward for Lilly in 2016, however, is solanezumab after its November failure in mild Alzheimer's disease. The company held out some hope that the amyloid-targeting therapy would help patients with prodromal Alzheimer's, but Lilly executives revealed during the fourth quarter earnings call that it terminated the EXPEDITION PRO study after further analysis of the EXPEDITION3 results. The investigator-sponsored DIAN TU and A4 studies, looking at preventing Alzheimer's in at-risk patients, are ongoing.

Lilly has not given up on the amyloid hypothesis yet, however, even though it essentially has given up on solanezumab. The company and its partner AstraZeneca PLC are studying the beta secretase (BACE) inhibitor AZD3293 in Phase III.

"My view is it's too early to say" if the amyloid hypothesis is wrong, president of Lilly Research Laboratories Jan Lundberg said during the company's earnings call. "We need to wait for even more powerful agents and the next in turn are the oral BACE inhibitors, which are more likely, I think, to have an even stronger effect on the amyloid beta in the brain."

Bernstein analyst Tim Anderson said in a Jan. 31 note that Merck's more advanced Phase III BACE inhibitor is likely to have at least a signal of positive efficacy in its first pivotal study, even without pre-screening patients for the presence of amyloid in the brain, because of the drug's potent mechanism. Those data are expected mid-year.

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Purdue Is Open For Business Deals

Purdue Pharma LP's initiative to diversify includes business deals on multiple fronts, including in its core area of pain but also in new "innovative" areas and through commercialization deals with ex-US partners, CEO Mark Timney said in a recent interview.

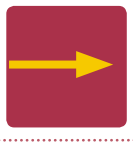
The chief executive has set deal-making as a top priority for Purdue since taking over the helm of the private specialty pharma in early 2014. The strategy is a key one to diversify the company away from its core specialty in opioid pain as the space comes under pressure from generics, more abuse-deterrent competition and pushback on overuse.

Purdue, based in Stamford, CT, signed several deals last year that took the company outside of its comfort zone in central nervous system disorders, a goal Timney has previously highlighted. One of the most significant was a deal announced in December with Exicure Inc. for up to $790m in payments for rights to ST-0005, a topically-applied spherical nucleic acid that targets tumor necrosis factor, and broader platform access.

"It's real diversification away from pain," Timney said of the deal during a sit-down at the J.P. Morgan Healthcare Conference. "We are not thinking [just] psoriasis. We are more thinking inflammation, which opens up a whole new world for us." Purdue has options on three additional targets under the collaboration but has yet to identify what those will be.

ST-0005 is in Phase I development, and Timney said the company hopes to see it move into Phase II later this year. The Exicure deal is one Timney described as being "higher innovation," where there is an opportunity "see where the science is going and then build an organization around it."

jessica.merrill@informa.com, 1 Feb 2017



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Merck's Keytruda Reaches Blockbuster Status

JOSEPH HAAS joseph.haas@informa.com

Merck's PD-1 inhibitor Keytruda brought in $1.4bn in 2016 and appears poised to take advantage of first-mover status among immuno-oncology agents in first-line NSCLC.

Merck & Co. Inc.'s *Keytruda* (pembrolizumab) finally reached the blockbuster benchmark in 2016 and while it still tails Bristol-Myers Squibb Co.'s PD-1 inhibitor Opdivo, there are signs Merck's anti-PD-1 cancer immunotherapy is positioned to dominate in the key first-line non-small cell lung cancer setting thanks to first-mover advantage and what one analyst called smart development and filing strategies.

The pharma reported flat overall revenues for fourth quarter 2016 on Feb. 2, but called Keytruda a key growth product that continues development in a number of cancer indications and drug combinations. Merck Research Laboratories president Roger Perlmutter noted during the investor call that the company is "supporting more than 430 studies of Keytruda in various settings, including an ever-larger fraction of combination protocols using novel immune modulators as well as traditional chemotherapeutic agents."

The comment underscores how integral Keytruda is to Merck's future performance.

Keytruda brought in $1.4bn for full-year 2016, up 148% from the $566m recorded globally in 2015. Worldwide sales came to $483m during the fourth quarter, up 125% year-over-year, including $311m in US sales. That compares to $3.77bn for Bristol-Myers Squibb Co.'s PD-1 inhibitor *Opdivo* (nivolumab) for 2016 and $1.3bn in the fourth quarter.

This was the first quarter where Keytruda had an edge over Opdivo, after Merck's drug cleared FDA last October for use in first-line non-small cell lung cancer (NSCLC) and Bristol's failed in the CheckMate 026 study in the same setting.

KEYTRUDA'S PERFORMANCE

Keytruda sales are seeing a boost from greater PD-L1 testing; management reported that about two-thirds of first-line patients are now getting tested, versus about one-third before the data presented at ESMO in 2016. Keytruda's first-line approval is for patients with at least 50% PD-L1 expression, and according to the company, the vast majority of eligible first-line patients are getting treated.

Of the $311m in the fourth quarter US sales, executive VP-global human health Adam Schechter estimated 40% were in melanoma – the drug's initial indication – 30% in lung, 15% in head-and-neck cancer and 15% in other cancers. That means the lung cancer share has only gained five points since the first-line approval; for the third-quarter 2016, Merck estimated 25% of Keytruda sales came from lung cancer, compared to 50-55% in melanoma with 5% in head-and-neck cancer.

But there are other signs of progress. Leerink Partners analyst Seamus Fernandez reported in a Jan. 25 note about monthly sales data from Symphony Health that Keytruda and Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab) were driving sales growth among immuno-oncology drugs, up 14% and 13% from November to December, respectively. This growth came at the expense of Opdivo, which generated 2% month-over-month growth. Keytruda sales also grew 14% from October to November.

COMBO WITH CHEMO

Merck does also stand to gain first-mover status with combinations, with its combination with chemotherapy – Eli Lilly & Co.'s *Alimta* (pemetrexed) and carboplatin. And while it isn't a dual checkpoint inhibitor combination, the chemo partnering will be less expensive than an all-immunotherapy combo.

Though there is some concern about the strength of the data supporting the pending FDA submission, Perlmutter maintained that the data are confirmatory of an earlier study, giving the application strong grounds for approval. The KEYNOTE-021G study showed a response rate of 55% and a near doubling of progression-free survival compared to chemotherapy alone, Perlmutter noted.

"These data represent, to my knowledge, the first controlled data comparing a combination with chemotherapy and, as a result, I think are quite significant," the exec said. "I will not predict how an FDA or any regulatory agency will respond to those data, but I do think the results stand on their own."

Bernstein analyst Tim Anderson estimated the filing's approval chances at 50/50 in a Feb. 2 note, but said investors may fail to understand that the supplemental biologic license application (sBLA) is not attempting to alter the treatment paradigm in first-line NSCLC since the standard of care is chemotherapy, except in high expressers of PD-L1 where Keytruda is now positioned as standard of care.

"It would be different if Merck were trying to substantially change the treatment paradigm – this is in fact what Bristol and AstraZeneca are attempting to do, by replacing chemotherapy altogether," Anderson said. Perlmutter indicated that the approval being sought for combination with chemotherapy is only the tip of the iceberg of what Merck is working on regarding additional approvals and treatment settings for Keytruda.

"Filings for US supplementary biologics licensing approvals for Keytruda are expanding logarithmically, which, together with our worldwide supportive filings, contributes to the enormous workload that we are experiencing in clinical research and regulatory affairs," he said. "I've said before that Keytruda is changing the landscape of cancer treatment, representing a fourth pillar, if you will, beyond surgery, radiation therapy, and traditional chemotherapy that provides hope for further progress in the treatment of malignant disease."

Asked about the possibility of combination with CTLA-4 inhibitors, Perlmutter was agnostic, saying that Merck wants to spread as wide a net as possible for therapeutic combinations and options.

"We remain interested in the broadest possible set of combinations that can have beneficial impact for patients. And that includes immunotherapies, not just CTLA-4, but other things as well," he said. "My expectation is that with time we will see that treatment regimens are more and more personalized. I do not expect that one size will fit all here and that every cancer patient will receive the same combination, whether it's chemotherapy or immunologic manipulation."

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CONTINUED FROM COVER

"We have to get prices down for a lot of reasons," he added. "We have no choice, for Medicare, for Medicaid, we have to get the prices way down. So that's what we're going to be talking about."

Trump also said that "competition is the key to lowering drug prices," and mentioning Medicare, said "we can increase competition and bidding wars big time, we have to, into that program."

At the same time he stated, "I'll oppose anything that makes it harder for smaller younger companies to take the risk of bringing a product to a vibrantly competitive market." So "we're going to basically work on innovation, we're going to work on price. We can save tens of millions of dollars and you people are going to do great."

Commenting on the meeting and Trump's stance on drug pricing, PhRMA reiterated a commitment to market-based solutions like value-based purchasing but said regulatory and legislative obstacles are standing in the way.

"Our industry takes seriously the concerns raised about the affordability and accessibility of prescription medicines, and we have expressed our commitment to working with the administration to advance market-based reforms," the trade group said.

"The current system needs to evolve to enable the private sector to lead the move to a value-driven health care system. To do this, we need to reform existing laws and regulations that are currently preventing private companies from negotiating better deals and paying for medicines based on the value they provide to patients and our health care system."

The industry has pointed to several regulatory obstacles to broader adoption of value-based payments, including FDA restrictions on communications between manufacturers and payers, a lack of legal "safe harbors" from anti-kickback rules and concerns that prices negotiated under outcomes-based contracts will trigger a new "best price" requirement in Medicaid.

US EXPANSION

Trump suggested that his Administration would work to reduce the tax and regulatory burden on US companies to encourage them to retain factories in this country or move production back from locations abroad. He promised faster FDA approvals as one important regulatory reform.

"A lot of companies have moved out. They don't make the drugs in our country any more. A lot of that has to do with regulation," he commented.

"I want you to move your companies back to the US. I want you to manufacture in the US. We're going to be lowering taxes, big league. We're going to be getting rid of regulations that are unnecessary, big league."

> 'Competition is the key to lowering drug prices'

"We're also going to be streamlining the [approval] process. So from your standpoint, when you have a drug, you can actually get it approved if it works instead of waiting many, many years. … We're going to be changing a lot of the rules."

At the start of the meeting, Novartis' Jimenez told Trump that lowering the corporate tax rate globally would be a "massive" help to companies.

"Yep, we'll get it," Trump answered.

Trump also suggested that he would work to ensure companies get a better return on drugs sold abroad.

"We're going to be ending global freeloading. Foreign price controls reduce the resources of American drug companies to finance drug R&D and innovation. I think you people know that very well. It's very unfair to this country. Our trade policies will prioritize that foreign countries pay their fair share for US manufactured drugs so our drug companies have greater financial resources to accelerate the development of new cures."

