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Dieter Weinand

Bayer's 2018 Financial Forecast Hit By Manufacturing Woes

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Getting its German manufacturing issues sorted as quickly as possible will be the biggest challenge for **Bayer AG** in 2018, according to the company's head of pharmaceuticals Dieter Weinand.

Until good manufacturing practice (GMP) violations at one of its sites in Germany are corrected, Bayer will only be able to run limited services. This situation is expected to set Bayer back by around €300m in 2018.

2017 FULL YEAR RESULTS AT A GLANCE

- Group sales for FY 2017: €35bn
- EBITDA before special items: €9.3bn
- Net income: €7.3bn
- Core EPS: €6.74

Bayer received a lengthy warning letter from the US FDA in November last year, which was published in February 2018, about significant manufacturing violations at the German group's Leverkusen facility. The warning letter stated that Bayer's "methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to current good manufacturing practice (CGMP)." And the list of violations is a long one.

Bayer stands accused of failing to establish and follow adequate written procedures for cleaning and maintenance of equipment, and not thoroughly investigating "any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed." Among the other charges is that Bayer's quality control unit did not sufficiently oversee adequacy of procedures at the facility to assure drug product quality.

During the company's 2017 full year financial results presentation on Feb. 28, the company highlighted that it was expecting temporary supply interruptions due to remediation measures in production. Bayer expects the impact on adjusted EBITDA to be about €300m. The largest proportion of this amount is related to the pharmaceuticals division and a minor part to the consumer health business unit.

Weinand, who is also a member of Bayer's management board, told *Scrip* after the company's earnings presentation in Leverkusen, "Our biggest challenge is to get the supply chain running… bringing the warning letter to a conclusion as quickly as possible because that is a limitation."

Weinand added that while in-market performance was good the company needed to quickly make adjustments at its Leverkusen plant to answer the FDA's qualms. "We are working diligently with the FDA to resolve the warning letter as fast as possible," he said. "We hope to do this by the end of the year… We have hired external support."

The FDA's warning letter relates to an inspection of the Leverkusen plant in January 2017. Products affected include some big-earners, such as the blood pressure treatment *Adalat* (nifedipine) and the erectile dysfunction drug *Levitra* (vardenafil).

Bayer has forecast sales of €16.5bn for the pharma unit in 2018, falling short of the €17.6bn previously predicted by analysts. This corresponds to a low-single-digit percentage increase on a currency- and portfolio-adjusted basis.

Published online 1 March 2018

Celgene MS Setback
FDA delay for ozanimod (p4)

Amgen's Investment Strategy
R&D Head Harper plays the long game (p6)

Artificial Intelligence
Who's doing what with whom? (p10-11)

from the editor

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This week's edition of *Scrip* paints a rather gloomy picture of the industry. While Bayer faces a €300m earnings hit this year because of manufacturing compliance violations in Germany, Celgene suffered yet another setback when the FDA sent back for more work its new drug application for the multiple sclerosis candidate ozanimod, which has been earmarked as a multi-billion dollar revenue generator (see p4). At Daiichi Sankyo there are job cuts (p5) and Biogen and AbbVie have pulled their MS drug *Zinbryta* from the market on safety grounds less than two years after its launch (p8).

It's not all doom and gloom. Mandy Jackson's interview with Amgen's R&D chief Sean Harper reveals how looking for a needle in a haystack need not be a thankless task when you commit to refining your methods and pick your needle carefully (p6).

That attention to how one seeks the needle in the haystack is also in evidence in Mandy's report from Biocom's Global Life Science Partnering Conference (p10), where big pharma business development heads highlighted their growing interest in partnering with those who can help them crunch data better, or who offer new approaches to drugging difficult targets. Lucie Ellis delves further into how artificial intelligence companies are expanding into drug discovery and development on p11.

Elsewhere in the issue we have interviews with executives from Merck KGaA (p18), Sanofi (p19) and the new AstraZeneca spinout Viela Bio (p20). Their focus on exciting areas of R&D innovation reminds us of the huge opportunities this industry enjoys – despite its setbacks.

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Pfizer Japan Cautious Over New Policies As Sales Slip
http://bit.ly/2D5oTBS

Despite a fall in local revenues, Pfizer remains bullish on its newer products and pipeline in Japan but is cautious about this year's planned price reforms in the country.

Turkish Pharma Outlook 2018: Growth Tempered By Lira Devaluation And Pricing Policies
http://bit.ly/2oMK5bG

Turkey's pharmaceutical market is likely to grow by around 12-15% this year, but tight pricing policies and a low fixed exchange rate for the euro at a time when the Turkish lira is volatile and weak against both the euro and US dollar spell trouble for the industry.

Dermira Ends Acne Program After Phase III Failure, Tries To Keep Focus On Hyperhidrosis Drug
http://bit.ly/2I7cLny

FDA approval for DRM04 in hyperhidrosis is expected at the end of June, but Phase III data for DRM01 in acne was the main event for investors. CEO Tom Wiggans said Dermira will try to understand what went wrong, while staying focused on DRM04 commercialization and lebrikizumab in Phase IIb.

Venture Funding Deals: Celularity Launches With $250m; Generation Bio Grabs $100m Series B
http://bit.ly/2FYaN8w

Celularity launched with $250m to develop cell therapies with technology licensed from Celgene and others, while mRNA specialist Moderna brought in another $500m mega round and Generation Bio closed a $100m Series B to fund ongoing gene therapy programs.

Sun's Key Halol Plant Flunks FDA Inspection Again
http://bit.ly/2G0b8Yj

The US FDA has flagged more issues at Indian firm Sun Pharma's largest manufacturing plant in Halol but analysts are hoping the infractions are minor and that the Indian facility will get the regulatory green light soon, ending a blacklist on the factory supplying new products to the US.

Deal Watch: Fresenius Buyout Of Akorn Potentially Threatened By Data Integrity Issues
http://bit.ly/2FYXCnV

AstraZeneca takes second license of antisense candidate under 2012 pact with Ionis, this time for kidney disease. Aldeyra is working with J&J on novel immune-modulating drugs for systemic inflammatory conditions.

inside:

Celgene Reveals Refuse-To-File Letter For Ozanimod

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Celgene Corp. revealed more bad news it didn't need on Feb. 27 when the company said it received a refuse-to-file letter from the US FDA for the new drug application (NDA) for ozanimod in multiple sclerosis, which generally was seen as a sure thing based on Phase III data.

Celgene does not expect an extremely long delay in FDA approval, because the agency's refuse-to-file (RTF) decision was based on nonclinical and clinical pharmacology – which the company said "were insufficient to permit a complete review" – and it does not appear that another pivotal trial will be needed to support the NDA. However, any delay in ozanimod's first approval is yet another setback for the company, which has been significantly hit by multiple disappointments since October.

After-hours trading saw Celgene's share price fall by more than 8% immediately following the ozanimod RTF announcement, with the stock ending the night down 6.4% at $89.65 – a slight improvement after the company's CEO Mark Alles and other executives spoke with analysts during a conference call to discuss the news.

While Alles reaffirmed Celgene's prior 2020 guidance of $19bn to $20bn in revenue, which assumes eventual ozanimod approval, management didn't provide a lot of clarity about why the FDA rejected the sphingosine 1-phsophate (S1PR1) and 5 (S1PR5) receptor modulator's NDA.

Celgene will update investors about the next steps for ozanimod in multiple sclerosis after it requests and completes a Type A meeting with the FDA to clarify what additional information is needed to refile the NDA, which is possible later this year. The company believes it has the information the agency wants or it may soon generate those data in ongoing clinical pharmacology studies.

"We will work very aggressively and actively to meet with FDA as fast as we can," Alles said.

Meanwhile, Celgene left the door open for delayed filings for ozanimod in additional markets while it awaits details from the US agency and possibly while it prepares the requested information for the FDA. "We are currently reevaluating other worldwide filings," the CEO noted.

However, Alles also pointed out that the conduct of Phase III trials for ozanimod in ulcerative colitis are not affected by the RTF letter. Data from the TRUE NORTH and extension studies are expected during the fourth quarter of this year. If positive, a supplemental NDA submission for ozanimod in ulcerative colitis could come in the first half of 2019. Celgene also recently initiated a Phase III trial for ozanimod in Crohn's disease.

The S1P receptor modulator is important for Celgene because it would double the number of approved drugs in the company's inflammation and immunology portfolio. The I&I franchise is a major focus for Celgene and its investors as the company seeks to diversify beyond its hematology and oncology franchise, which is dominated by *Revlimid* (lenalidomide). The multiple myeloma blockbuster generated $8.2bn in 2017 sales – almost two-thirds of the company's $13bn in total revenue.

That's why setbacks in Celgene's pipeline – including acquired and partnered assets – and disappointing sales for its only approved I&I drug *Otezla* (apremilast) have sent the company's stock price markedly lower.

SETBACKS

First, Celgene said on Oct. 19, 2017 that it would discontinue development of mongersen (GED-0301) in Crohn's disease and reevaluate the drug acquired from **Nogra Pharma Ltd.** after receiving results from an ongoing ulcerative colitis study. The company's stock fell into the low $120 per share range based on that news after closing at its one-year high of $146.52 on Oct. 4.

The stock sank below $100 later in the month after Celgene revealed lower-than-expected Otezla sales in the third quarter of 2017, admitting that its revenue expectations set earlier in the year misjudged how competitive the psoriasis and psoriatic arthritis market would become after recent approvals for new drugs in those indications. Mongersen, Otezla and other factors contributed to the company lowering its 2020 guidance from $21bn in revenue to a range of $19bn to $20bn.

INVESTOR CONFIDENCE NEEDS REBUILDING

But with FDA approval for ozanimod in multiple sclerosis in the back of investors' minds as a sure win for Celgene based on positive Phase III results reported soon after the disappointing third quarter earnings report, the company's stock has been trading between $90 and $110 since the end of October. A swift reversal of this latest setback with ozanimod will be needed to regain investor confidence.

Jefferies analyst Michael Yee said in a Feb. 27 note that "this just adds even more uncertainty and credibility questions, which is not helpful right now given Celgene is in a period where they need to instill confidence after the recent disappointments (e.g. GED-0301 failure, Otezla and 2020 guidance reduction, ozanimod UC recruitment delay, etc.)."

Asked during the conference call whether the ozanimod RTF letter and apparent data deficiency leading to the FDA decision would change the company's interest in deal-making to build its R&D pipeline, Celgene Chief Financial Officer Peter Kellogg said he didn't think so. "We're in the process of building a very exciting pipeline for the next decade and will continue to do that," Kellogg added.