He also pledged to work against currency "devaluation" in foreign markets to help bring operations back to the US.

"A lot of countries take advantage of us with their money supply and devaluation because we don't know anything about it. Our country has been run so badly we don't know anything about devaluation. Every other country lives on devaluation. You look at what China is doing, you look at what Japan has done over the years. They play the money market, they play the devaluation market and we sit here like a bunch of dummies."

Published 31 January 2017

Novo Still Seeking Superior Tresiba Follow-On

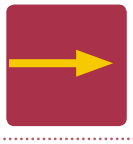
Despite dropping its Phase II oral insulin program in the second half of 2016, Novo Nordisk's chief scientific officer says the company is quietly continuing to explore options for an oral therapy better than its leading insulin option, Tresiba.

Novo Nordisk AS's full year earnings for 2016 and financial outlook for the coming year were littered with disappointments; and analysts have highlighted that the company is facing the repercussions of its diabetes-only mindset amid tough market conditions for these products sector-wide. Still R&D leader, Mads Krogsgaard Thomsen, had a lot to say about Novo Nordisk's continued hunt for better type 2 diabetes options.

During the Danish company's full year earnings press conference call on February 2, Thomsen responded to queries around Novo Nordisk's Oct. 2016 decision to end development of its oral insulin degludec product – a follow-on therapy to Tresiba in tablet form. He said the choice was difficult to make but the program had been made redundant due to a sharp decrease in prices for insulin products that would make a new oral option hard to market. The oral insulin compound dropped by Novo Nordisk last year, NN1953, had been in Phase II studies. However, while shelved for the time being, the idea of a superior, oral insulin for type 2 diabetes has not been dismissed.

"It was traumatic to have to say that oral insulin in this pricing environment is not going to make it," Thomsen said. "Hence we have to wait for a breakthrough that might come from our collaborations with MIT or others one day, who knows. We may, one day, be able to rejuvenate such products but it will have to be on the basis of commercial viability."

lucie.ellis@informa.com, 2 Feb 2017



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Novartis' Bradner On CAR-T, CRISPR & DNA Libraries

STEN STOVALL sten.stovall@informa.com

The head of Novartis' early drug discovery engine NIBR has a zealous sense of mission and says he is being given the resources and talent to accomplish it. "Nothing is undruggable," is his premise.

James Bradner

Moderation isn't the first word that comes to mind when hearing James Bradner describe his ambitions for the Novartis Institutes for BioMedical Research, which he has headed since March 2016. "I came to lead NIBR to make NIBR the most impactful and most productive biomedical research institute in the world. I'm very excited about having the opportunity to reshape NIBR for the future," he said, outlining his mission.

Bradner's remit, as underscored in an interview with *Scrip* and at an R&D update to investors by Novartis AG, includes advancing the company's discovery and developments of CAR T-cell therapies to potentially treat solid tumors, developing targeted therapeutics such as sickle cell disease using CRISPR gene editing, targeted protein degradation to discover new drug targets, and the building of an huge DNA library of 300m compounds "to give expanded scope of chemistry and give us more starting points." He talked to *Scrip* about the company's use of these advanced technologies.

CAR-T EMPHASIZED

Novartis was the first big pharma to jump at the promise of chimeric antigen receptor T cell (CAR-T) therapy, but in 2016 it moved to disband that standalone unit and take its assets back into internal R&D in a move aimed at centralizing control over drug discovery and curbing costs.

Bradner acknowledged the move, which triggered some high-level personnel changes and job cuts, sowed uncertainty over what Novartis was ultimately planning in CAR-T.

"There was some confusion in the community regarding the news to reintegrate the CAR-T research and development unit into Novartis, and that is understandable. The integration of these units has gone incredibly well if not uneventfully. It has allowed us to be much more strategic in how we resource these projects," Bradner said, adding that NIBR today has 18 immuno-oncology medicines in its pipeline "and a suite of targeted therapies."

Bradner said resulting synergies have given NIBR sharper focus and higher potential for discovering CAR-T medicines and freed up funding so NIBR can now double its investment in the manufacturing of CAR-T treatments, which involve extracting immune cells and genetically engineering them to find and destroy cancer cells before putting them back in the patient's body. He did not give details on the amount that would be spent, however.

Along with researchers at University of Pennsylvania, NIBR plans to test CAR-T treatments in the solid tumor space, targeting cancers of the brain, lung, pancreas, colon, and ovary.

"With our colleagues at University of Pennsylvania, we are currently interrogating two targets. [These are] the variant III isoform of the epidermal growth factor receptor that's expressed at about 20% or so of glioblastoma multiforme, a lethal brain cancer, as well as mesothelin, a cell surface protein that's expressed on many important adenocarcinomas such pancreas, colon, ovarian and lung," Bradner said, adding: "It's early days, but, either used alone or potentially in combination with any one or more of our 18 immune-oncology therapies we are well positioned to thoroughly explore the hypothesis of CAR-T cell therapy in solid tumors."

Novartis' lead CAR-T cell therapy, CTL019, involves T-cells that are removed from patients and reengineered to express CD19 so that the boosted T-cells attach and kill cancer cells expressing the antigen. Bradner said Novartis aimed to file CTL019 for the treatment of pediatric acute lymphoblastic leukemia (ALL) in the US in the first quarter, and in Europe later in the year. CTL019 is one of 13 late-stage pipeline assets that Novartis believes have blockbuster potential.

"Further, in diffuse large B-cell lymphoma we intend to file in the second half of the year, the same CD19 directed therapy. Beyond CD19, we're very excited about BCMA," he added. BCMA is a cell surface protein on plasma cells which when they become cancerous are called multiple myeloma cells. "It's very early days at NIBR but we have innovated a BCMA-directed CAR-T cell therapy that we are presently studying with the University of Pennsylvania, and as presented at recent hematology congresses, we are seeing early and inspiring activity from that product as well."

CRISPR OBJECTIVES

Like nearly all pharma companies, Novartis is now heavily involved in CRISPR, a method in which the snipping out and splicing in of DNA takes place in situ, within the organism.

Human biology laboratories all over the world now have the ability to discover, validate and model targets in disease biology in a way that they couldn't before,

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and CRISPR is already widely used in NIBR to understand the biology and direct drug discovery. NIBR wants to use a proprietary CRISPR technique to find a potential therapy for sickle cell disease, a debilitating condition, primarily affecting children of African descent who later move on to adulthood and have very truncated life expectancy. There hasn't been a new medicine to come to market in 15 years.

"There are diseases such as sickle cell disease and others where the disease biology has been understood at molecular detail for decades, yet there is no targeted therapeutic. As yet, mutated hemoglobin has proven an intractable drug target. So we need to therefore reconsider what it means to be a therapeutic, perhaps, to make a definitive treatment for sickle cell disease and we believe CRISPR has this potential," Bradner told *Scrip*.

STEM CELLS

NIBR has created a capacity to grow patient derived stem cells and then edit the stem cell genome so as to re-express the unmutated fetal hemoglobin. "In this way, we believe we can compensate for the heritable cause of sickle cell disease. Although it is early days, we have transitioned this project into an active stage of preclinical development and moved very much forward in bringing medicine based on CRISPR to patients with sickle cell disease in years to come."

Novartis and NIBR have been pursuing stem cell biology and stem cell directed therapeutics for many years, and the study of hematopoietic stem cell transplantation and blood stem cell biology have been particular areas of focus. "An outcome of that research was the discovery of a series of molecules that when added to growth media can dramatically enhance the cultivation of blood stem cells. The ability to expand blood stem cells in our proprietary way presents a unique opportunity to then edit those stem cells with the CRISPR cas9 system. Bradner said NIBR was therefore well positioned to consider CRISPR cas9 as a therapeutic technology for diseases of the blood.

DNA ENCODED LIBRARY

Meanwhile, the complicated nature of drug discovery has necessitated the establishment of a next generation DNA encoded library platform at NIBR, which Bradner says will open huge possibilities in future. The dramatic expansion of chemical diversity afforded by DNA encoded libraries presents an unparalleled opportunity for lead discovery, he believes.

"We are organized around the high hanging fruit of drug discovery, where targets are difficult to drug, and therefore, having powerful discovery chemistry platforms is essential. This is where DNA encoded library technology comes in," he said.

NIBR has highly proprietary DNA encoded libraries and through their use has identified leads for targets that have escaped drug discovery efforts for generations, he explained. Novartis has shared its insights into building such DNA libraries with other pharma groups, the premise being that "like the rising tide that floats all boats we believe this is a powerful discovery technology that the world should have better access to," Bradner said.

> 'Often, in biopharma drug discovery, people collect the lowest hanging fruit. This company has shown historically that it is best positioned'

Bradner believes NIBR and Novartis as a company will maintain its leading position with drug discover going forward.

"Often, in biopharmaceutical drug discovery, people collect the lowest hanging fruit. And this company has shown historically that it is best positioned; its greatest contributions are when we reach the highest hanging fruit. This requires innovating a new science of therapeutics from which breakthrough drug molecules can be developed.

The NIBR head says Novartis currently has more than 100 projects and 70 NMEs in exploratory clinical studies. "That will allow us to keep fueling this pipeline for the future," he concluded.

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Takeda Adds Exelixis Arrow To Oncology Quiver

Takeda's acquisition of Japanese rights to Exelixis' lead product fills a gap in the oncology portfolio while adding another piece to the US company's global licensing jigsaw.

Takeda Pharmaceutical Co. Ltd. has paid $50m upfront to acquire exclusive commercialization rights in Japan to Exelixis Inc.'s oral small molecule cancer drug cabozantinib, for all potential indications including advanced renal cell carcinoma (RCC).

South San Francisco-based Exelixis is also eligible for further development, regulatory and first sales milestone payments totaling up to $95m for the first three developed indications, plus sales royalties.

The agreement will provide Takeda with a therapy in a disease where it has so far not had a developed presence, despite a rising incidence of RCC in major markets including Japan, and further builds out the company's strategic interest in oncology in the wake of the planned $5.2bn acquisition of Ariad Pharmaceuticals Inc.

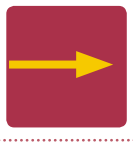
Takeda's only other disclosed pipeline asset for renal cancer is the mTORC1/2 inhibitor TAK-228, in US Phase IIb trials.

Following the new agreement, Takeda and Exelixis said in a joint statement they would work together on completing the additional clinical studies needed in Japan to enable an approval filing in RCC as the initial priority "as soon as we're able."

The hope is to build on some early-stage clinical work, including a Phase I study in solid tumors, that has already been conducted in the country by Exelixis. Takeda in Tokyo told *Scrip* that it was still too early to say when an approval filing for RCC might be made in Japan.