Celgene bought ozanimod in the $7.2bn purchase of **Receptos Inc.** in 2015 with the expectation that the acquired company's lead drug candidate eventually would add $4bn to $6bn in revenue to the buyer's balance sheet.

Chief Medical Officer Jay Backstrom asserted that the RTF letter for ozanimod in MS does not signal a deficiency in Celgene's due diligence during the Receptos acquisition. The company thought it had all of the data necessary for its NDA when it filed the drug with the FDA.

Going forward, Alles said any delay in ozanimod approval may be offset by the "optionality" the company created through its acquisitions announced earlier this year of **Impact Biomedicines**, which has the NDA-ready drug fedratinib, and **Juno Therapeutics Inc.**, which gives Celgene full rights to partnered chimeric antigen receptor T-cell (CAR-T) development programs.

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More US Positions Go As Daiichi Sankyo Refocuses

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For many companies, taking steps to maximize opportunities for the current commercial portfolio and prepare for an upcoming oncology pipeline might mean taking on new sales staff and specialist marketing representatives.

In **Daiichi Sankyo**'s case however, these considerations are spelling the loss of around 280 personnel from various sites in the US as it streamlines and tightens focus, and looks at what the Japanese company says is necessary for its long term success.

"Our priorities are to bring spending into line with revenue, shift resources to maximize Injectafer and our abuse-deterrent pain treatments," and to prepare for new cancer products, president of Administrative and Commercial at Daiichi Sankyo, Inc, Ken Keller explained in a statement.

Daiichi Sankyo in Japan declined to say which specific US sites and functions would be most affected or to provide further details, but noted the bulk of the cuts are in the sales rep area. The company said it would provide outplacement assistance, severance and other support to those affected.

The Japanese firm's main corporate HQ site in the US is at Basking Ridge, New Jersey, and it also owns **Luitpold Pharmaceuticals Inc.** (Shirley, New York) and **Plexxikon Inc.** (Berkeley, California) in the US. *Injectafer* (ferric carboxymaltose injection) is marketed by Luitpold and expected to grow amid a changing anemia in chronic kidney disease market precipitated by the rise of new treatments such as **AstraZeneca PLC**'s roxadustat and the erosion of **Amgen Inc.**'s *Epogen* (epoetin alfa) by biosimilars.

Meanwhile, revenues from Daiichi Sankyo's longstanding top product olmesartan (sold as *Olmetec/Benicar* and others) are declining amid rising global generic competition, with the company forecasting worldwide sales of the molecule and combinations will fall by 33% in the fiscal year to March 31, to JPY146bn ($1.37bn).

Building mainly on its antibody-drug conjugate technology and growing acute myeloid leukemia franchise, Daiichi Sankyo has said it is aiming to build oncology sales to JPY40bn in the fiscal year to March 2021 and to JPY300bn by the end of fiscal 2025.

The firm has set up a dedicated oncology enterprise whose R&D head (Dr. Antoine Yver) was recruited from AstraZeneca and sees the anti-HER2 antibody/topoisomerase I inhibitor conjugate DS-8201 in particular as a "flagship asset". Now in early clinical development, the therapy is being developed for HER2+ breast and gastric cancer and other HER2-expressing solid cancers.

Four clinical assets are also in the pipeline for AML, including the FLT3 inhibitor quizartinib, which came with the 2014 acquisition of **Ambit Biosciences Inc.**

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R&D Head Sean Harper On Amgen's Long-Term Investment View

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Amgen Inc. Executive Vice President-Research and Development Sean Harper is a proponent of big, lengthy investments that the company has made in an effort to make better drugs, and he thinks several programs moving through the clinic now may show whether the money and time were well spent.

Scrip spoke with Harper about therapeutics that are moving ahead based on Amgen's acquisition of **deCODE Genetics** and its investments in drug development platforms. He noted that while many of the company's peers are invested in foundational immuno-oncology agents, Amgen has kept its focus on its own contributions to the field via bispecific T-cell engager (BiTE) and oncolytic virus technologies that could boost the efficacy of checkpoint inhibitors.

Amgen paid $415m to acquire deCODE at the end of 2012 with plans to use the Icelandic genomic sequencing firm's data to validate novel drug targets. Since then, the company has done some "pruning and remodeling" of its R&D pipeline based on deCODE's insights. "One would expect to see a two-fold improvement in our success rate," Harper said.

PUTTING DECODE TO WORK

He noted that Amgen's new knowledge about genetic drivers of disease "has influenced quite a bit what we're doing in our cardiovascular area. A good example is our [lipoprotein(a) or (LPa)] program where we're looking to silence the expression of the lipoprotein component of LPa, which is a kind of an LDL-like particle that about 15% of the world's population has at elevated levels. Using deCODE's resources we were able to convince ourselves that there's a clear causal relationship between LDL and LPa in advanced premature atherosclerotic disease."

Amgen is working with **Arrowhead Pharmaceuticals Inc.** on an RNA silencing (siRNA) approach to silence the expression of LPa under a 2016 licensing agreement; their candidate ARC-LPA is in preclinical development.

"We have also just introduced into the clinic a bispecific antibody for inflammatory bowel disease, which is based on deCODE insights," Harper said, referring to AMG 966 in Phase I for Crohn's disease and ulcerative colitis. He added that other cardiovascular programs, some Alzheimer's disease R&D and some other projects also have been influenced by deCODE data.

Cardiovascular disease is a big area of investment for Amgen, although a lot of other companies shy away from the space given the enormous investment required for those large, lengthy clinical trial programs. For instance, Amgen and partner **Cytokinetics Inc.**initiated the 8,000-patient Phase III GALACTIC-HF clinical trial for omecamtiv mecarbil in heart failure at the end of 2016 and it is rapidly enrolling patients, according to Harper, but data still are not expected for another two-and-a-half to three years.

Even so, he said cardiovascular disease is an attractive area for Amgen's drug development, because it remains the number one cause of morbidity and mortality in the world and has a lot of unmet need.

"As opposed to 2,000 agents in development in immuno-oncology, you have a relatively limited amount of effort going into [cardiovascular disease]. That's because in part it's been very hard to come up with good targets, but the genetics can help you with that," Harper said. "There are some targets that arise through genetics and there's others that arise through more classical approaches, but can be confirmed by the genetics. It is an area that we feel there's significant opportunity, whether it's atherosclerosis or heart failure, which are the two areas we're focused in in cardiovascular. Those are huge unmet needs."

He said there still are not a lot of satisfactory therapeutics available for heart failure, despite how widespread it is, but noted that "we feel that the science is there to get reasonable traction. It's not for the faint of heart, because you have to do long cardiovascular outcomes trials, but from a competitive perspective, it's very attractive in terms of the dearth of companies that are really focusing in the area compared to the competitive intensity that exists in immuno-oncology right now."

LOOKING FOR ITS OWN WAY IN IO

That's not to say that Amgen isn't focused on immuno-oncology, however, but the company is not developing a checkpoint inhibitor, like many of its peers. The company invested in its BiTE and oncolytic virus platforms before immuno-oncology became the biopharmaceutical industry darling that it is today.

The BiTE technology behind the leukemia drug *Blincyto* (blinatumomab) came from the $1.16bn purchase of **Micromet Inc.** in 2012. Amgen's first approved oncolytic virus therapeutic *Imlygic* (talimogene laherparepvec) for melanoma came from the 2011 acquisition of **BioVex Inc.** for $425m up front.

Harper said Amgen invested in the BiTE platform much earlier than other big companies now working with similar technology based on very early yet compelling data in hematological malignancies with a hint of activity in solid tumors. The oncolytic virus investment was also an early-stage bet.

"While there may be literally hundreds of companies working in that particular space, the only approved products in that space are Amgen products," he said. "We're continuing to push hard in those areas, because we feel these are important potential platform technologies to integrate into a world where checkpoint inhibitors are a foundational type of therapy, but they don't work for all patients [and] they don't work for all tumor types; there's plenty of headroom available still to help patients."

With Imlygic approved and the oncolytic virus technology validated, the company is now looking at combination therapy regimens where an oncolytic virus might be able to recruit T-cells into tumors so that checkpoint inhibitors are more active. Amgen has published clinical data in *Cell* based on early human research conducted with Antoni Ribas, an oncologist and professor at the **University of California, Los Angeles**.

"We've seen a rough correlation with complete responses – at least a doubling of complete response," Harper said. "The whole field is out there trying to find these situations where you can get something that really has synergistic activity mechanisti-

cally with checkpoint inhibition. Despite the thousands of experiments out there looking for this kind of activity, there's very few examples where anybody's actually observed it and we have so we're excited about it."

IN-HOUSE COMBINATIONS

Even so, he said that developing yet another PD-1 inhibitor is not something that Amgen wants to do, but noted that the company may consider acquiring one to offer oncologists as part of a combination treatment with a drug it developed internally.

"We just consider PD-1/PD-L1 and [the CTLA-1 inhibitor *Yervoy* (ipilimumab) from **Bristol-Myers Squibb Co.**] to be the foundational important first step in what is the beginning of this whole immuno-oncology revolution. You can build on that; you don't have to do the same thing. That's not what I want to be doing," Harper said.

Amgen is, however, investing in chimeric antigen receptor T-cell (CAR-T) therapies – another hot immuno-oncology area – via a partnership inked with the **Gilead Sciences Inc.** subsidiary **Kite Pharma Inc.** in early 2015.

Their lead CAR-T program is a preclinical candidate directed against an antigen in small cell lung cancer, which soon will move into a clinical trial, but the partners are getting additional CAR-T candidates ready for investigational new drug (IND) application submissions to support early human trials.

"I think we may end up being the only company that can do some of these head-to-head comparisons between what we see in the clinic with a bispecific T-cell-engaging type molecule – plus or minus a checkpoint inhibitor – and a CAR-T directed at the same antigen," Harper said. "I think that's what's really needed for the field to understand what are the pros and cons; when does it make sense to go through all the rigmarole and the expense to do a CAR-T versus something that you take off the shelf and treat the patient with? When might one approach work better than another? I think in the end it's going to turn out that there's going to be applications for both of these kind of technologies."

He noted that "it's going to take some time for all of this to play out. But at least we're doing something meaningful for cancer patients now. I've been doing this for a long time and we weren't doing a whole lot to help people in the past with most of the efforts we were making in the industry directed to cancer, in retrospect. There were a few exceptions, but generally we weren't doing a whole lot. Now we have patients that are essentially functionally cured of their disease."

NEEDLE IN A HAYSTACK

As for additional deal-making to bring in new drug candidates, Amgen constantly is looking, but it has had a hard time finding assets that are reasonably priced, especially in oncology. "We're always looking in the very early space for technology platforms that can help us – modality platforms and other technologies. We find quite a bit of interesting things going on there," Harper said. "And in some cases we're just watching technologies carefully, like the gene therapy technology or gene editing technologies right now – monitoring the space, but not really getting too involved directly ourselves with it."

Amgen also is "looking for those needle-in-a-haystack molecules or portfolios of molecules, where we see more value in it than the market does," he said.

As for mid- to late-stage assets, there aren't many left for Amgen or its peers to buy "and the valuations are reflecting that."

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Biogen, AbbVie Withdraw Struggling MS Drug Zinbryta Due To Safety Issues

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There were indications during **Biogen Inc.**'s most recent earnings call in January that it was getting ready to pull the plug on struggling multiple sclerosis drug *Zinbryta* (daclizumab), but with the European Medicines Agency revealing it's begun an "urgent review" of cases of inflammatory brain disease in patients who've taken the drug, the decision became more clear-cut.

Biogen and its US marketing partner **AbbVie Inc.** announced on March 2 that they were voluntarily withdrawing worldwide marketing authorizations for Zinbryta, an antibody that targets both interleukin-2 (IL-2) and cluster of differentiation 25 (CD25). On the market less than two years, Zinbryta struggled to find a niche in the MS market and generated just $72.7m in 2017 sales for Biogen, an MS leader with blockbusters *Tecfidera* (dimethyl fumarate) and *Tysabri* (natalizumab), as well as *Avonex* (interferon beta-1a), *Plegridy* (peginterferon beta-1a) and *Fampyra* (fampridine).

> 'Discontinuing Zinbryta makes financial sense, given its limited uptake in the saturated relapsing MS segment of the market'

Little noticed during Biogen's fourth-quarter and full-year 2017 earnings call on Jan. 25 was that the big biotech revealed it had taken a $20m inventory charge related to Zinbryta during the fourth quarter. BMO Capital Markets analyst Ian Somaiya referred to the write-down in a March 2 note as "a potential prelude to the announcement today."

Biogen and AbbVie both declined to comment, but when *Scrip* asked specifically about the inventory charge, a Biogen spokesman noted that due to restrictions placed on the use of Zinbryta by Europe's Committee for Medicinal Products for Human Use (CHMP) last fall, the company recorded net impairments related to intangible assets, inventory, property, plant and equipment and prepaid tax assets of $190.8m, which was offset partially by tax benefits for Zinbryta-related assets that totaled $93.8m.

The European Medicines Agency in October restricted use of Zinbryta to relapsing MS patients who had inadequate response with at least two prior disease-modifying therapies (DMTs) and could not use other DMTs. The agency also said patients receiving the drug should be monitored for liver function once a month and up to six months after stopping the drug.

This decision followed an Article 20 review by EMA's Pharmacovigilance Risk Assessment Committee following reports of severe hepatic adverse events in patients treated with Zinbryta, including one death due to fulminant liver failure.

Zinbryta gained EU approval in April 2016 and US FDA approval for third-line use in relapsing/remitting MS roughly one month later. The US approval, however, carried a black box warning that the monthly injectable could cause liver toxicity based on adverse event reports during clinical trials.

BRAIN INFLAMMATION CASES WORSENED POOR SAFETY PROFILE

The liver toxicity issues likely limited the drug's use and may already have caused the sponsors to think about pulling the drug. However, the seven cases of serious inflammatory brain disorders in Germany and one in Spain cited by the EMA on March 2 probably sounded the death knell for Zinbryta. The EU agency said it was investigating cases of both of encephalitis and meningoencephalitis related to the drug's use.

The EMA directed doctors not to start patients on Zinbryta and to review patients currently taking the drug and start them on alternative therapy as soon as possible. Biogen said it would continue working collaboratively with regulators and health care providers in the management of Zinbryta patients.

Biogen and AbbVie said in a statement that they decided to withdraw the drug because of the nature and complexity of the adverse events being reported and their conclusion that "characterizing the evolving risk/benefit profile of Zinbryta will not be possible going forward."

BMO's Somaiya called it "a surprise with little consequence" for Biogen in his note about the withdrawal. Loss of Zinbryta revenue would have little impact on the biotech's 2018 performance, he opined, and would not deter BMO from continuing to expect improved MS franchise sales this year at Biogen.

However, Somaiya did reduce his target price for Biogen shares from $403 to $393. He attributed this to a projection that roughly half of Zinbryta patients would transition to Tysabri, while the other half would switch to **Genentech Inc.**'s *Ocrevus* (ocrelizumab). Launched in April 2017, the anti-CD20 therapy realized sales of $935m in its first nine months on the market.

In addition to competition from Ocrevus, Somaiya said the longer-term concern for Biogen in the MS space is Tysabri's patent expiration in 2023.

Morningstar analyst Karen Andersen updated her valuation of Biogen on March 2 by lowering her fair value estimate of the stock from $386 per share to $382. Her take on the MS market sees Tecfidera plateauing at earnings of about $4bn per year and Tysabri sales falling off gradually, as Ocrevus builds to a sales peak of $5bn in 2024. At that point, Biogen will hold a 16%-20% market share in MS, Andersen wrote.

Biomedtracker, which projected that Zinbryta's peak annual sales would fall short of $300m, said the decision to withdraw the drug was the right one. "Discontinuing Zinbryta makes financial sense, given its limited uptake in the saturated relapsing MS segment of the market," Biomedtracker's analysis noted. "Zinbryta cannot compete with alternative brands such as *Lemtrada* (alemtuzumab, **Sanofi**), Tysabri and Ocrevus."

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Valeant Claims Progress, Asks Investors For Patience

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Valeant Pharmaceuticals International Inc. has made important debt-reduction progress, meeting its goal ahead of schedule, but the company's near-term growth story remains lackluster. The company told investors during a fourth quarter sales and earnings call that revenues will continue to decline in 2018, but pointed to a "significant seven" of newer products and some yet-to-be-approved opportunities that will drive its return to sales growth from 2019 through 2021.

The Laval, Quebec, specialty pharma still faces massive debt – although most now has been pushed back several years – and a cratering dermatology franchise. Executives pledge that a 25% increase in the dermatology sales force and several new products will turn dermatology around. They predict a doubling of franchise sales by 2022, and note that the **Bausch & Lomb Inc.** eye-care division and **Salix Pharmaceuticals Ltd.** gastrointestinal business already are performing in solid fashion.

Not quite two years into a multi-year plan to turn around Valeant's fortunes, Chairman and CEO Joseph Papa claimed the company is on track with that strategy. "After working to stabilize the company, we are now well into the second phase of the plan, the turnaround, where we're taking steps to drive shareholder value," he said during Valeant's fourth quarter and full-year 2017 earnings call Feb. 28. "Our three main areas of focus are: resolving legacy issues and de-risking the balance sheet; investing in core franchises with attractive growth; and launching new products with meaningful opportunities."

Valeant faced a $32.6bn debt load at the end of the first quarter in 2016, but has reduced that total by more than $6.7bn since, including its efforts during the first two months of 2018. Specifically, the company reported that it cut debt service by $4.4bn during 2017, while reducing its debt-repayment requirements through the end of 2020 by more than $10.8bn since the end of 2016. In doing so, the company has exceeded a goal of $5bn in debt reduction by the end of February 2018.

Chief Financial Officer Paul Herendeen said Valeant has used net proceeds from divestitures – such as the sale of companies **Dendreon Corp.**, **iNova Pharmaceuticals Pty. Ltd.** and **Obagi Medical Products Inc.**, and the offloading of three branded skincare products to **L'Oreal SA** – along with cash generation and "successful note offerings" to substantially pay down its debt due by 2020. With the financing of $1.5bn in unsecured notes during the fourth quarter, the company has regained some of its prior access to the capital markets, he added.

"Regaining access to the unsecured debt markets was an important step as we work to ensure that we have the runway to continue the turnaround and transformation of Valeant," Herendeen told the call. "Sitting here today, our long-term debt is down to $25.5bn, and our next maturities are out in 2020. [There is] plenty more work to do, but we made very substantial progress over the course of 2017, including in the fourth quarter."

With each taking a similarly cautious optimistic view, market analysts lauded Valeant for its debt stabilization to date and said they could see potential for growth in several franchises, but maintained that the company still faces multiple issues including the impact of debt on its ability to participate in business development, the safety issues facing one of its seven expected growth catalysts (the psoriasis drug *Siliq*) and losses of exclusivity in the GI portfolio that may impede the effort to turn that franchise around.

"Management now believes they have a plausible pathway forward to manage a still massive debt load," wrote Jefferies analyst David Steinberg on March 1. "It's all about execution and that begins with delivering solid Rx gains for key franchises – particularly *Xifaxan* (rifaximin) and other GI brands and delivering on a turnaround in dermatology via new product launches. It won't be easy and overhangs still remain [but] with a 2.5-year runway, they have a chance."

Overall, Valeant reported $8.72bn in aggregate sales in 2017, down 10% from 2016, including a total of $2.16bn for the fourth quarter, also a 10% drop. Its Bausch & Lomb/International segment yielded 56% of full-year revenue, $4.87bn, down 1% from 2016. The Branded Rx segment, which includes dermatology, declined 19% year-over-year to $602m. Valeant said decreased volume in dermatology combined with the impact of divestitures accounted for $194m of the reduction in revenue compared to 2016.

On the positive side, Valeant's Salix GI business generated 2% growth in 2017 to $1.57bn, comprising 18% of total sales revenue. The franchise delivered mid-single-digit or higher sales growth in each of the second, third and fourth quarters last year, the company pointed out, while the B&L/International unit posted single-digit growth during each of the four quarters in 2017.

"Our underlying core businesses were essentially flat compared with the prior year … and I think you can see, as we put the contraction of our dermatology business behind us, you can start to see the future growth potential of our core assets," Herendeen said.

Morningstar analyst Michael Waterhouse said the company "remains in the midst of a complicated turnaround, but underlying results show stability in the business," in a Feb. 28 note. Headwinds remain, such as potential generic competition to ulcerative colitis drugs *Apriso* (mesalamine) and *Uceris* (budesonide) in 2018, but the overall picture brightens in 2019.

Apriso and Uceris, the company's third and fourth-largest sellers after Xifaxan and the divested cancer vaccine *Provenge* (sipuleucel-T), yielded a combined sales total of $284m in 2017 – Valeant said generic competition is expected between the second half of 2018 and the second half of 2019, but could not be more precise.

ARE VALEANT'S GROWTH PROJECTIONS REALISTIC?

Still, the company's projection of 4%-6% annualized growth on average between 2018 and 2021 may be overly optimistic, Waterhouse cautioned, as some of its intended growth leaders faced entrenched competition. This includes glaucoma drug *Vyzulta* (latanoprostene bunod) and psoriasis drug Siliq (brodalumab), as well as topical *Duobrii* (IDP-118), also for psoriasis, which has a US FDA action date of June 18.