See p19 for Takeda's Q4 earning.

ian.haydock@informa.com, 30 Jan 2017



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Allergan's Ophthalmology Focus Grows

Allergan PLC frequently talks about wanting to "own the face" in terms of its aesthetic medicine business, but the company also is increasing its focus on the eye with products for various ophthalmic conditions – an area in which Allergan management has deep experience. The second highest-selling product in Allergan's portfolio – behind the wrinkle-reducing and migraine-busting *Botox* (onabotulinumtoxinA) – is the blockbuster *Restasis* (cyclosporine) for dry eye disease, which is facing new competition. But the company also inherited as part of its $66bn namesake acquisition in 2015 a portfolio of glaucoma drugs, a drug-device combination product, and the beginnings of a diverse ophthalmology research and development pipeline, including therapeutics, devices and surgical procedures. Allergan's R&D and commercial heads, interviewed during the J.P. Morgan Healthcare Conference in January, believe that the company best serves its customers – and ultimately its bottom line – by sending its sales representatives into ophthalmologists' offices with a bag full of varied products.

mandy.jackson@informausa.com, 3 Feb 2017

Isofol's Modufolin Could Change Mainstay Therapy

Gothenberg, Sweden-based biotech Isofol Medical AB expects to start a pivotal Phase III study at the end of 2017 with its single asset, Modufolin, potentially a more effective product to combine with 5-fluorouracil (5-FU) than conventional *Leucovorin* (folinic acid). The company is currently working on raising new funds for the study that could include an initial public offering. Over the years Isofol has raised around €20m ($21m) from its private investors. If the trial is successful, Isofol will likely look for a company to buy or commercialize the new product, said its CEO, Anders Rabbe. Back in the 1970 and 80s, the use of Leucovorin was found to increase the proportion of patients that responded to 5-FU; in patients who responded, Leucovorin was converted to the active metabolite, methylene tetrahydrofolate. It was hypothesized that those patients unable to convert folinic acid might instead respond to the administration of the active metabolite, but that at the time that couldn't be done because of the instability of methylene tetrahydrofolate. But in the past few years, a specific salt of one isomer of the active metabolite, [6R]-5,10-methylene-tetrahydrofolate, has been discovered to be stable and this is now the active ingredient in Modufolin. Its global development and marketing rights in colorectal cancer were obtained from Isofol's manufacturing collaborator, Merck & Cie, part of Merck KGAA.

john.davis@informa.com, 31 Jan 2017

Novo Uses UK Academia To Feed Diabetes Pipeline

Novo Nordisk AS is investing DKK1bn (£115m) over 10 years into a new research center at the University of Oxford in the UK to boost its waning type 2 diabetes pipeline, regardless of the ambiguity around access to talent for UK establishments post-Brexit. Financial analysts have recently highlighted Novo Nordisk's lack of a transformational pipeline in type 2 diabetes as a blockade for growth of the business in the coming years. But the company believes this collaboration with the University of Oxford will provide several partner and collaboration opportunities within type 2 diabetes drug development. "Co-creating early-stage research projects is not something we have done to a great extent at Novo Nordisk," the company highlighted. "The establishment of this new research center allows for more focused early-stage research in type 2 diabetes. To Novo Nordisk it means more focus on project progression." Novo Nordisk has already started work to establish the new research center in the UK. Its activities in the coming months will include on-boarding of new employees and setting up the research facility with needed equipment. The strategic collaboration with the University of Oxford will be initiated at the time of inauguration of the research facility, Novo Nordisk said. The university will be responsible for discovering new therapies, while the pharma firm will carry out clinical development of drug candidates.

lucie.ellis@informa.com, 30 Jan 2017

Pfizer To Take Zinplava Rival Into Phase III For C Diff

Top-line data for Pfizer Inc.'s investigational vaccine PF-06425090 for the prevention of Clostridium difficile infection from a pre-planned interim analysis are strong enough to warrant taking the product into a Phase III trial due to start in the first half, the company says. Pfizer is spying territory currently occupied by Merck & Co. Inc.'s *Zinplava* (bezlotoxumab) which was finally approved by the FDA in October despite some concerns by its Antimicrobial Drugs Advisory Committee at its meeting in June, and also recently received EU approval on Jan. 18. The two major studies supporting its approvals – MODIFY I and II – have just been published in the *New England Journal of Medicine*. But Pfizer is competing with Sanofi, which has a similar candidate ACAM-CDIFF already in Phase III testing, plus smaller company Valneva SE, which also has a vaccine product that has completed Phase II (the company is looking for a licensing partner for Phase III). The new non-antibiotic products are taking different but closely related approaches to the disease.

alex.shimmings@informa.com, 30 Jan 2017

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Canada First To OK Sanofi/Regeneron's Sarilumab, But Struggle To Differentiate Looms

Sanofi/Regeneron's Kevzara (sarilumab) has won its first worldwide approval for treating moderately to severely active rheumatoid arthritis from Health Canada. But as more regulators follow, the companies will face a battle to differentiate the drug from chief rival, Roche/Chugai's Actemra (tocilizumab).

FRANCESCA BRUCE francesca.bruce@informa.com

Health Canada has become the first regulator to approve Sanofi /Regeneron Pharmaceuticals Inc.'s rheumatoid arthritis treatment and IL-6 receptor inhibitor Kevzara (sarilumab). Analysts expect further approvals and launches in the second and third quarters of 2017, but, without competitive pricing, a lack of head-to-head data comparing *Kevzara* with its main competitor and first-to-market IL-6 receptor antagonist, Roche/Chugai Pharmaceutical Co. Ltd.'s Actemra, could prevent the drug from taking a significant market share, according to Datamonitor Healthcare.

> 'If sarilumab is priced very much less than Actemra, then we will be told by our pharmacists and managers that we have to use that preferentially'

Canadian authorities have approved Kevzara for treating adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more biologic or non-biologic disease-modifying anti-rheumatic drugs (DMARDs). The news comes after the US FDA sent the companies a complete response letter back in October, citing concern over deficiencies identified during a routine good manufacturing practice inspection of Sanofi's French Le Trait facility, where sarilumab is filled and finished.

Sanofi declined to comment on whether the manufacturing issues had been a problem for Health Canada or any other regulator, but said it has provided its "responses to the FDA based on the manufacturing deficiencies that were identified and believe them to be comprehensive and robust." The company did not say when it expected an approval in the US, although Datamonitor Healthcare expects the green light to come during the second quarter of 2017 before a third quarter launch. Assuming a positive decision from the EU, Datamonitor believes European launches will begin in the fourth quarter of 2017, starting with Germany and the UK, and with France, Italy and Spain to follow in the final quarter of 2018.

Sanofi declined to comment on it launch strategy, but said that it is in "full execution mode for our launch preparations for sarilumab." Launch will be handled by its Specialty Care Business Unit (Sanofi Genzyme), "which has successfully launched our MS franchise," the firm noted. "We expect to leverage many of those experiences for the sarilumab and dupilumab launches."

Meanwhile, pricing strategies have taken into account biosimilar entry and competitive discounts, the firm said: "We believe our positioning and data will ensure our price is competitive and sustainable." Datamonitor expects that the drug will be priced in line with Actemra. Details of the Canadian price will be released next week when the product is launched there.

PRICE TO COMPENSATE

However, a lack of differentiation between the two IL-6 receptor inhibitors, namely the absence of a head-to head study, will likely will prevent sarilumab from capturing significant market share, unless Sanofi and Regeneron are competitive on price, said Datamonitor Healthcare analyst Christina Vasiliou.

"Key opinion leaders stress that sarilumab's clinical performance to date has been comparable to that of Actemra and, as a result, they would consider using it in the same treatment setting where they currently use Actemra, ie primarily in non-responders to anti-TNF biologics, and as a first-line biologic in rare cases of high disease activity, co-morbidities, or safety concerns," she said.

To boot, Kevzara will be at a disadvantage after launch because of the availability of Actemra post-marketing data and physician's experience with the product. Without a significant price advantage, Actemra will remain the IL-6 inhibitor of choice, Vasiliou predicted. "Indeed, key opinion leaders stress that that sarilumab's ultimate success will depend upon its pricing relative to Actemra; in order to gain significant market share, sarilumab needs to secure preferential reimbursement to the first-to-market IL-6 receptor inhibitor."

One EU key opinion leader told Datamonitor that the big issue in choosing between the two drugs will be price. "If sarilumab is priced very much less than Actemra, then we will be told by our pharmacists and managers that we have to use that preferentially."

Asked if it had any plans for a head-to head study against Actemra, Sanofi responded that it is "confident in [the] body of clinical evidence."

Nevertheless, Vasiliou pointed out that sarilumab demonstrated improvements in methotrexate inadequate responders in the Phase III SARIL-RA-MOBILITY study, as well as superiority to Humira in the Phase III SARIL-RA-MONARCH study. In addition, the IL-6R antagonist demonstrated positive efficacy in TNF inadequate responders in the Phase III SARIL-RA-TARGET study. Regulatory filings were based on the positive data from the global SARIL-RA Phase III program.

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Amgen's Repatha Passes CVOT Test, But Contribution To 2017 Sales Growth Unclear

MANDY JACKSON mandy.jackson@informausa.com

Amgen's PCSK9 inhibitor Repatha succeeded in the FOURIER cardiovascular outcomes study, but the data may not impact the company's revenue until 2018 – after a potential revenue decline in 2017.

Amgen Inc. delivered a mixed bag of news to investors on Feb. 2, first revealing that the cholesterol-lowering therapy *Repatha* (evolocumab) passed its much-anticipated cardiovascular outcomes test, then reporting 2017 financial guidance that suggests the company will continue to see slow uptake for the PCSK9 inhibitor while sales for key products slump in the face of competition.

Repatha met the primary composite endpoint in the FOURIER cardiovascular outcomes trial (CVOT), showing a benefit versus placebo in statin-treated atherosclerotic patients in terms of the number of cardiovascular deaths, non-fatal myocardial infarctions and strokes, hospitalizations for unstable angina or coronary revascularizations.

Amgen did not report the magnitude of benefit, which will be crucial for increasing prescriptions and improving reimbursement, but the data will be presented in a March 17 late-breaker session during the American College of Cardiology (ACC) 66th Annual Scientific Sessions.

SECONDARY ENDPOINT MET

Repatha also met a key secondary composite endpoint in FOURIER, which assessed the incidences of cardiovascular death as well as non-fatal myocardial infarction (MI or heart attack) and strokes. No new safety signals were observed, including in the EBBINGHAUS study conducted within FOURIER, which assessed Repatha's effects on cognitive function; the product was non-inferior to placebo. EBBINGHAUS data will be presented in a late-breaker session at ACC on March 18.

Amgen executive vice president of research and development Sean Harper noted during the company's fourth quarter earnings call after the stock market closed that just because other secondary measures were not highlighted in the FOURIER announcement that did not mean the results were negative, but he didn't provide any additional color on the data.

Harper did say in Amgen's FOURIER statement, however, that the results "show unequivocally the connection between lowering LDL cholesterol with Repatha and cardiovascular risk reduction, even in a population already treated with optimized statin therapy."

The FOURIER data generally were expected to be positive, but the degree of cardiovascular benefit is a wild card. Amgen's GLAGOV study, which showed a regression in atherosclerotic plaque in November, hedged the bet that the CVOT study would be positive in early 2017, but added no certainty about the magnitude of cardiovascular risk reduction.

FOURIER was powered to show a cardiovascular risk reduction of at least 15%, but a greater benefit may be required to sway payers.

"The company has previously mentioned to investors that it expects a 20% to 30% benefit over control," Mizuho analyst Salim Sayed said in a Feb. 20 note. Based on such estimates, analyst consensus projects peak annual sales of about $4bn.

ADDING REPATHA?

"What matters next is how the cardiovascular impact compares to statins [alone]. If it's similar, Repatha is unlikely to be reimbursed. If it shows a big benefit, insurers will almost have to reimburse," Datamonitor Healthcare analyst Kevin Shannon told *Scrip*.

"In this next month and a half [leading up to ACC], it's unlikely that anything is actually going to change. Insurance companies typically won't change their decision until the data is added to the drug's label," Shannon said.

"Right now, doctors will prescribe Repatha and if it's denied and the patient really needs it the doctor will write a letter to the insurance company. In the next month and a half, doctors now have a stronger argument to reimburse on a patient-by-patient level, but it will probably not have a noticeable effect [on Amgen's revenue]."

Amgen did not provide a timeline for when it will submit the FOURIER data to the US FDA to update Repatha's label to communicate the cardiovascular benefit seen in the study. The company did note during the J.P. Morgan Healthcare Conference in early January, however, that it did not expect FDA approval of the updated label until 2018, an Amgen spokesperson told *Scrip*.

Anthony Hooper, executive vice president of global commercial operations, could not confirm during Amgen's fourth quarter earnings call when medical guidance is likely to be updated with a recommendation for using Repatha to treat statin-intolerant patients and patients whose cholesterol levels are insufficient despite statin therapy.

"If the data is robust enough, we would hope the guidelines come forward fairly soon," Hooper said.

BLOCKBUSTER STATUS IN FLUX

Amgen's financial guidance for 2017 reflects the uncertainty that remains for Repatha as well as increasing competition for the company's legacy neutropenia, anemia and autoimmune disease medicines, despite newly launched products. Amgen expects to bring in $22.3bn to $23.1bn in 2017 revenue, which would be as much as 3% lower than the $23bn in revenue the company reported for 2016 – a 6% jump from 2015.

A large cardiovascular benefit could propel Repatha to blockbuster status versus the $141m in sales reported for 2016, but if treatment guidelines take a while to be updated in favor of the PCSK9 inhibitor and if the product's label update isn't approved until 2018, it could take a while for Amgen to realize the benefits of FOURIER's apparently successful outcome. The out-

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come of Amgen's patent litigation against Sanofi and Regeneron Pharmaceuticals Inc., which market the competing PCSK9 inhibitor *Praluent* (alirocumab), also could push Repatha revenue higher, but probably not in the near term. Amgen won an injunction to halt Praluent sales based on the company's patent infringement claim, but Sanofi and Regeneron have appealed the court's decision.

Patent law experts seem to agree, Datamonitor's Shannon noted, that it would be unprecedented for the injunction halting Praluent sales in the US to stand. However, any settlement between the companies or an alternative court decision is likely to sway in Amgen's favor, with significant royalties from Praluent sales.

"Management expects the federal court will rule on granting a stay of the injunction pending appeal before Feb. 21 and believes resolution of the whole case will take roughly four to 10 months," Evercore ISI analyst Mark Schoenebaum said in a Feb. 2 note to investors.

'The President wants to promote innovation on behalf of patients' as well as economic growth and job creation

COMPETITION AND PRESSURES

With Repatha's blockbuster potential hanging in the balance, Amgen is facing substantial competition and pricing pressure, which led to the company's prediction that 2017 revenue could fall below 2016.

However, 2016 ended on an upswing for Amgen, which surprised investors in early November with a slight decline in revenue during the third quarter from its blockbuster TNF inhibitor *Enbrel* (etanercept) for rheumatoid arthritis and other autoimmune conditions. The dip reflected both competitive and payer pressures.

Like the full-year figures, Amgen's revenue increased on a year-over-year basis in the fourth quarter to $6bn, which was an 8% increase driven by Enbrel and other products. Enbrel sales rose 14% to $1.64bn in the fourth quarter and 11% for the year with $6bn in 2016 sales. The fourth quarter Enbrel increase was attributed to price increases and a $150m boost in inventory levels among customers, offset by increased competition.

Biosimilar and other competition as well as pricing pressure continued to hurt sales of Amgen's neutropenia products; sales fell 34% to $173m for *Neupogen* (filgrastim) in the fourth quarter and 3% to $1.12bn for *Neulasta* (pegfilgrastim). Anemia drug *Epogen* (epoetin alfa) also felt competitive pressures, including the shift of some customers to Amgen's *Aranesp* (darbepoetin alfa).

Hooper indicated during Amgen's earnings call that biosimilar competition would pick up for Neulasta in 2017. He also noted that the company's contract with dialysis provider DaVita HealthCare Partners Inc. recently was amended and extended through 2022, keeping most patients on Epogen and others on Aranesp, but at lower unit costs starting in 2017.

ENCOURAGED BY TRUMP

CEO Robert Bradway said Amgen continues to invest in new medicines and new markets for its products to boost revenue in the future.

Bradway noted that he was encouraged by President Donald Trump's interest in biopharma innovation, which Trump expressed during a meeting with industry executives on Jan. 31 to discuss tax and regulatory reforms as well as drug pricing.

"The President wants to promote innovation on behalf of patients" as well as economic growth and job creation, Bradway said, noting that the conversation also covered intellectual property protection and trade policy.

"The President also was clear about the need to bring down costs of drugs in the US," he said. "He will seek to advance changes that allow more Americans to have access to life-saving medicines."

Bradway said Amgen looks forward to discussing legislation related to tax and regulatory reforms with the Trump Administration and Congress, but he declined to comment on when such legislation or actions related to drug pricing would move forward.

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Ossianix Cracks Open The Blood-Brain Barrier

By using the binding region of shark antibodies as a carrier to cross the blood-brain barrier, Ossianix reckons it has made significant progress against an issue that has held back the development of CNS-active neurological therapies.

US biotech Ossianix Inc.'s CEO Frank Walsh is pleased with the progress the company has made in cracking a problem that's been "at the heart of neuroscience" for some time: the difficulty in getting therapeutic antibodies to cross the blood-brain barrier.

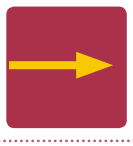
The company has developed a novel lead antibody that contains the variable new antigen receptor (VNAR) region from a shark antibody linked to rituximab (Roche's *Rituxan*), and this is expected to enter preclinical development shortly, with the eventual aim of being evaluated in patients with progressive multiple sclerosis or CNS-metastatic lymphoma.

Ossianix's progress has not gone unnoticed. "We are also in detailed discussions with a number of major pharmaceutical companies at the moment, including doing pilot studies with their antibodies to prove we can get them into the brain," Walsh explained.

And one company, Denmark's H. Lundbeck AS, has engaged in a research collaboration with Ossianix since 2014, and announced on Jan. 26 the successful completion of that work and the payment of an undisclosed milestone to Ossianix. Lundbeck has licensed the biotech's platform technology for use with several drug targets.

Ossianix's research on the blood-brain barrier has also attracted the attention of venture capital firms, interested in backing the firm, Walsh reported. "We are well-funded at the moment, but we will need to expand our operations to get our own targets into the clinic."

john.davis@informa.com, 2 Feb 2017



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From Onivyde To OTx

French pharma Ipsen made a splash earlier this year by acquiring oncology drug Onivyde for $525m upfront, but this doesn't mean it is moving away from investing in its primary care business unit. In fact, Ipsen is boosting primary care to support the growth of its much larger specialty care franchise. Ipsen has signed a new deal to take an equity stake in Akkadeas, a privately-held consumer health care company in Italy with a gastrointestinal-focused portfolio including probiotics, medical devices and food supplements. The deal also gives Ipsen an option to take control of the company in the future. Ipsen split its business into two, specialty care and primary care, in 2013. The primary care business generates less than 20% of the company's €1.5bn in annual revenues. However, "Primary care is a key part of our portfolio and delivers positive results which we can reinvest in our business. R&D is an important piece of this [company]," Jean Fabre, head of the Ipsen's primary care business, told

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Scrip. Former Baxalta oncology chief David Meeks took over at the top of Ipsen around six months ago. He has moved swiftly to build up Ipsen's specialty care business, particularly in oncology, where half of Ipsen's revenues come from. Fabre noted that Ipsen had made a "firm commitment to specialty care in oncology (which represents now more than 50% of sales), neurosciences and endocrinology"; however, "for the past 40 years [Ipsen has] built a significant presence in primary care with well-known brands like [the antidiarrheal product] *Smecta* (diosmectite)."

sukaina.virji@informa.com, 1 Feb 2017

Arix To Nurture Next Generation Biotechs

A year-old healthcare and life science operating company, Arix Bioscience PLC, has announced its intention to raise up to £100m ($125m) in an IPO on the main market of the London Stock Exchange, driven by what it sees as a burgeoning demand from universities, small companies and research accelerators for financial and operational support to develop a veritable flood of good ideas for new therapeutics. Life science initial public offerings (IPOs) on the UK Stock Exchange have been few and far between over past months, and scarce across European bourses for that matter, knocked back by political uncertainty, the attractions of floating in the US, and changes in investor sentiment. Although private financing by VCs and institutional companies have held up, that's a volatile and tough environment for small biotech companies to navigate, with different investor groups having to be accessed at research, IND submission, or clinical trial stages. What research teams need is "permanent capital" – in other words, capital that can be accessed over the long period of time that it takes to develop new drugs – Arix believes. And to supply permanent capital, Arix needs access to the public capital markets, explained CEO Joe Anderson. It wasn't an instant decision: "We considered a wide variety of options," he noted. "What's driven the IPO timing is not a stock market issue but the scale of the opportunity we see in life sciences. Since we set up a year ago, we've received 450 good ideas from researchers and executed on five," Anderson said. He also noted the UK has a tradition of supporting the life sciences business. Admission to the stock exchange is expected by the end of February, 2017.

john.davis@informa.com, 3 Feb 2017

Incyte Enhances IO Pipeline

Incyte Corp. is gaining an asset from Calithera Biosciences Inc. that may offer an ideal therapeutic complement to the key asset in Incyte's immuno-oncology pipeline, the Phase III IDO1 inhibitor epacadostat. The collaboration and licensing agreement for the arginase inhibitor CB-1158, which has Incyte paying Calithera $53m up front, is the second deal in as many months for the firm. Incyte paid $120m to partner with Dutch biotech Merus BV in December to discover and develop bispecific antibodies. Incyte has been working to develop a broad portfolio in oncology, and the Delaware-based company itself is considered a prime target for other companies looking to bolster their immuno-oncology portfolios, such as Sanofi. Incyte has a host of candidates in mid-stage development for lung, ovarian, brain and hematologic cancers beyond epacadostat. But epacadostat, in Phase III in melanoma, Phase II in ovarian cancers and Phase I/II in other solid tumors including lung cancer, is its lead candidate and the most advanced IDO1 inhibitor, a new class of immunotherapy agents that could be used in combination with other immuno-oncology (IO) drugs. Incyte gets worldwide research, development and commercialization rights under the Jan. 30 agreement to CB-1158, an arginase inhibitor being tested with Bristol-Myers Squibb Co.'s *Opdivo* (nivolumab) in a Phase I dose-escalation study. Calithera CEO Susan Molineaux said during a same-day conference call that after her firm completes that study a joint development team from both companies will plan development from there, likely to include combination therapy studies with epacadostat and potentially other IO agents.

joseph.haas@informa.com, 30 Jan 2017

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Teva's AirDuo: A Discounted Version Of Advair?