BTIG analyst Timothy Chiang pointed to the market potential of Duobrii in a Feb. 28 note, saying it could be first topical product that psoriasis patients could use for longer than several weeks. But he voiced the oft-heard doubts about Siliq's prospects, noting that its black box warning for suicidal ideation probably "narrows the number of patients who are likely to be prescribed the treatment."

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Biopharma Investing In Better Success Rates Via AI, Data And New Modalities

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Biopharmaceutical company business development executives speaking at **Biocom**'s recent Global Life Science Partnering Conference in San Diego are all looking for the same thing: technology that can analyze data or approach a therapeutic target in a way that increases chances of drug development success.

That could come in the form of artificial intelligence and machine learning that can determine the viability of novel therapeutic targets and drug candidates, or new drug modalities that hit targets previously viewed as difficult or impossible to drug. The Feb. 28 and March 1 partnering meeting sponsored by Biocom, a California life science industry organization, gave small and mid-sized firms with technologies in these and other areas a chance to meet with investors and potential partners.

Estimates vary, but it's generally accepted that it takes billions of dollars to develop a single commercial biopharma product. Taking into consideration the cumulative research and development costs for an approved drug as well as the R&D time and capital invested in programs that eventually fail, the success rate is astoundingly low. That's why investors and biopharma companies are putting more money into platforms that have tried to reduce risk or that could screen for success. Read the full article here

"As a scouting and innovation function, we really are customer-focused on what our researchers are looking for and what our development groups are looking for. There is a lot of emerging interest in artificial intelligence, machine learning and machine reasoning, and how these approaches can help you with target discovery or working through toxicity issues or lead identification,"**Daiichi Sankyo Co. Ltd.** Senior Vice President, External Scientific Affairs Jeff Warmke said during a March 1 panel discussion about what to expect in business development in 2018 and beyond.

As a result, in the next year, Daiichi will be doing a lot of pilot studies in the areas of AI and machine learning to help enhance the company's discovery efforts.

NEW MODALITIES GARNER INVESTMENT

Bayer AG Vice President Chris Haskell confirmed that data science for drug discovery and emerging technologies are important areas for the big pharma's business development. Haskell, head of Bayer's West Coast Innovation Center in San Francisco, noted that the company also is placing significant long-term bets on companies with new drug modalities that are potentially curative, including the $525m that Bayer has invested in **Casebia Therapeutics** and **BlueRock Therapeutics**.

"Our systems and internal processes don't allow for the type of creativity and long-range risk-taking that's going to be necessary to solve the challenges to actually get gene editing into patients," Haskell said, noting that Bayer will incorporate Casebia and BlueRock therapeutic candidates into its pipeline as the technologies mature.

Casebia is a gene-editing company that emerged from Bayer's joint venture with **CRISPR Therapeutics AG**, which the partners set up with $300m in initial financing. BlueRock is developing induced pluripotent stem cell-derived therapies for cardiovascular and neuroscience indications.

"The pivotal theme is really going after what is considered undrugable, until now," **Sigilon Therapeutics** Chief Scientific Officer David Moller said during the business development panel.

Moller noted that many new companies are being formed in this space with a lot of new modalities going after both known and new targets – technologies such as targeted protein degradation, the delivery of RNA silencing (siRNA) to places other than the liver, CRISPR gene editing, gene therapy and synthetic biology. "You already are seeing that most pharma companies are beginning to dip their toes in the water here," Moller said.

Otsuka Holdings Co. Ltd. Senior Vice President of Business Development Ron Newbold noted that the Japanese company is one of the few major pharma firms focusing on neuroscience, so it is looking for innovation in that area. However, Newbold also noted that investing in the US in general is a big priority, since this is where a lot of health care innovation is occurring and where pricing for novel products generally rewards the investment made in new technology.

Two years ago, all of the business development executives on the Biocom stage would've said they were looking for immuno-oncology assets, noted Avi Spier, business development and licensing director for the **Novartis Institutes for BioMedical Research Inc.** (NIBR). Now, **Novartis AG**'s search for new technology is shifting from understanding the role of the immune system in cancer to immunology more generally in a variety of diseases.

"New technologies that open up new areas of drug discovery, that's what we're interested in," Spier said.

DEALING WITH DISRUPTORS

GlaxoSmithKline PLC Vice President of Alliance Management, Business Development Strategy and Operations Bill Mendez said he was intrigued by **Roche**'s surprising $1.9bn acquisition of the health care data company **Flatiron Health Inc.**, but viewed the transaction giving Roche access to real-world evidence as a smart move that could help get new drugs approved and reimbursed.

"Data is critical. The more data you have, the better chance you have of figuring out: can you actually get the drug approved," Mendez said. "I think [Roche's Flatiron deal] is an indication of where the industry's going on a broader scale."

When the business development panel was asked what their companies are doing to work with "disruptors" like **Amazon.com Inc.**, **Apple** and **Google** that are moving into health care and looking for inroads in the biopharma industry, Mendez noted GSK's partnership with Google.

The UK-based big pharma and Google's life science investment arm announced a joint venture in 2016 to invest in bioelectronics. Mendez said the partners see a potentially disruptive opportunity in the area of implantable devices.

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Who's Who In Artificial Intelligence Drug Development

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Scrip has formed a list of 18 artificial intelligence companies using novel technologies to discover drug targets, highlighting those with pharma partnerships or internal development pipelines that could be disruptive to the innovative life science sector.

There has been a lot of hype around the use of artificial intelligence (AI) for drug discovery and development, and a batch of start-ups have emerged in this space with various computer driven technologies.

AI companies come in all shapes and sizes, and just within healthcare there are various forms of these businesses. Some companies promote technologies able to aggregate information for rapid analytics, others are focused on increasing understanding of certain diseases, and several use AI to repurpose old drugs, better design clinical studies, recruit for trials or improve data publication.

However, there is a set of AI companies using advanced technologies to generate and evolve novel drug candidates. The majority of these companies have sprung up in the past decade and have deals and partnerships in place with pharma and academic institutes.

As well as working with pharma and biotech groups though, a handful of these AI companies are advancing in-house drug discovery and development programs. These hybrid businesses have caught the attention of big pharma, securing many deals over the past five to 10 years. They are also starting to enter clinical development with early-stage assets. Go online for the full list of AI drug development companies: http://bit.ly/AICompaniesTable

PHARMA FAVORITES

Exscientia Ltd., founded in 2012, appears to have the most pharma partnerships out of the AI driven companies on the list: one major collaboration with **Evotec AG** and four partnerships with large pharma companies. Exscientia's CEO, Andrew Hopkins, told *Scrip* in an exclusive interview at the end of 2017 that "it feels like the world is coming to us now," and that there is an increased interest in the firm's technology.

Hopkins said Exscientia was built on pharma deals, and that these partnerships over the past five years had helped to validate its technology. "Companies are now approaching us because we have done the hard work, we have validated the technology and we have examples of clear deliveries of successes," he said.

"We are in the position now to demonstrate what is really possible and that it's not just hype," Hopkins added.

With its major partner Evotec, Exscientia is developing a joint portfolio of immuno-oncology drug candidates. In September 2017, Evotec invested €15m into Exscientia for a minority stake, becoming the first strategic shareholder in the UK-based company.

Exscientia's technology works by applying a rapid design-make-test cycle. Its AI system actively learns from the preceding experimental results and rapidly evolves compounds towards the desired candidate criteria. Exscientia's systems learn from both existing data resources and experimental data from each design cycle. The principle is similar to how a human would learn, but the AI process is effective at identifying and assimilating multiple subtle and complex trends to balance potency, selectivity and pharmacokinetic criteria.

Meanwhile, Californian companies **Numedii Inc.** and **Numerate Inc.** have secured several pharma partners, with four deals each.

Numerate has been using an algorithm-centric process to drive its preclinical drug discovery and development decisions for several years – but the company chose to act under a more traditional biotech façade in its earlier days in order to secure funding. The company's CEO Guido Lanza told *Scrip* in an interview last year that until recently the industry had not been ready to listen to a story about AI in drug development – the world was not interested until some success stories emerged.

While the early questions for AI companies in healthcare focused on 'Can I use AI to help me identify a target for a disease?' or 'Can I use AI to help me define a patient population?', these questions are evolving.

Numerate has been focusing instead on the translational aspects of AI in drug development. "Our view is that the biggest impact AI can play is on changing those attrition rates that are the biggest issue in our industry," Lanza said. Numerate is looking to answer questions like, 'Can we change the rate at which we transform an exciting emerging target into drug program and then the rate at which that drug program becomes a clinical candidate?'

BENEVOLENTAI EXPANDS IN UK

BenevolentAI, which is working with **Janssen Pharmaceutical Cos.** to evaluate an undisclosed number of novel clinical stage drug candidates for hard-to-treat diseases, recently acquired a drug discovery and development facility in Cambridge, UK.

BenevolentAI will use this site to advance drug programs into the clinic more quickly and on a larger scale. The company highlighted that the acquisition "marks the first time an AI company will be able to work across the entire drug development process 'end-to-end' from drug discovery to late stage clinical development."

BenevolentAI is heavily focused on developing an in-house pipeline. The company has rapidly expanded its research portfolio to include 19 programs since establishing its drug development subsidiary BenevolentBio less than two years ago.

Through BenevolentBio, the company is working with Janssen and has licensed other development compounds; the company also works with charities and other funders, especially in rare disease areas.

BIG PHARMA'S ON BOARD

Many of the larger industry players have started to promote the use of AI for pipeline development. **GlaxoSmithKline PLC**, which is working with Exscientia in the drug discovery space, has also been leading the way with internal initiatives such as its ADaM collaboration – a data sharing initiative.

Furthermore, **Novartis AG**'s newly appointed CEO Vas Narasimhan is a big proponent of automation and artificial intelligence in drug discovery. He has previously said that Novartis will ramp up its efforts when it comes to big data technologies and AI.

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MEETING GROWTH CHALLENGES ROUNDTABLE PANEL PART 1:

Laying The Foundation For A Sustainable Business

BY MIKE WARD

Developing products that are clinically meaningful requires more than a novel approach to an unmet medical need. A panel of biotech executives and venture investors discuss how to meet the challenges of building a sustainable business from day one.

Starting up life science companies has probably never been easier. Our understanding of disease biology continues to grow, the pool of experienced biotech executives with the battle scars of entrepreneurship has never been deeper, and the cash pile to bankroll their development continues to grow. The challenge these days is what do company executives have to do to ensure they can translate their ground breaking ideas into sustainable businesses that develop products that make a meaningful difference to patients.