FDA approved Teva's AirDuo RespiClick, which contains the active ingredients in GlaxoSmithKline's Advair, but in the RespiClick device, which means it will not be an interchangeable generic.

JESSICA MERRILL jessica.merrill@informa.com

Teva Pharmaceutical Industries Ltd. is poised to launch what is expected to be the first discounted version of GlaxoSmithKline PLC's blockbuster asthma drug *Advair* (fluticasone/salmeterol) in the US, AirDuo *RespiClick* (fluticasone/salmeterol), which comprises the same active ingredients as Advair delivered through a different device than GSK's Diskus. But the launch may have lost some of its punch. Novartis AG's Sandoz unit is also rushing to develop a generic and filed a citizen petition aiming to block FDA approval of other generics last year.

Teva announced Jan. 30 that FDA approved AirDuo and *ArmonAir* (fluticasone), and that both drugs will launch "later this year." GSK also markets fluticasone as monotherapy as Flovent.

AirDuo, which combines the inhaled corticosteroid fluticasone with the long-acting beta2 adrenergic agonist salmeterol, will not be directly interchangeable with Advair because of dosing and delivery differences and because it was approved through the FDA's 505(b)2 pathway for new drugs in which some of the data is based on studies conducted for an existing medicine, rather than the traditional abbreviated new drug application (ANDA) for generics. As a result, it's not clear how much of a threat AirDuo will be to brand Advair.

Teva's drugs are also only approved for asthma maintenance, and not chronic obstructive pulmonary disease (COPD), while Advair is approved for both indications. Teva said it did not choose to pursue the COPD indication. In another variation, Advair is approved for children four and older, while AirDuo and ArmonAir are approved for children 12 and older. Teva said it is currently running pediatric studies.

Teva outlined ambitions to develop a competitor to Advair using the 505(b)2 pathway back in 2010. At the time, the company wasn't convinced an interchangeable generic would be approved by FDA within a mid-term horizon timeline. However, FDA unveiled bioequivalence standards to guide sponsors in the development of an interchangeable generic in 2013, at which time Teva reprioritized the development of a substitutable generic.

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The company now has two potential substitutable generic versions of Advair in development, one gained through the acquisition of Allergan PLC's generic drug business last year, but it is behind rivals Mylan NV and Hikma Pharmaceuticals PLC, both of which have ANDAs pending at FDA, with action dates of March 28 and May 10, respectively. Teva has previously said it is on track to file a substitutable generic in late 2017 or 2018.

Given the challenges associated with developing generics of complex respiratory drugs, particularly one like Advair that combines two active ingredients, there is no guarantee FDA will approve the drugs on a first review, which means generic Advair is one of the biggest potential commercial opportunities for generic manufacturers in 2017 but remains in question. US sales of Advair were £1.87bn ($2.35bn) in 2015.

GSK, in an email, downplayed the approval, highlighting the asthma-only indication and the fact that AirDuo is not a substitutable version of Advair. Indeed, management has talked frequently about how it believes GSK will be able to defend Advair against limited generic entry because the price of the brand has dropped significantly in the last three years amid increased competition and pushback from payers. The company, meanwhile, is turning attention to new respiratory drugs like the next-generation, once-daily ICS/LABA combination Breo Ellipta and a LABA/long-acting muscarinic antagonist (LAMA) combination Ellipta.

Teva would not say how it plans to price the drugs, only that they will be priced "competitively." The company already sells *ProAir* (albuterol), a rescue inhaler on the RespiClick platform. According to an analysis by Evercore ISI analyst Umer Raffat, the wholesale acquisition cost of Advair currently ranges from $291 to $475 per month depending on the dosing. The WAC for Breo is $322 per month.

"I believe pace of launch will be contingent on whether Teva is aggressive with its pricing strategy," Raffat said in the same-day email to investors. He pointed out that management previously guided to $200m in peak sales for AirDuo and forecast minimal sales in 2017.

AirDuo and ArmonAir are each approved in three strengths and administered twice daily. The approval was based on three Phase III clinical trials evaluating the safety and efficacy of the drugs in adolescents and adults with asthma. Both therapies demonstrated greater benefit versus placebo in the improvement of lung function after 12 weeks of treatment as measured by Forced Expiratory Volume in one second (FEV1).

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10 Approvals To Watch For In Early 2017

Dupixent, Austedo, brigatinib and Olumiant are among a raft of new drug approvals expected in the first four months of the year. Here, with help from Informa Pharma's Biomedtracker, we take a look at 10 of the more interesting products looking close to reaching the market, some for the second time of asking.

ALEX SHIMMINGS alex.shimmings@informa.com

SANOFI'S DUPIXENT

US PDUFA Date: Mar. 29, 2017
First Review
Breakthrough Therapy Status
EU Approval under review
BMT LOA – Above average 79%
First in class

The increasingly crowded immunology/inflammation market is set to receive some new entrants this year, with Sanofi/Regeneron Pharmaceuticals Inc.'s *Dupixent* (dupilumab), a potential first-in-class IL4-receptor antibody that inhibits signaling of IL-4 and IL-13, two key cytokines required for the type 2 (including Th2) immune response. The indication under review is atopic dermatitis, but Dupixent is being developed under five different allergic indications, with pivotal Phase III trials in asthma ongoing and filings due by year end. Regeneron believes it has found the "control point" for a variety of allergic diseases and that this drug can be expanded to indications including food allergies.

The drug has a breakthrough therapy designation for the treatment of adults with moderate-to-severe atopic dermatitis who are not adequately controlled with topical prescription therapies or for whom these treatments are not appropriate. The BLA is supported by the SOLO 1 and 2 studies which looked at it as a monotherapy, and the CHRONOS study that tested it in combination with topical corticosteroids.

TEVA'S AUSTEDO

US PDUFA Date: Apr. 3, 2017
Second Review
Orphan Drug Status
BMT LOA – Above group/class average of 69%
First in class

Teva Pharmaceutical Industries Ltd. is hoping for better luck second time round at the FDA for its potential new treatment for the treatment of chorea associated with Huntington's disease, *Austedo* (deutetrabenazine). The PDUFA goal date is Apr. 3.

The original NDA was based on positive results from two Phase III trials: First-HD and ARC-HD, but Teva received a complete response letter from the FDA in May 2016 – the agency, possibly exercising extra caution with this first deuterated drug to be up for approval, asked Teva to examine the blood levels of certain metabolites. If the resubmission is successful, Austedo will be the first deuterated drug to be approved in the US, and only the second FDA-approved drug in Huntington's disease.

ASTRAZENECA'S ZS-9

US PDUFA Date: Apr. 18, 2017
Second Review
Orphan Drug Status
EU Approval Due: 1H 2017
BMT LOA – Above group/class average 61%

AstraZeneca PLC's crystallized zirconium silicate product ZS-9 is another one set to receive the outcome of its second review in April. The product is designed as a sorbent, specifically trapping potassium ions over other ions in the gastrointestinal tract for use in hyperkalemia. The expected PDUFA date is Apr. 18, and approval is also under review in Europe.

Last May, a manufacturing issue at a plant in Texas resulted in an FDA complete response letter, dashing AstraZeneca's hopes that its potential best-in-class treatment would be approved in the first half of 2016.

AstraZeneca acquired the asset when it bought US-based ZS Pharma Inc. for $2.7bn in 2015 in the hope that it would start contributing to its top line by early in the second half of 2016, and the delay was a setback to its pipeline ambitions in the cardiovascular/metabolic area.

Fortunately, the US agency required no new clinical data on the drug. A response from AstraZeneca was quickly submitted by October 18, 2016, and the FDA indicated this was a class 2 response, with a six-month review time.

LEXICON/IPSEN'S TELOTRISTAT

US PDUFA Date: Feb. 28, 2017
First Review
Orphan Drug Status
BMT LOA – Above group/class average of 81%

Lexicon Pharmaceuticals Inc. has suffered a three-month delay already for telotristat etiprate under review by the FDA for the treatment of carcinoid syndrome.

Armed with positive Phase III results from the TELESTAR trial, and a Phase III companion study TELECAST, plus fast track and orphan drug designations, Lexicon filed the US NDA in March 2016 and was assigned an original PDUFA target action date of Nov. 30. But it later transpired that the FDA wanted more time to complete its review, and clinical data analyses, pushing back the target action date to Feb. 28, 2017.

Telotristat etiprate is an orally-delivered small molecule targeting tryptophan hydroxylase, an enzyme that triggers the excess serotonin production within metastatic neuroendocrine tumors (mNET) cells that leads to carcinoid syndrome. Serotonin plays a role in regulating several physiologic processes of the gastrointestinal (GI) tract, including secretion, sensation, and motility.

BIOMARIN'S BRINEURA

US PDUFA Date: Apr. 27, 2017
First Review
Orphan Drug Status
Breakthrough therapy designation
EU Approval under review
BMT LOA – Above group/class average of 69%

Promising results from a pivotal Phase I/II trial of BioMarin Pharmaceutical Inc.'s *Brineura* (cerliponase alfa) showing a significant reduction in neurodegenerative decline are supporting its US BLA for the treatment of children with CLN2 disease, a form of Batten disease.

The enzyme replacement therapy, which is infused into the brain ventricles of patients, showed an average rate of clinical decline for

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motor and language function that was about 80% less than the expected rate of decline in an untreated natural history population, preserving essential function in the majority of treated patients. Results from an ongoing extension study have also shown continued stability overall in the Brineura group.

Nevertheless, during its initial review, the FDA requested an updated efficacy data cut from the ongoing extension study and counted it as a major amendment to the application, extending the PDUFA action date by three months to April 27. The agency also plans to hold an advisory committee meeting regarding the BLA and as comparisons with natural history data can be tricky, observers will be keen to see what issues the FDA raises, especially given the drug's side-effect profile.

ARIAD'S BRIGATINIB

US PDUFA Date: Apr. 29, 2017
First Review
Orphan Drug Status
Breakthrough therapy designation
BMT LOA – Above group/class average of 81%

The anaplastic lymphoma kinase (ALK) inhibitor space is set to get more crowded with the impending approval of Ariad Pharmaceuticals Inc. brigatinib for non-small cell lung cancer patients with ALK mutations that are resistant to crizotinib, the primary ALK inhibitor used as first-line therapy.

The NDA is based on data from two early studies: the first a preliminary Phase I/II trial which showed early positive signs of activity in ALK+ or crizotinib-refractory patients, and led to the pivotal Phase II ALTA study.

With these positive top-line results, Ariad initiated a rolling NDA in June 2016 which was completed in August 2016. Having received orphan and breakthrough designation from the FDA during the development phase, ARIAD obtained priority review once its application was accepted by the FDA. The FDA set a PDUFA action date of Apr. 29, 2017.

SHIONOGI'S SYMPROIC

US PDUFA Date: Mar. 23, 2017
First Review
BMT LOA – Above group/class average of 33%

Shionogi Inc. is hoping for Japanese and US approvals for its novel treatment for opioid-induced constipation (OIC), *Symproic* (naldemedine), this year.

In Japan, the NDA is for the treatment of OIC in adult patients, while the NDA currently under FDA review is for the treatment of OIC in adult patients with chronic non-cancer pain (CNCP), with an expected PDUFA target action date of March 23.

The NDA submissions for the peripherally acting mu-opioid receptor antagonist include data from the Phase III COMPOSE program comprised of seven clinical studies in patients with OIC with cancer or CNCP.

The FDA will likely want to confirm that the data also meet the composite endpoint of OIC response, defined more specifically than just an improved mean number of SBMs over placebo.

ELI LILLY'S OLUMIANT

US PDUFA Date: March 23, 2017
First Review
EU Approval Due: Q1
BMT LOA – Above group/class average of 60%

Another me-too set to arrive this year is Eli Lilly & Co.'s *Olumiant* (baricitinib), a once-daily oral JAK inhibitor for the treatment of moderately-to-severely active rheumatoid arthritis (RA).

In January 2017, the FDA extended the review period for the NDA to review additional data analyses that were submitted by Eli Lilly in response to the FDA's Information Requests. The additional information constituted a major amendment, resulting in an extension of the PDUFA goal date by three months to Apr. 19.

In its large Phase III program involving four pivotal studies, baricitinib showed efficacy in combination with conventional disease-modifying anti-rheumatic drug therapy (cDMARDs), following cDMARDs, and as a front-line treatment. Most importantly, baricitinib showed significant superiority over AbbVie's Humira (adalimumab) in ACR 20/50/70.

Little information is provided on the nature of the Information Requests from the FDA, but given the plethora of positive data, baricitinib should be well positioned for approval and a subsequent strong market uptake.

Olumiant won an EU CHMP positive opinion in December, meaning that approval there should also come in the first quarter.

NEUROCRINE'S INGREZZA

April 11 should see the US FDA's verdict on Neurocrine Biosciences Inc.'s NDA for Ingrezza (valbenazine) for the treatment of tardive dyskinesia. Ingrezza is a selective vesicular monoamine transporter 2 (VMAT2) inhibitor

US PDUFA Date: April 11, 2017
First Review
Priority review
EU Approval Due: 2017
BMT LOA – Above group/class average of 44%

designed to provide low, sustained, plasma and brain concentrations of valbenazine to minimize side effects associated with excessive dopamine depletion.

The NDA filed in August 2016 was based on results from the Phase IIb Kinect 2 and Phase III Kinect 3 clinical trials. In the Kinect 3 trial, Ingrezza was associated with a significant improvement in tardive dyskinesia in subjects with schizophrenia, schizoaffective disorder or mood disorder.

After further review of the NDA for Ingrezza, the FDA decided to cancel the Psychopharmacologic Drugs Advisory Committee meeting which was scheduled for Feb. 16, 2017, which was generally viewed as a positive development, indicating that the FDA had no review issues with the NDA.

RADIUS' ABALOPARATIDE

US PDUFA Date: March 30
First Review
EU Approval Due: 2017
BMT LOA – Above group/class average of 53%

Radius Health Inc. has reason for optimism over the fate of its new bone strengthener abaloparatide at the FDA this spring. The subcutaneously delivered analog of the PTHrP (parathyroid hormone-related protein) was filed in March 2016 as a once daily treatment for postmenopausal women with osteoporosis, and the PDUFA date is estimated to be Mar. 30.

The NDA is supported by data from the 18-month Phase III ACTIVE trial in 2,463 postmenopausal women with osteoporosis and the first six months of the ACTIVExtend trial in 1,139 of the ACTIVE participants, which suggested that it was better for improving bone mass with less hypercalcemia than Lilly's first-in-class Forteo (teriparatide).

The ACTIVE and ACTIVExtend trials have met the primary and secondary endpoints essential for submission of the NDA, including the primary endpoint of reduction of vertebral fractures as well as key endpoints of reduction of nonvertebral, clinical, and major osteoporotic fractures.

For more information, see *Biomedtracker*.

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Pfizer To Compromise On NICE Price?

It looks as though Pfizer Inc. might have to offer a discount or some other type of patient access scheme if it wants to secure a positive recommendation from NICE, the HTA for England and Wales for its breast cancer drug *Ibrance* (palbociclib). NICE has issued preliminary recommendations declining to recommend

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the drug for hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer. It says the benefits of the drug, widely expected to become a standard of care, do not justify its costs. On Feb. 3 NICE published draft guidance rejecting Ibrance in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer. The initial recommendations are not a surprise as the high cost of the cyclin-dependent kinase 4/6 inhibitor has been "a noted concern," says Datamonitor Healthcare analyst Zachary McLellan. Despite acknowledging that Ibrance stalled the growth of the cancer for an extra 10 months on average and would likely improve overall survival, NICE had its doubts. "Taking the costs into account, the committee concluded that it could not recommend palbociclib for NHS use at present," said Carole Longson, director of NICE's centre for health technology assessment. Ibrance costs £2,950 for a pack of 21 capsules. A full course of treatment costs around £79,650, based on median progression free survival of 24.8 months seen in the PALOMA-2 clinical trial for patients taking the drug, says the institute. The estimated incremental cost-effectiveness ratios for the drug were estimated to be between £150,869 per QALY gained and £132,872 per QALY gained. These were well above the £20,000-£30,000 per QALY range that NICE usually considers to be cost-effective. Although Pfizer may argue that the relative efficacy of Ibrance in comparison to other breast cancer treatments certainly justifies a higher price, the company will likely have to engage in some sort of patient access scheme to guarantee access through the NHS, says McLellan.

francesca.bruce@informa.com, 2 Feb 2017

Opdivo, Keytruda Bladder Cancer Race

Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab) has the clear lead in the bladder cancer market, following approval as a second-line therapy in May 2016. But it now faces competition: Bristol's PD-1 inhibitor *Opdivo* (nivolumab) cleared FDA Feb. 2 with accelerated approval for urothelial cancer after progression on platinum-based chemotherapy or after progression on neoadjuvant or adjuvant chemotherapy. Some 76,000 people in the US were diagnosed with bladder cancer in 2016, 11% of which were in advanced stages, according to the American Cancer Society. PD-1/L1 inhibitors represent the first important treatment advance in decades. Bristol's filing, which had breakthrough therapy designation, was supported by the CheckMate 275 study of 270 patients, in which there was a 19.6% response rate, including 2.6% with complete responses. The median duration of response was 10.3 months. The drug has benefited from broad labeling, now with eight indications. Bristol declined to comment on its regulatory strategy for filing in first-line bladder cancer. It did note that it is running two Phase III studies – CheckMate 274 of Opdivo vs. placebo in the adjuvant setting, which is due to report in the fourth quarter of 2020, and CheckMate 901 of Opdivo with the firm's CTLA-4 checkpoint inhibitor *Yervoy* (ipilimumab) in first-line bladder cancer, which is due to report in the third quarter of 2020. For the time being, Opdivo has a lead in the indication over Merck's PD-1 inhibitor *Keytruda* (pembrolizumab). Merck announced Feb. 3 that FDA has accepted two filings for Keytruda in bladder cancer, both of which have priority review.

emily.hayes@informa.com, 3 Feb 2017

Flexion CEO Makes The Case For Zilretta

Flexion Therapeutics Inc. has been planning the commercial, and pricing, strategy for its long-acting corticosteroid Zilretta for a long time, and has the market research to support it, CEO Mike Clayman explained in an interview with *Scrip*'s Emily Hayes. Following submission of a new drug application for *Zilretta* (FX006) for knee osteoarthritis in mid-December 2016, Clayman is hoping for priority review with the US FDA and market entry by the end of the year. Zilretta is an extended release formulation of the steroid triamcinolone acetonide. Steroid injection is a common treatment upon diagnosis, but pain relief wanes after two to four weeks. Flexion is positioning Zilretta as a longer-acting corticosteroid – the candidate is formulated to stay in the knee joint for three months – and a more potent pain relief option for patients with knee osteoarthritis. Competing against generic steroids, which cost only $10 to $20 per dose, presents a big commercial challenge, however. In an interview at the Biotech Showcase, which was held in parallel with the J.P. Morgan Healthcare Conference, Clayman explains the rationale for pricing a long-acting steroid at $500 per dose and the company's commercial strategy, including plans to launch shortly after approval.

emily.hayes@informa.com, 3 Feb 2017

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Takeda Raises Guidance, Eyes Emerging Market

IAN HAYDOCK ian.haydock@informa.com

Takeda sees an increase in core earnings offsetting the expected impact on its operating profit this fiscal year of the Ariad acquisition, and is eyeing another possible modest M&A deal in an undisclosed emerging market.

Takeda Pharmaceutical Co. Ltd. has raised its underlying core earnings and earnings per share guidance for the full fiscal year ending March 31, based on a performance in the April-December period that showed solid increases in these indicators.

President and CEO Christophe Weber said the continued global success of Entyvio and Ninlaro "gives us the confidence to improve the full-year outlook for FY2016."