Scrip spoke with Gil Van Bokkelen, chairman and CEO of Athersys, Inc., Daniel R. Orlando, chief operating officer of Vericel Corporation, Robert McNeil, general partner and managing director of Sanderling Ventures and CEO of Dalcor Therapeutics, Ali Fattaey president and CEO of Curis, Inc., Mei Mei Hu, co-founder and CEO of United Neuroscience, Inc., Gregory Hanson, CFO of MabVax Therapeutics Holdings, Inc., and Dennis Podlesak, COO at Domain Associates LLC, in a roundtable interview about the challenges company executives face as they try to build their business. Sponsored by Freyeur & Trogue, Impactiv and rbb Communications, the roundtable took place during the J.P. Morgan Healthcare Conference in San Francisco.

Focus on clinically meaningful outcomes

One of the strongest foundation stones life science entrepreneurs can lay when starting to build a company around an idea they have is a thorough understanding of the indication they are targeting and develop a way to dramatically change the treatment paradigm.

"Until 10 years ago, if a drug was approved, the general sense was it could have an important role in treating patients and that would be seen as a success. If you look at how the landscape has changed over time, no entrepreneurs or business leaders would invest either time or money unless the treatment has the potential to be truly differentiated," warned Domain's Podlesak.

"Venture firms and companies both look at how the to grow the business. Unless they can dramatically change the treatment paradigm they tend not to be able to attract capital," he added.

An example of a paradigm-shifting approach in the Domain portfolio is Adynxx, a San Francisco-based biotech that is testing brivoligide, a molecule that inhibits EGR1, a transcription factor that plays a critical role in establishing and maintaining pain following injury or trauma, as a potential non-opioid, disease-modifying therapeutic for post-operative pain. The drug is in a second Phase II trial. If it works it would be the first drug to actively prevent chronic pain.

"Given the prevalence and severity of chronic pain following surgery, combined with the lack of safe, effective and non-addictive treatment options, we believe it can fundamentally transform the treatment paradigm for post-surgical pain. It is an example of how the bar can be raised," added Podlesak.

The challenge comes when the indication has historically been intractable or the endpoints for the clinical trial is not obvious.

"Stroke is a perfect example. Everyone is aware that it is one of those areas where there has been a lot of disappointments – outright failures. Current practice is to either give the patient a thrombolytic like tissue plasminogen activator or take one of the recently developed surgical procedures. Both require treating the patient in the first few hours of the stroke and the clinical reality of that is only a small percentage of patients – roughly 8% – will benefit," noted Athersys' Van Bokkelen.

Athersys is developing an approach that will buy clinicians and patients more time testing MultiStem, a proprietary stem cell product manufactured from human stem cells obtained from adult bone marrow or other non-embryonic tissue sources, in the treatment of multiple distinct diseases. The company is currently evaluating in a Phase II study the administration of MultiStem therapy to patients who have suffered a heart attack, or acute myocardial infarction.

"Our clinical data show that we can effectively treat patients up to 36 hours after a stroke has occurred. It's a very simple procedure that involves an intravenous drip. We believe it will dramatically improve clinical outcomes," added Van Bokkelen.

A lack of meaningful endpoints has been a major stumbling

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Curis Inc.

Robert McNeil
Managing Director
Sanderling Ventures & CEO
Dalcor Therapeutics

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Holdings Inc.

block for companies in the neuroscience space. "That is what has been holding back neuroscience for so long – it's a chicken and egg situation – we needed to figure out the outcomes that we could measure against. It is also a regulatory challenge as the endpoints we have are a bit fuzzy," explained United Neuroscience's Hu. As neurodegeneration takes place over years it is difficult to identify objective and clean endpoints.

United Neuroscience's lead program is UB-311, its novel synthetic peptide vaccine targeting beta amyloid in the treatment of Alzheimer's disease. So far, the company has reported from an ongoing Phase Ii study that UB-311 was able to generate antibodies to specific beta amyloid oligomers and fibrils with no decrease in antibody levels in patients of advanced age. Moreover, amyloid PET imaging and genetic screening for APOE4 status demonstrated an efficient method to identify subjects with mild Alzheimer's for disease modification trials in early-to-mild Alzheimer's.

Predictability as a valuable as clinical outcome

Oncology is one of the areas where the outcomes are more clearly defined and standard clinical trial endpoints are already well established. Emerging oncology companies, however, have to look beyond those endpoints – which normally revolve around durability of the clinical benefit. "It is more important that you can enhance the predictability of choosing the right patients – knowing who may or may not benefit," noted Curis' Fattaey.

Being able to identify the best patients for a particular treatment clearly not on benefits patients, it helps payers, investors and the companies too. "For us, it impacts our way of thinking about how we grow. Do we have enough infrastructure and technologies to be able to tell who is going to benefit or not," Fattaey added.

Curis' lead program, CUDC-907, an orally-available, small molecule inhibitor of HDAC and PI3 kinase enzymes, is currently in a Phase II, open-label, multicenter trial designed to evaluate its efficacy and safety in subjects 18 years and older with relapsed/refractory (RR) MYC-altered diffuse large B-cell lymphoma (DLBCL). Patients with RR DLBCL are eligible for treatment with CUDC-907, as long as they have tumor tissue available that can be tested for MYC-altered disease.

Marrying assets that help improve the predictability of outcome, according to MabVax Therapeutics' Hanson, are probably more important for building a business than the market opportunities or intellectual property.

"We are in pancreatic cancer, an area that many companies have failed when trying to come up with effective treatments. Why would we want to go after it? It just so happens our antibody targets a particular antigen that is expressed on more than 90% of pancreatic tumors and so has a high probability of success," he added.

MabVax Therapeuitics' approach was to develop the HuMab-5B1 antibody, which was discovered from the immune response of cancer patients vaccinated with an antigen-specific vaccine during a Phase 1 trial at Memorial Sloan Kettering Cancer Center and subsequently in-licensed, as a therapeutic. Moreover, noting that the HuMab-5B1 antibody has excellent tumor targeting capabilities, as well as being internalized by pancreatic cancer cells, the company created a tumor-targeting platform.

The company conjugated the antibody, MVT-5873, with the radiolabel zirconium 89, to create MVT-2163, a PET agent as an important tool to aid in the diagnosis, monitoring and assessment of pancreatic cancer patients as well as an attractive companion diagnostic for the MVT-5873 therapeutic product.

"The problem with pancreatic cancer is by the time it is discovered it's too late. Your life expectancy is such that you would be lucky to get beyond a year. So by being able to identify the metastatic sites you can know whether the patient is suitable for surgery or not. This is a new paradigm because many surgeons find out after that surgery was not a good decision. We feel that we are going to do something that has not been possible before," he added.

MabVax Therapeuitics is testing both MVT-5873 as a monotherapy or in combination with the current standard of care chemotherapy regimen in subjects with metastatic pancreatic cancer and MVT-2163 in the diagnosis, monitoring and assessment of pancreatic cancer patients and as a potential companion diagnostic for the MVT-5873.

Investors are particularly keen on sifting out the probable from possible. "One way of thinking about it – a lot of our job becomes sorting out what is more probable. You are looking for things that are disproportionately more likely to succeed," noted Podlesak.

One way of increasing the probability of success is to take underappreciated and underperforming assets and revive them. In 2014, Vericel, created when Ann Arbor, Mich.-based Aastrom Biosciences bought Sanofi's cell therapy and regenerative medicine business, a holdover from Sanofi's 2011 acquisition of Genzyme Corp. Vericel paid $4m in cash plus a $2.5m promissory note to get access to Carticel and MACI cell therapy products for the treatment of cartilage defects in the knee and Epicel (cultured epidermal autografts) a permanent skin replacement for the treatment of patients with severe deep-dermal or full-thickness burns, a business with about $44m in annual revenue. In the first nine months of the current year, these products posted net revenues of just under $41m.

At the time Aastrom was a struggling company but the acquisition of the cell therapy portfolio, the name change the shiftof its headquarters to Cambridge were, according to Vericel's Orlando crucial steps in the transformation of the business from a clinical-stage company to a fully integrated, commercial-stage specialty biologics company. "We believed with the right attention we could get leverage more of the potential of the products we had acquired," he added.

This is the first instalment of a multi-part coverage of the Meeting Growth Challenges Roundtable, sponsored by Freyeur & Trogue, Impactiv and rbb Communications, conducted during the J.P. Morgan Healthcare Conference in San Francisco.

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The Most Successful Oncology Launches Of A Decade

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Cancer drugs launched over the last 12 years generated roughly $50bn in sales in 2017 and a cumulative $179bn during that time, highlighting just how important the therapeutic area is to the drug industry – and how pivotal it is poised to remain.

The investment banking firm Leerink analyzed 94 cancer drugs approved by FDA from 2006 to 2017, collecting information on the launch dates, indication and quarterly revenue performance (when publicly available) to determine which drugs were most commercially successful and which drug manufacturers stood out from the competition.

Shutterstock: Sergey Nivens

The most commercially successful new cancer drugs introduced in the 12-year period were **Johnson & Johnson**'s prostate cancer drug *Zytiga* (abiraterone) and **Pfizer Inc.**'s *Sutent* (sunitinib), approved for kidney cancer, pancreatic cancer and gastrointestinal stromal tumors (GIST), according to Leerink. Zytiga generated cumulative sales of $12.2bn over the period and Sutent generated $11.8bn.

The most commercially successful launches, however, were newer drugs – **Bristol-Myers Squibb Co.**'s immune checkpoint inhibitor *Opdivo* (nivolumab) and Pfizer's CDK4/6 inhibitor for breast cancer *Ibrance* (palbociclib). In three years of cumulative sales, Opdivo generated $8.3bn and Ibrance generated $6bn, Leerink said.

In contrast, for the 50 drugs with at least three years of sales, the average one generated $152m in first-year sales, growing to $612m in year three. The top decile generated $493m in the first year, growing to $2.88bn in three years, while the bottom decile generated $11m in year one sales and $25m in year three. The US generally contributes 65% of revenue by year three post approval.

"It is also apparent that the most successful cancer drugs (top 10%) started off on the right foot and then grew much more rapidly than the other 90% afterwards, making the gap between them even wider over time," the Leerink analysts said. Geoffrey Porges, Seamus Fernandez and Michael Schmidt conducted the analysis.

While **Roche** has had a long period of leadership in oncology, it wasn't at the forefront of immuno-oncology. The success of Opidvo catapulted Bristol into the number one position in terms of cumulative worldwide sales of new cancer drugs between 2006 and 2017. "This makes Bristol the most commercially successful company in oncology, especially in the context of the immuno-oncology boom in recent years," the analysts said. Novartis was second with the leukemia drug *Tasigna* (nilotinib) being the single biggest contributor to the cumulative sales.