Full-year guidance for underlying core earnings (reported gross profit minus SG&A expenses and R&D expenses) has now been raised to "high-teen" percentage growth, from "mid- to high-teen," and underlying core EPS to mid-teens from the low- to mid-teens.

The forecast increase in core earnings will offset the expected JPY9-10bn ($80-88.8m) impact on operating impact in the current fiscal year of the $5.2bn Ariad Pharmaceuticals Inc. acquisition (expected to close by the end of this month), chief financial officer James Kehoe told an earnings call.

> The continued global success of Entyvio and Ninlaro 'gives us the confidence'

Takeda now expects reported revenue of JPY1,670bn (from JPY1,700bn forecast earlier), and net profit of JPY93.0bn (from JPY91.0bn) for the financial year to March 31. The revised forecast includes costs related to the R&D transformation program of JPY47bn in the fiscal year (out of a planned total of JPY75bn).

Underlying revenue in emerging markets was up 5% to JPY204bn in the nine months, with China rising 8%, although the overall figure fell by 11% on a reported basis, hit by currencies.

It also emerged during the earnings conference that Takeda is considering another potential M&A deal, Kehoe disclosing that a payment of JPY40.8bn had been put into escrow "for a potential future potential transaction in emerging markets."

The CFO stressed that "We cannot disclose more at this point in time," including on location and therapy area, but commented that "there's a series of conditions that need to occur to make us comfortable with completing the acquisition."

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View Takeda Q3 results here:
http://bit.ly/2kizzHp

Scrip Awards Winner 2016

Best Partnership Alliance
(Sponsored by INC Research)

This long-term genomic partnership aims to harness the power of genomic information to propel the discovery and development of novel medicines. The companies hope their partnership will drive new drug target and biomarker identification to select patients who can respond to treatment, and believe it could change the way clinical trials are designed.

Sponsored by INC Research

Winner: **AstraZeneca and Human Longevity's genomic partnership**

"It's great to see the judges recognise the unprecedented scale and scope of our collaboration with Human Longevity and it's significant potential. Over the next ten years we will undertake genomic sequencing and analysis of hundreds of thousands of samples drawn from AstraZeneca's clinical trials."

Iain Comley, Business Development Director, Scientific Partnering & Alliances, IMED Biotech Unit

Scrip Awards
Pharma intelligence | informa

Laying The Groundwork For Value-Based Healthcare In Europe

DAVID PISTOR ELISABETH ALOY

Elisabeth Aloy and David Pistor, healthcare and life sciences advisors at Monitor Deloitte, outline five design principles to create a value-based care project.

Most healthcare systems are battling with the challenge of delivering both better patient outcomes – in an environment of increasing prevalence of diseases – while managing escalating costs. So how can we ensure the best possible care and access to innovation for patients, while being mindful of these costs and healthcare budget pressures?

In the past decade, the introduction of Health Technology Assessments (HTA), and the impact of austerity measures, have started to address standards of care and budget pressures respectively. However, the value created by services and more holistic solutions are often overlooked in the healthcare delivery equation.

A Deloitte analysis (2016) showed that solutions combining new drugs, devices, processes and digital platforms (e.g. patient portals, registries), are more likely to improve performance and reduce costs than medical innovations alone. Yet, the impact of the treatment, interventions and patient experience of a medicine are typically not assessed in a robust way. They are also not usually considered as a key performance indictor when contracting or selecting a supplier.

Healthcare measures are often standalone, consequently failing to optimize both care and value for money. However, new thinking and public interest in relation to the value of paying for innovative pharmaceuticals has recently been sparked. For example, GlaxoSmithKline's gene therapy has been priced at over half a million dollars, but with money back guaranteed if it is ineffective. Novartis has recently entered performance-based agreements with two insurers (New Aetna and Cigna) for testing the ability of its heart failure therapy Entresto to cut down on hospitalizations and improve real world patient outcomes.

The recognition of the need to adopt a more value-based care approach (VBC) to healthcare is escalating. It has even led to a panel discussion among life sciences leaders at this year's World Economic Forum in Davos. The wide-spread adoption of this concept is seen as increasingly likely, but much more needs to be done.

VBC aims at shifting payment and reimbursement models from volume to agreed measures of value delivered to patients. The concept of value captures evidence-based clinical, social and economic benefits. VBC can be deployed at the ward, hospital or even national level, and the journey can be structured into four action steps.

VBC is being tested successfully in a real world environment, but only in small scale experiments. For example, three years after their introduction in Stockholm, bundled payments for hip and knee replacements led to a 26% reduction of complication risks and 20% reduction of costs, whilst significantly decreasing waiting times and resource utilisation. Based on an assessment of successful and aborted trials, we believe that there are five design principles to ensure a successful VBC pilot:

- Establish clear collaboration between stakeholders (innovator, care giver and the payer) with defined goals and roles.
- Define outcome indicators with clear target definitions (based on clinical end points, economic and social outcome) and measurement methodologies for the therapeutic area.
- Establish simple and viable value-based procurement models.
- Ensure that stakeholders are incentivized, in order for lasting adoption of new ways of working. These include tracking and reporting of health indicators and regular analysis of patient outcomes.
- Design detailed operating models from the start, ensuring comprehensive testing and the ability to scale up.

VBC remains a challenging transformational journey, paved with complexity, potential high costs, implementation risks and a cultural change for all stakeholders engaged. But success is possible.

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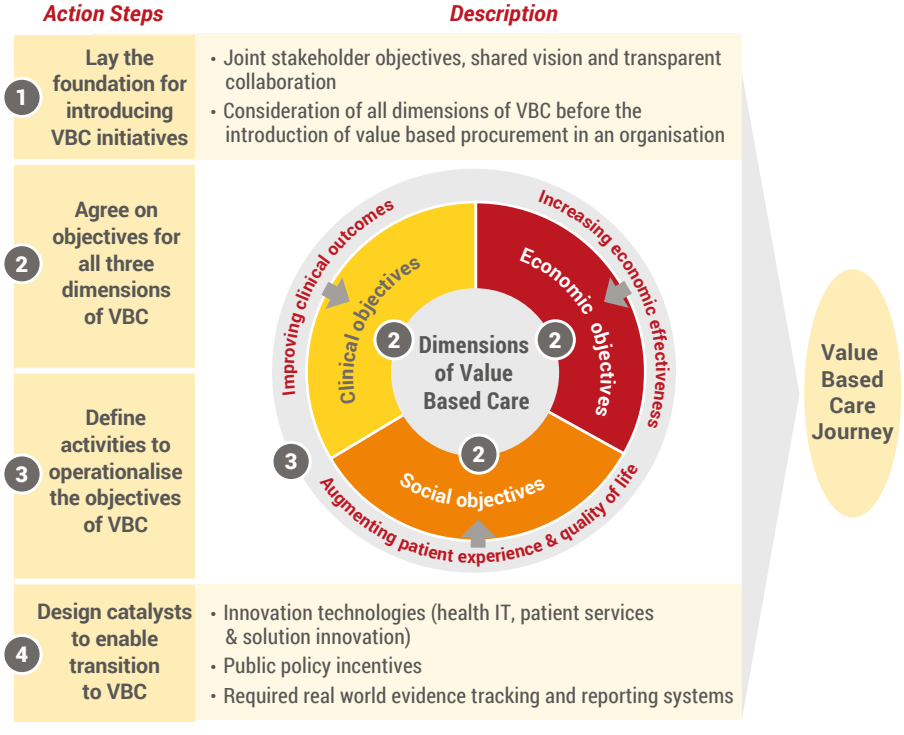

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Pfizer, Roche, AZ, Novo Prolong Pharmaceutical Winter

Lackluster reports from Pfizer, Roche, AstraZeneca and Novo Nordisk in a second week of earnings season pervaded by below consensus 2017 guidance followed a first week punctuated by missed sales estimates. So much bad news hanging over the sector feels like a nuclear winter.

ANDY SMITH

Two weeks into fourth-quarter earnings season, most of the biggest companies have now reported and the clouds that descended after the first week continued to roll in, hanging over the sector like a pea souper of London's past or the smog of Beijing's present. Towards the end of the week the cumulative lackluster prompted the analysts from Leerink Partners to capture the mood perfectly by described the season so far as being "tepid at best, with no impressive upside surprises."

Longer-term observers of the sector will remember the "nuclear winter" when blockbuster product patent expiries reduced sales of pharmaceutical companies, but by now, those patent cliffs should be well behind us. However, the first two weeks of earnings season have been characterized by quarterly sales or annual sales guidance shortfalls compared with analysts' consensus estimates, so when Punxsutawney Phil predicted an extended winter last week, it felt like he had the pharmaceutical sector in mind.

Pfizer Inc. went some way to redress the sales shortfalls of companies reporting during the first week of earnings season by announcing fourth-quarter sales that were in line with analysts' estimates. It further departed from the previous week's script by missing analysts' estimates of its earnings by about 6%. Unfortunately, Pfizer was back on the message of the previous week when it guided to 2017 earnings that were 3% below analysts' mid-point estimates thanks to lower sales. Pfizer's sales shortfall would be due partly to the divestment of its infusion business and the strong US dollar but also – according to the analysts from JP Morgan – to about $2.4bn in generic competition. Pfizer's stock price finished the week up 2.2%, which was just under the weekly rise in the NYSE ARCA Pharmaceutical Index. Both had benefited from the president's remarks on tax breaks and quicker drug approvals despite his continuing stance on drug price cuts.

In a similar vein, Roche reported fourth-quarter sales that were in line with analysts' estimates after benefiting from a strong US dollar and a good seasonal quarter for its anti-influenza drug *Tamiflu* (oseltamivir). Roche's earnings were, however, 2% below consensus estimates. Analyst and social media commentary was briefly diverted by the key oncology franchises of *Avastin* (bevacizumab) and *Herceptin* (trastuzumab), which were slightly below expectations, and a rumored then denied sale of its diabetes business. Attention soon returned to Roche's 2017 sales guidance which was – like that of Johnson & Johnson (J&J) and Pfizer – between 2 and 3% below analysts' expectations despite about a 1% benefit from the strength of the US dollar. Also like J&J and Pfizer, Roche's subdued 2017 guidance took into account impending (probably biosimilar) generic competition.

The headline results from AstraZeneca PLC might have given investors a brief respite from the sector's surprise disappointments since it met analysts' expectations of its decline and beat earnings expectations by 6%. However, as the analysts from Citigroup pointed out, AstraZeneca's results were of low quality, having been driven in part by mature brands such as *Synagis* (palivizumab) and even *Nexium* (esomeprazole) – the latter in the middle of its genericization – but also by $325m of externalization revenue. Accountants would classify externalization revenue as "other, or non-core income" but in AstraZeneca's case it is analogous to selling off the family silver as quickly as it can be listed on eBay.

Two of the UK's biggest pharmaceutical companies can be thought of as building sites in 2017. Whereas Shire PLC is coming to grips with knocking its building together with the wreck next door after its acquisition of Baxalta Inc., AstraZeneca is letting the demolition teams roam freely over its sites. AstraZeneca's 2017 earnings are not just expected to continue with a mid-teen percentage decline, but even that rate of decline is dependent on externalization revenue. It is probably little comfort to AstraZeneca's investors that one third of the CEO's long-term bonus may not be paid because of the company's financial decline. That decline looks likely not only to continue long after he previously promised, but probably long after what must be his now imminent departure.

It was difficult to assign a wooden spoon for last week's fourth-quarter earnings reports, although according to the sell-side analyst reports, Novo Nordisk AS (whose CEO retired last year) more than inched it from AstraZeneca. Novo – the former doyen of narrowly focused, highly valued biopharmaceutical businesses – reported sales that met analysts' estimates – which had been lowered as a result of its third-quarter report – but earnings that missed by 2%. Novo's lowered 2017 earnings guidance is likely to result in a 6% cut to consensus estimates.

With price pressure across its diabetes business even before the launch of Eli Lilly & Co.'s generic insulin, and the threat of healthcare reform shifting dual eligible patients back to Medicaid (with a corresponding pricing implication), the analysts from JP Morgan described Novo's results as "disappointing" while those from Citigroup pronounced that Novo had "sentiment scuppered for 2017." Novo's stock price cratered, finishing the week down 6.4%.

Novo's second successive quarterly earnings disaster after many years of virtually faultless performances certainly shows that CEO retirements can be a harbinger of doom. While its investors may be wondering how many more shoes are left to drop, I am more worried about other sector-wide shoes that will be drop this earnings season. Specialty pharmaceutical companies including Valeant Pharmaceuticals International Inc., Endo International PLC, Perrigo Co. PLC and Mylan NV are still yet to report.

Andy Smith gives an investor's view on life science companies. He has been lead fund manager for four life science–specific funds, including 3i Bioscience, International Biotechnology and the AXA Framlington Biotech Fund, and was awarded the techMark Technology Fund Manager of the year for 2007.

Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage, Phase III clinical trial developments for the more than 10,000 drug candidates under active research worldwide. To see changes to the progress of product candidates further back in the development pipeline, and a table of the week's product approvals, please visit our Pipeline Watch webpage at scrip.pharmamedtechbi.com.

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Selected clinical trial developments for the week 27 January – 2 February 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Suspended			
Eli Lilly & Co.	solanezumab	prodromal Alzheimer's disease	EXPEDITION PRO; after lack of efficacy in other Phase III studies.
Phase III Results Published			
Swedish Orphan Biovitrum AB/ Bioverativ Inc.	*Alprolix* (eftrenonacog alfa)	hemophilia B	Kids B-LONG; Phase III study in Feb. issue of The Lancet Haematology.
Gilead Sciences Inc.	*Zydelig* (idelalisib)	chronic lymphocytic leukemia	Published online Jan. 27 in The Lancet online.
US NIH	immunosuppression and stem cell transplant	multiple sclerosis	HALT-MS; final five-year results published online Feb. 1 in Neurology.
Updated Phase III Results			
Allergan PLC	*Avycaz* (ceftazidime and avibactam)	complicated urinary tract infections, pyelonephritis	RECAPTURE; REPRISE; data supported sNDA approval.
Rigel Pharmaceuticals Inc.	fostamatinib (a SYK kinase inhibitor)	chronic immune thrombocytopenic purpura	Study 047, 048 and 049; they continue to support NDA filing in 2017 first-quarter.
Phase III Completed			
AEterna Zentaris Inc.	zoptarelin-doxorubicin conjugate	uterine cancer	ZoptEC; results to be reported in Apr. 2017.
Phase III Interim/Top-line Results			
Amgen Inc.	*Repatha* (evolocumab)	dyslipidemia	FOURIER & EBBINHAUS trials; significantly reduced CV outcomes, no effect on cognitive function.
AstraZeneca PLC /FibroGen Inc.	roxadustat	anemia due to chronic renal failure, on or off dialysis	In China, two Phase III studies met primary endpoints.
Novan Inc./Sato Pharmaceutical Co. Ltd.	SB204 (a nitric oxide releasing compound)	acne	Mixed results from three Phase III studies.
Chugai Pharmaceutical Co. Ltd.	peretinoin	liver cancer	Did not meet primary endpoint.
Kyowa Hakko Kirin Co. Ltd.	KHK-7580	secondary hyperparathy-roidism	Met primary endpoint on parathyroid hormone levels and reduced ADRs.
Tenax Therapeutics Inc.	*Simdax* (levosimendan)	acute decompensated heart failure	Missed primary endpoints but effective against secondary endpoints.
Ironwood Pharmaceuticals Inc./ Astellas Pharma Inc.	*Linzess* (linaclotide)	chronic constipation	Potential additional indication, met endpoint.
Stallergenes SA/Shionogi & Co. Ltd.	*Actair* (house dust mite sublingual tablet)	allergic rhinitis	Positive results in Japanese children.
Phase III Initiated			
Roche	emicizumab	hemophilia A	HAVEN 4; dosed every four weeks.

Source: Biomedtracker

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Agenovir Corporation has appointed ***Bolyn Hubby*** to the newly-created position of chief scientific officer. Hubby has over 15 years of experience in infectious disease and oncology and joins the company from Synthetic Genomics, where she was vice president of vaccines and antimicrobials research and development. Before this, she was executive director of vaccines at Liquidia Technologies Inc. and served as head of discovery immunology at AlphaVax Inc.

Margaret K. Feltz has been appointed **Purdue Pharma L.P.**'s vice president and chief ethics and compliance officer. She will succeed ***Bert Weinstein***, who retired from the company in December 2016, and will also serve as a member of the Purdue Pharma's executive committee. Feltz joined Purdue in 2004 as a senior manager and before this, she worked as a health attorney at McDermott, Will & Emery and later as compliance counsel for Boehringer Ingelheim Pharmaceuticals Inc.

Jeff Barton has been nominated by Abbott Laboratories Inc. to join **Allergy Therapeutics Plc.**'s board as a non-executive director. This announcement follows the retirement of ***Jean-Yves Pavee*** from the board – effective Feb. 7, 2017. Barton joined Abbott in 1990 in the financial development training program and is currently vice president, licensing and acquisitions. He previously served as divisional vice president and controller for Abbott's North American Nutrition Business and as area finance director for its Asian, African, and Middle Eastern Pharmaceutical unit.

Genmab A/S has appointed hematologist ***Judith Klimovsky*** executive vice president and chief development officer. Most recently, she was senior vice president and global head of oncology clinical development at Novartis AG and has previously held senior roles at Merck & Co. Inc. and Bristol-Myers Squibb Co.

Gilead Nordics' former general manager ***Kennet Brysting*** has been appointed **Gilead Sciences Canada Inc.**'s general manager and has also joined Gilead's North America commercial senior leadership team. Brysting succeeds ***Ed Gudaitis***, who left the company in October 2016 for another opportunity. Brysting carries nearly 20 years of industry experience and previously, he was general manager for Gilead Nordics.

HealthTell Inc., a company developing diagnostic, prognostic and monitoring tests for immune diseases, has appointed ***Gary Riordan*** vice president of regulatory and quality. Riordan started his career at the FDA and has held executive commercial positions at companies including NanoString, Accumetrics, Sequenom, PrimeraDx, and Roche Molecular Systems.

Baxter International Inc. has named ***Stephen N. Oesterle*** to its board of directors. He previously was senior vice president, medicine and technology at Medtronic and a member of Medtronic's executive committee. Oesterle has also held prior roles as associate professor of medicine and director of Invasive Cardiology Services at Harvard Medical School-affiliated Massachusetts General Hospital, Stanford University Medical Center and Georgetown University Medical Center.

Promethera Biosciences SA has appointed ***Henrik L. Luessen*** chief business officer (CBO), ***Nancy Veulemans*** vice president clinical & medical affairs and Decebal Bora vice president regulatory affairs. Luessen is the founder and managing director of Tytonis B.V and previously was CBO at OctoPlus NV. Previously, Veulemans was senior advisor regulatory at Promethera and has worked for Bristol Myers Squibb International and Pfizer. Bora joins Promethera from PTC Therapeutics, where he was executive director regulatory affairs and has worked for Biogen Inc., F. Hoffmann-La Roche Ltd.

Scrip

ELEANOR MALONE @SCRIPELEANOR
eleanor.malone@informa.com
ALEXANDRA SHIMMINGS @SCRIPALEXS
alex.shimmings@informa.com
SUKAINA.VIRJI @SCRIPSUKI
sukaina.virji@informa.com
ANJU.GHANGURDE @SCRIPANJUG
anju.ghangurde@informa.com
MANDY JACKSON @SCRIPMANDY
mandy.jackson@informausa.com
JOANNE SHORTHOUSE @SCRIPJO
joanne.shorthouse@informa.com
FRANCESCA BRUCE @SCRIPFRANCESCA
francesca.bruce@informa.com
STEN STOVALL @STENSTOVALL
sten.stovall@informa.com
IAN SCHOFIELD @SCRIPIANS
ian.schofield@informa.com
ASHLEY YEO @ASHLEYPYEO
ashley.yeo@informa.com
MARY JO LAFFLER
maryjo.laffler@informa.com
LUCIE ELLIS @SCRIPLUCIE
lucie.ellis@informa.com
LUBNA AHMED @SCRIPLUBNA
lubna.ahmed@informa.com
PAUL WILKINSON @PAUL__WILKINSON
paul.wilkinson@informa.com
JOHN HODGSON @SCRIPJOHN
john.hodgson@informa.com
MIKE WARD @SCRIPMIKEWARD
mike.ward@informa.com
PETER CHARLISH @PETERCHARLISH
peter.charlish@informa.com
JOHN DAVIS @JOHN023DAVIS
john.davis@informa.com
EMILY HAYES @EMILYKATEHAYES
emily.hayes@informa.com
JESSICA MERRILL @JESSCIAMERRILL
jessica.merrill@informa.com
JOSEPH HAAS
joseph.haas@informa.com
IAN HAYDOCK
ian.haydock@informa.com
YING HUANG
ying.huang@informa.com
JUNG-WON SHIN
jungwon.shin@informa.com
BRIAN YANG
brian.yang@informa.com

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Customer Services
Tel: +44 (0)20 7017 5540
or (US) Toll Free: 1 800 997 3892
Email: Subscriptions@informa.com
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scrip.pharmamedtechbi.com
To advertise, contact
christopher.keeling@informa.com

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