Bristol and most companies (excluding Roche, **Novartis AG** and Pfizer) have their top 3 drugs accounting for over 90% of revenues generated from new cancer drugs.

"We think this reflects the wide gap between successful and ordinary cancer drugs as well as the difficulty for any company to identify and develop more than a couple of good drug candidates," the analysts said. Leerink pointed to one caveat in the analysis when it comes to the biotech **Celgene Corp.**, because two of its blockbuster cancer drugs were approved in 2015 *Revlimid* (lenalidomide) and *Abraxane* (paclitaxel protein-bound) – and therefore did not make the approval cut-off of 2006 of FDA's public archive. If Revlimid had been included, it would most likely be the best-selling cancer drug in the period and would have greatly impacted Celgene's rankings in the analysis.

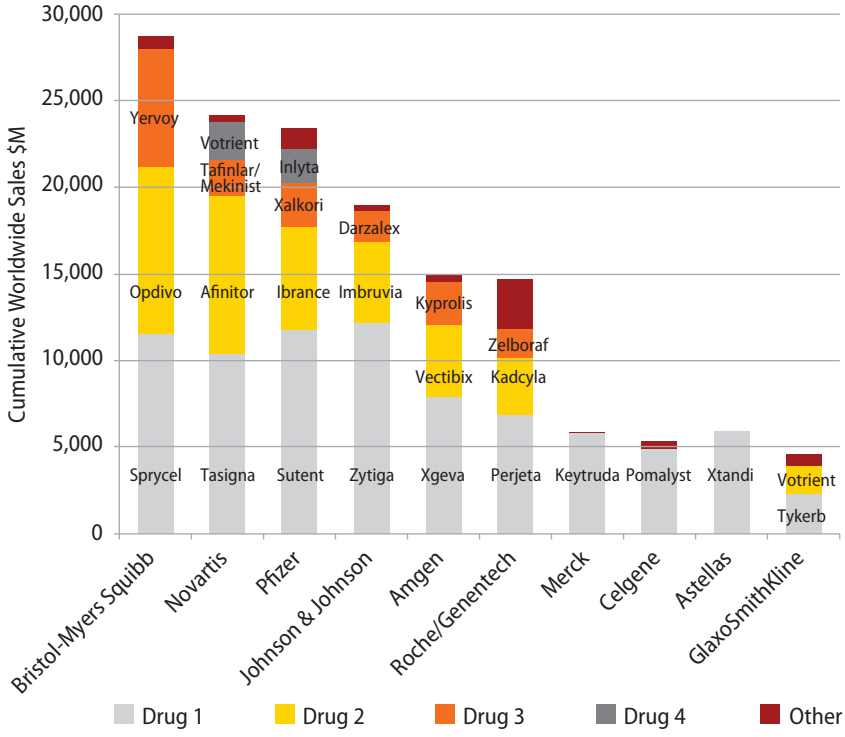
The top two most successful oncology companies in terms of number of new molecular entities approved during the period were Roche and Novartis. Roche and Bristol stood out for having the most new indications approved. Roche launched nine new cancer drugs over the 12 years, while

Top 10 Indications for Cancer Drug Approvals in 2006-2017

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
NSCLC	1	0	1	1	1	1	2	3	2	7	4	6
NHL	4	0	3	2	0	2	0	2	3	1	1	6
Breast cancer	1	3	1	0	2	1	2	2	0	1	1	5
Melanoma	0	0	0	0	0	3	0	2	3	6	0	1
MM	2	1	2	0	0	0	1	1	0	5	1	2
CLL/sLL	0	0	1	1	1	0	1	1	5	0	2	1
RCC	1	2	0	3	0	0	1	0	0	1	2	2
CML	2	1	0	0	2	0	3	0	0	0	0	2
Colorectal cancer	2	1	0	0	0	0	3	1	0	2	0	1
ALL	1	0	0	0	0	1	2	0	2	0	0	3

Source: FDA.gov: Leerink Partners Research

Cumulative Sales of New Cancer Drugs in 2006-17, by Companies



Source: FactSet; Leerink Partners Research

Novartis launched eight. Nonetheless, the analysts viewed Novartis' portfolio as more innovative in that the products reflected multiple mechanism of action, while many of Roche's new drugs were directed against targets like CD20 and HER2 that the company knows well.

"The approval pattern shows concentration of development successes in a few indications, which has led to intensified competition in those indications, while leaving many cancer types still in need of breakthrough treatment options," Leerink analysts said. The most common indications for new drugs have been non-small cell lung cancer (NSCLC), non-Hodgkin's lymphoma and breast cancer, consistent with the large addressable patient populations in those cancers and therefore the large commercial potential. Cancers with less activity include kidney cancer, head and neck cancer, bladder cancer, pancreatic cancer, colorectal cancer, gastric cancer and liver cancer, the authors pointed out.

Five EGFR inhibitors, four ALK inhibitors and three PD-1/L1 inhibitors have been approved for NSCLC in the last 12 years. "This is a prime example of rapid follow-on development leading to heightened competitive intensity in specific indications," the analysts added.

The goal of the project, they said, was to assess the reliability of their financial forecasts and to consider whether other approaches might be more valuable than traditional patient-based forecasts. A follow up analysis will examine predictability of cancer drug revenue, they said.

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Mylan Plans To Compete In US HIV Market

Having supplied HIV treatment regimens to more than 8m patients worldwide in 2017, **Mylan NV** now is turning its attention to the US with a pair of single-tablet combination regimens recently approved by the US FDA. It seems likely that the generics titan will focus mainly on Medicaid and other economically disadvantaged patient groups with a strategy of pricing its regimens below what competitors like **Gilead Sciences Inc.** and **ViiV Healthcare** are charging for their combination pills.

Mylan announced on March 2 that it will launch the three-drug combo *Symfi Lo* in the coming weeks, with two-drug therapy *Cimduo* to follow, reaching market during the second quarter. Each fixed-dose, single-tablet regimen is comprised of generically available antiretrovirals approved for HIV treatment, but both are novel to the US market as single-pill combinations, Anil Soni, the firm's head of global infectious diseases, told *Scrip*.

Mylan's strategy, he explained, is to build upon the platform it has developed in the past decade of providing HIV medicines and other antiretrovirals to more than 100 countries, many of them emerging markets, through licensing agreements with Gilead, ViiV's parent **GlaxoSmithKline PLC** and other firms. Symfi Lo, approved in February, combines a 400 mg dose of efavirenz (**Bristol-Myers Squibb Co.**'s *Sustiva* and generics), a 300 mg dose of lamivudine (GSK's *Epivir* and generics) and a 300 mg dose of tenofovir disoproxil fumarate (Gilead's *Viread* and generics), while Cimduo, likewise approved in February, contains the latter two of those drugs.

Since March 2017, Mylan has been able to sell Symfi Lo outside the US under a tentative approval from FDA, as part of PEPFAR. Although not yet offering specifics, Mylan says each product will be "discounted significantly" compared to the wholesale acquisition costs of other HIV single-tablet regimens currently on the US market.

joseph.haas@informa.com, 5 March 2018

Novartis Teams With Pear Therapeutics In Neurological Digital Health Pact

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Signalling its intent to embrace emerging digital technologies in the realm of neuro-degenerative and psychiatric diseases, **Novartis AG** has joined **Pear Therapeutics** in a collaboration on prescription software applications aimed at treating patients with schizophrenia and multiple sclerosis. Prescription digital therapeutics are clinically validated, FDA-cleared software applications that show safety and efficacy in randomized clinical trials to improve patient outcomes.

"We see digital therapeutics as a potentially vital part of future treatment models across a range of diseases with high unmet medical need – offering patients pharmacological drug treatments prescribed alongside proven digital therapeutics to better address the full burden of their disease," a Novartis spokesman said.

The two companies will work to advance clinical development of the US-based group's THRIVE digital therapeutic for patients with schizophrenia. The duo will also design and develop a new therapeutic application to address underserved mental health burden in patients with multiple sclerosis.

Pear is one of nine companies selected to the FDA's Digital Health Pre-Certification Pilot Program to help guide the agency in defining new regulatory guidelines for digital health products. Read the full article here

Its prescription digital therapeutics are designed to deliver clinically proven treatments, such as cognitive behavioural therapy, to patients through mobile and desktop applications. Once approved, they may be prescribed alongside drug therapies and have the potential to be developed to treat a range of diseases.

Last September, Pear's lead product candidate, reSET, became the first prescription digital therapeutic cleared by the FDA for the treatment of substance use disorder. Its second digital therapeutic, reSET-O, designed as an adjunct to pharmacotherapy to treat opioid use disorder, recently received Expedited Access Pathway designation from the FDA.

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FUTURE MEDICAL WAVE

Pear Therapeutics said it aimed to integrate clinically validated software applications with previously approved pharmaceuticals and treatment paradigms. Its alliance with Novartis will combine the Swiss pharma's expertise in biomedical research and clinical development with Pear's expertise in digital therapeutics.

The medical need for such treatments is growing worldwide.

Psychiatric and neuro-degenerative diseases place a heavy physical, emotional and economic burden on patients and their families. This burden will only grow in the coming decades as the population gets older. Patients with neuro-developmental diseases also have very few options and need therapies that have better efficacy and fewer side effects.

The Swiss pharma giant thinks it can join Pear in that journey, using its therapeutic expertise to help ride the next wave of medical innovation.

Pearl's digital therapeutic for patients with schizophrenia THRIVE has demonstrated potential usability, retention and preliminary efficacy in patients with schizophrenia in early clinical studies. The companies will also collaborate to design and develop a new therapeutic application to address under-served mental health burden in patients with multiple sclerosis. "It's too early in the collaboration with Pear to discuss specific drug therapies that would be involved," the Novartis spokesman said, adding that "at this early stage, we are pursuing digital therapeutics independently of our early pharmacological pipeline."

The Novartis R&D therapeutic expertise would involve the Novartis Institutes for Biomedical Research (NIBR). "At NIBR we are harnessing new technologies to build human models of neurological disease. We believe that we can make new treatments that will modify the course of a disease and dramatically improve patient lives," the spokesman said. Neuroscience is one of seven key research focus areas at the early discovery unit.

Researchers at the NIBR neuro-psychiatric research programs are investigating such diseases as bipolar disorder, depression, and schizophrenia and, in neuro-degeneration, they are pursuing diseases such as Alzheimer's and multiple sclerosis.

"Many neurological diseases that were intractable can now be attacked thanks to the advent of new technologies that have been helping us fill the gaps in our understanding. Among these advances are platforms for the creation of human neurons in the lab and for manipulating neuronal circuits in preclinical models," the Novartis spokesman said.

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Nektar's IO Deal With Bristol Looks Even Sweeter

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Nektar Therapeutics' data update for the up-and-coming immuno-oncology candidate NKTR-214 – just partnered in a high-priced deal with **Bristol-Myers Squibb Co**. – along with better-than-expected earnings revved up even more excitement and expectations among investors.

The company's fourth quarter and full year 2017 earnings call late on March 1 followed on the heels of a deal with Bristol to co-develop and commercialize the pegylated IL-2 agonist NKTR-214 in combination with Bristol's PD-1 inhibitor *Opdivo* (nivolumab) and CTLA-4 inhibitor *Yervoy* (ipilimumab), an agreement worth $1.85bn upfront plus $1.78bn in milestone fees. The deal is vast, spanning 20 indications for nine tumor types and the partners say development will be rapid, with Phase III studies in melanoma and renal cell carcinoma kicking off in the middle of the year.

Nektar's report of some enticing new data tidbits from the dose escalation phase of the Phase I/II PIVOT study during the call was well-received.

The company previously reported strong, durable objective response rate (ORR) data for the combination of NKTR-214 and Opdivo in the dose escalation phase, in 38 patients with renal cell carcinoma (RCC), metastatic melanoma and non-small cell lung cancer (NSCLC), at the Society for Immunotherapy of Cancer (SITC) meeting in November. These data were updated at the J.P. Morgan Healthcare Conference in January and looked even better at that time, generating more enthusiasm.

The latest announcement shows the data continued to improve with longer follow-up, as more participants convert to responders, Nektar said March 1.

In first-line metastatic RCC, the objective response rate at the time of SITC was 46%, but this improved to 57% by J.P. Morgan and further to 71% in the latest report.

CEO Howard Robin noted that all of the partial and complete responses observed in this phase of the study have been confirmed and there were no relapses in any tumor types.

"This highlights that the length of time patients spend on treatment with the combination of NKTR-214 plus nivolumab is correlated with further tumor shrinkage and improved and continued response," Robin said.

For 20 patients with the tougher-to-treat PD-L1 expression-negative status, the company reported a 60% ORR.

"In addition, our safety profile across the entire PIVOT population continues to be encouraging, with no patients discontinuing because of treatment-related AEs [adverse events] and a low 11% [Grade 3] adverse event rate and over 150 patients treated to date," Robin said.

Chief Medical Officer Mary Tagliaferri said that no one particular treatment-related adverse event stands out. The most common symptoms are flu-like and tend to occur in the first cycle of treatment; these can be treated readily with over-the-counter medications and resolve quickly, within a few days, Tagliaferri reported.

Overall, the PIVOT study will enroll 330 patients in 13 different expansion cohorts in five tumor types.

The company plans to share its first presentation of data from the expansion phase of the PIVOT study in June at the American Society of Clinical Oncology (ASCO) annual meeting.

Nektar will also present four separate nonclinical datasets, including combinations with other types of therapies, at this year's SITC meeting in April. The company plans to establish the drug as the "backbone of cancer care across multiple indications" and will be announcing additional development collaborations toward that goal this year.

News about better responses came after a better-than-expected quarter. The company reported that royalty revenue from its opioid-induced constipation drug *Movantik/Adynovate* (naloxegol) continues to grow nicely, bringing in $33.5m in 2017, up by 72% from 2016.

Nektar reported $95.5m in total revenue for the fourth quarter of 2017 versus $37.5m in the year-ago period.

"Revenue in the fourth quarter of 2017 included a total of $60m of non-recurring revenue related to a new sublicense agreement, a contract settlement agreement and the recognition of deferred revenue from several collaboration agreements," the company said.

Excluding a one-time $16m impairment charge, Nektar reported a $0.11 earnings per share (EPS) loss versus an expected loss of $0.43, due to the much higher non-recurring license revenue than expected for several partnered programs, Jefferies analyst David Steinberg noted on March 2. The narrower loss, however, was somewhat offset by higher than projected R&D spending – $81m versus $14m, the analyst added.

Including upfront payments from the Bristol collaboration, the company expects to end the year with $1.9bn-$1.925bn in cash.

Investors viewed the updated data as validation for the NKTR-214 mechanism of action and the deal with Bristol.

Prior to the SITC meeting in November, Nektar was trading at around $25 and afterward rose to the $40 to $45 range. Before the Bristol announcement on Feb. 13, Nektar's share price closed at $76 and after the deal it was trading at $83. The stock closed up 21.67% at $102.87 on March 2.

Cannacord Genuity analyst Arlinda Lee raised her stock target to $94 from $80. "In our view, this update further solidifies the central positioning for wholly-owned drug candidate NKTR-214 in combination with anti-PD1, and highlights efficacy regardless of PD-L1 status and across tumor types, benign safety profile, and mechanism of expanding and activating T-effector cells," Lee said in a March 2 note.

Meanwhile other immunotherapies in the pipeline will enter the clinic this year – NKTR-255 and NKTR-262.

GEARING UP FOR FILING

Nektar's immuno-oncology pipeline clearly is stealing the limelight, but the company is advancing in other therapeutic areas as well.

It is gearing up for submission of a data package for its mu opioid agonist pain reliever NKTR-181 to the US FDA in the second quarter.

The company had two "highly productive pre-NDA meetings with the agency to discuss our clinical, nonclinical and CMC [chemistry manufacturing and controls] data packages that will go into our NDA submission" during the past two months, Robin said.

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How Merck KgaA Is Riding The Gene Therapy Wave

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Merck KGAA, which has been involved in gene and cell therapy manufacturing tools and services for close to three decades, is ramping up to tap into emerging opportunities in these exciting new areas of medicine.

The German multinational, which has been building on the expertise that the $17bn acquisition of Sigma-Aldrich brought with it in areas like gene editing, has recently been granted patents for its CRISPR technology in a number of countries.

"With our expertise in zinc fingers [a gene editing technology that Sigma-Aldrich had worked on], we looked at what can we do with CRISPR-CAS9 that has been done with zinc fingers. And the first was the application in cutting and replacement of the genome. Those are foundational patterns, so anyone who uses the technique has to in-license those techniques from us," Udit Batra, Member of the Merck KGaA Executive Board and CEO, Life Science, told *Scrip* in an interview on the side lines of BioAsia 2018 in Hyderabad recently.

While Batra referred to efforts in developing the technology further for "many applications", Merck also expects to make the technology available for research and medical uses.

"So, we license our technology to many research institutions. If it ever has a therapeutic use, we would get licensing fees for it as well," added the CEO, who started his career as a research engineer fellow at the other Merck, **Merck & Co. Inc.**, and has also previously held leadership positions in **Novartis AG**.

CRISPR genome-editing technology, which essentially allows the precise modification of chromosomes in living cells, is helping progress treatment options for a range of medical conditions. Among others, last month the Korean Intellectual Property Office and the Israel Patent Office each issued notices granting Merck's patent applications for its CRISPR technology used in a genomic-integration method for eukaryotic cells. Merck also has patent filings for its insertion CRISPR method in the US, Brazil, China, India and Japan.

VIRAL VECTOR MANUFACTURING

Merck is also fortifying its play in the gene therapy segment. It has been engaged with most of the top 10 gene therapy companies and expanded its Carlsbad, California, US, manufacturing facility, which provides its BioReliance viral and gene therapy manufacturing services.

"We saw huge opportunity in the area. We've advanced the quality requirement and regulatory output at the site quite dramatically," Batra said. In October 2017, the facility completed both a US FDA prelicense inspection and a European Medicines Agency (EMA) marketing authorization inspection.

In the area of viral vector production, Merck hopes to ensure that customers who rely on it for the production of viral vectors "get serviced". "So we've industrialized the site – made quality systems better, increased the productivity, expanded the capacity." Technology development in viral vector production is another key thrust area, given that the sudden pick-up in demand has caught even players like Merck "off guard", Batra indicated.

Typically, to create personalized therapy products, genes are delivered into immune cells using viral vectors like the ones manufactured by Merck. In December last year, Merck entered into a commercial supply agreement to manufacture viral vectors for **bluebird bio Inc.**, of Cambridge, Massachusetts, US, for its use in potentially transformative gene therapies.

Batra also sees significant opportunities in the area of cell therapy – including areas like chimeric antigen receptor T-cell (CAR-T) cell therapy which he referred to as rather "dispersed" currently.[A#SC100116]

"For each patient you take out their T cells at an academic medical centre, then you take those T cells and ship them to a cell therapy centre and you replicate them there. So, you ship it, then the viral vectors come from us to that site, you do the manipulation and then you ship it again," Batra explained.

Given the time and significant costs involved in producing and delivering the therapies to patients – it could take an estimated 30-45 days for each individual patient - Batra believes there are more efficient ways to get things done drawing on the combined expertise of people from academic medical centers, pharma and technology firms and manufacturing companies.

"As a consequence, there are three or four areas that we are working on – introducing technology so that we can do this whole process bedside; improving technology as it stands and also creating a decentralized cell therapy approach – meaning you set up a cell expansion facility right next to where the patient is," he said.

E-COMMERCE PLATFORM

Significantly, as more pharma firms deploy data analytics and explore the world of artificial intelligence and machine learning, Batra outlined how the life science unit's well-oiled industry leading e-commerce platform and supply chain capability has been effectively delivering the goods using some of these already.

Millions of customers already use Merck's e-commerce channel - it also boasts an estimated 80-100 million page views every year.

"But what is not known as much is that we ship 15,000-20,000 packages within 24-48 hours. E-commerce is the best example of using data analytics in real time," Batra said.

Some of the interesting aspects of Merck's e-commerce platform are the "intelligent recommendations", possible, in part, due to its association with resources like PubMed.

"If you order a chemical that is referenced in a publication, the computer will indicate that if this was ordered there were say, for example, 15 other chemicals that were referred. Some of most mentioned ones will then pop up. That's through AI, machine learning. When you click on the second one, then it tries to figure out what you are trying to synthesize. And by the time you do the third one, the algorithms can figure out what you are trying to synthesize."

Batra says that Merck's e-commerce effort already has the performance "of the level of Amazon or Alibaba for the scientific space"; moreover, he underscores that in addition roughly 50% of Merck's employees have scientific training and those who don't are "immersed in it".

"While these other companies can replicate what we do over time, one has to have respect for the science part of it. It would probably take long time to replicate that. There, I believe, we are in a unique position."

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How Sanofi Is Stepping Up Blue Sky Research

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Sanofi's Innovation Awards (iAwards) program, which aims to help convert successful and high potential academic projects into sponsored research programs and subsequently create in-licensing and start-up opportunities, has seen significant traction in the US. It is now set to offer similar opportunities in Asia. iAwards is geared to support early stage innovative and translational research proposals from participating academic institutions.

Dr Sridaran Natesan, head of strategic initiatives and scientific relations (North America) at **Sanofi**, said that a similar initiative had recently been introduced in Europe covering some leading French and German institutions and plans were in store to expand the effort further.

"Our goal later this year and early next year is to make this a global program where we will expand in Asia as well and potentially, we are going to extend the program in the US to more than 10 institutions this year," Natesan told *Scrip* in an interview on the side lines of BioAsia 2018 in Hyderabad recently.

Each year, Sanofi "gets to see" about 300 ideas submitted to it through the program and it funds somewhere between 20-30 projects. Typically, the program, launched in 2015, provides one-year seed funding of $125,000 to each selected proposal, a dedicated Sanofi project champion, in-kind resources and expertise deemed necessary by Sanofi.

Big Pharma has a long been keen to pursue collaborative linkages with academia as it tackles, among other challenges, patent expiry of blockbusters, and looks for innovative ideas for novel targets. For academic scientists, such associations help bridge the gap of limited government funding. **GlaxoSmithKline**, with its Discovery Partnerships with Academia (DPAc) program and **Pfizer**'s Centers for Therapeutic Innovation (CTI) are some efforts in the area, though the latest updates on these could not immediately be ascertained.

SUPPORT BLUE-SKY RESEARCH

Sanofi's US iAwards leg already has top-notch academic institutions participating in the program – Brigham and Women's Hospital, Boston Children's Hospital, Children's Hospital of Philadelphia, Columbia University, Johns Hopkins University, Massachusetts General Hospital, University of Pennsylvania, University of California San Francisco, University of Texas System and Weill Cornell Medical College.

"We said to the top 10 universities in the US that we really want to support blue sky research with potential to deliver something to our early-stage pipeline in a two-three year time frame or some very specific therapeutic molecule that's in very early stages that we can work together to bring to our pipeline and develop together. And it's been working very well," Natesan said.

Eventually, Natesan hopes to potentially have the top 50 institutions in the world working with Sanofi via the program and helping it build a portfolio of exciting early stage research projects.

The other path of the program is to also help academic investigators to set up their company, "if it makes sense", Natesan said, referring to Sanofi's Sunrise initiative that seeks out transformative, at times high-risk, opportunities to drive innovation by partnering with external life science pioneers and venture capital firms.

"We send [on] some of the opportunities we see as ideal for a start-up ….so therefore the Sunrise guys can get involved and evaluate them and if it makes sense they will set up a company."

ASIA PUSH, GLOBAL ECOSYSTEM

Natesan hopes to extend the iAwards program "down the road" in China but said that he also sees lot of opportunities in India, though many Indian institutions are not organized enough yet to put together "a good package" for pharmaceutical companies to review the opportunities.

"There is no tech transfer-like equivalent still in many Indian institutions and top academic investigators here have no idea about how to take their concepts to a pharma company and do your contract...so that process has to evolve further," he said. He hopes Sanofi can help on that front – potentially in a way that can serve as a model for others to follow.

While the jury may still be out on India's discovery research capabilities, Natesan emphasized that "not everyone has to be good at everything".

"I see a future where it's a global ecosystem and everyone is going to play a part," he said.

He explained that the Boston ecosystem for example is one that's "pretty good" and probably one that everybody wants to emulate; but it's generally an ecosystem that's still very good in the early stage of the drug discovery development process.

"It may change into an end-to-end best ecosystem but right now we are still focusing on very early stages... that means there are other ecosystems that could fill in other parts just as well as what Boston is doing in the research space and there I see great opportunities for India to think about," Natesan added.

CHANGING CULTURE

Natesan also referred to a change in culture in academia from generally "getting lot of money and trying to figure out something" to "we have some specific ideas that we want to take forward to the clinics together with the pharma partner very quickly."

He referred to "tons of opportunities" in the US, and typically the very big ideas get funded by venture capital companies that nurture and bring them to some realization.

"But then there are a lot of therapeutic-specific ideas that may or may not get the attention of the VCs because there are so many of them these days. And we want to have access to them, evaluate them and if it fits our strategy we want to fund them and bring them to the market, so that's the focus of this academic initiative."

Natesan, however, underscored that the iAwards isn't the only way that Sanofi works with academia. The French multinational also does more traditional research program sponsorship when it sees value therein. It also has strategic collaborations with institutions that are focused on only one therapeutic area, e.g. the Joslin Diabetes Center, and may consider similar partnerships for other therapeutic areas.

"There are many ways we engage with academia but I have certain bias in saying that the iAwards program would set a new standard and will emerge as a good model for industry academic partnership," Natesan said.

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AstraZeneca Keeps R&D Focus, Spins Out Phase II Neuromyelitis Optica MAb Into New Biotech

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Shutterstock: Holly Michele

A biologic, inebilizumab, in Phase II for the treatment of an autoimmune disease, neuromyelitis optica, is the lead compound for a new stand-alone company, **Viela Bio**, spun-out of **AstraZeneca PLC**'s biologics arm, **MedImmune LLC**, with financing from a group of Chinese private equity funds. The new company is helmed by CEO Bing Yao, previously head of MedImmune's respiratory, inflammation and autoimmunity (RIA) innovative medicines unit.

> Viela Bio is the latest in a series of spinouts and licensing-out activities conducted by AstraZeneca for therapeutic activities deemed to be non-core to the company's rather broad three-way focus

"Auto-immune diseases are a group of around 80 disorders, the majority of which have no specific therapies, and they represent a therapeutic area of high unmet need," Bing explained to *Scrip*. Viela Bio intends to develop a number of biologic therapies for such disorders, many of which share the same disease pathway, in a similar manner to how anti-TNF antibodies are effective in a number of different conditions. The company will grow rapidly, Bing noted, with around 40-50 employees in the next three months, and 100 in the next three to five years. Viela Bio is the latest in a series of spin-outs and licensing-out activities conducted by AstraZeneca for therapeutic activities deemed to be non-core to the company's rather broad three-way focus on oncology; respiratory, cardiovascular and metabolic diseases; and infections and vaccines. This "externalization" strategy has included licensing rights to two dermatologics to **Leo Pharma AS**, a Phase IIb Crohn's disease product to **Allergan PLC**, and the spin out of antibiotics assets into **Entasis Therapeutics**.

Viela Bio is being financially supported by a Series A funding round of up to $250m from a consortium of Chinese/US private equity funds co-led by Boyu Capital, 6 Dimensions Capital, and Hillhouse Capital. "We went to potential investors with specific criteria that included being committed to a longer-term investment in order to build a successful biotech," Bing noted. And the size of the Series A reflects the richness of Viela Bio's pipeline, with three investigational products in clinical studies, Bing said.

AstraZeneca will benefit if Viela Bio is a success, as the pharmaceutical company is also the largest minority shareholder in the new company. Other investors include Temasek and Sirona Capital. The Series A is the largest deal that 6 Dimensions Capital has been involved with since it was formed in 2017 by the merger of Frontline BioVentures and WuXi Healthcare Ventures.

Other founders of the new company, based in Gaithersburg, Maryland, the site of MedImmune's R&D campus, include Jorn Drappa, previously vice president, clinical, at MedImmune, who has been appointed head of research and development and chief medical officer at Viela Bio.

Compounds transfered by AstraZeneca to Viela Bio include two compounds in Phase I: VIB4920 (previously MEDI4920), an anti-CD40L-Tn3 fusion protein, which has potential in the treatment of primary Sjogren's syndrome, and VIB7734 (MEDI7734), an anti-ILT7 MAb with potential in the treatment of myositis.

Viela Bio's lead compound, inebilizumab, is an anti-CD19 MAb that has already been granted orphan drug designation by the US FDA and Europe's EMA, which is being evaluated in neuromyelitis optica, a rare condition that affects the optic nerve and spinal cord in approximately five in 100,000 people. The MAb binds to and depletes certain B cells called plasmablasts that produce auto-antibodies to the protein aquaporin-4, and the results of Phase IIb studies are expected at the end of 2019, or the start of 2020.

AstraZeneca has not, however, transferred certain inflammation/autoimmune products in which it has made significant investments. Anifrolumab, an investigational product that is in late-stage Phase III trials for the treatment of lupus, is remaining with AstraZeneca, although there has been speculation that this too might be spun out, as it is not in the three main therapeutic areas of focus for AstraZeneca.

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Dupixent FDA Asthma Review Bolsters Sanofi And Regeneron

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Sanofi and **Regeneron Pharmaceuticals Inc.**'s hopes to turn their eczema drug *Dupixent* (dupilumab) from a big-seller into a mega-blockbuster have been raised by the news that the FDA is reviewing the therapy as a treatment for asthma.

Dupixent, which was approved in March 2017 by the FDA for the treatment of moderate-to-severe atopic dermatitis in adults whose disease is not adequately controlled with topical therapies or for whom the latter are not advisable, had sales of €118m in the fourth quarter, almost all of which came from the US. However bagging an asthma approval would significantly boost growth and a supplemental Biologics License Application for the interleukin-4 and -13 inhibitor as add-on maintenance treatment in adults and adolescents (12 years of age and older) with moderate-to-severe asthma is under review.

The application is supported by data from 2,888 adults and adolescents in three pivotal trials from the LIBERTY ASTHMA clinical development program and Dupixent demonstrated that when added to standard therapies it reduced severe asthma attacks and improved lung function. Detailed results from the Phase III QUEST and VENTURE trials from the program will be submitted for presentation at medical meetings later this year, Sanofi noted, adding that the target action date is Oct. 20, 2018.

Quite how much getting this label extension will push up Dupixent sales divides analysts. In an investor note, issued a week before the asthma filing announcement, Canaccord Genuity's John Newman noted that current Dupixent estimates worldwide are in the region of $6bn by 2025, compared to his forecast of $3bn. "We do believe that our estimate is conservative, but we also believe that the $6bn consensus number is too aggressive," he said, noting that multiple potential competitors are in development, including in asthma, which could alter thinking on Dupixent peak revenues long-term."

Specifically on the eczema front, Newman, who downgraded Regeneron to hold from buy and lowered his price target to $356 from $522, focused on the threat from **AbbVie Inc.**'s investigational JAK1 inhibitor upadacitinib (ABT-494), saying that the latter's oral formulation gives it an advantage over Dupixent's subcutaneous injection. While he believes that growth will accelerate substantially for Dupixent, that will not happen until pediatric approval around 2021 – those patients make up around two-thirds of the atopic dermatitis market.

Commenting on the Canaccord note, Datamonitor Healthcare analyst Chris Mulligan told *Scrip* that Newman "makes a good point about pediatric patients but Dupixent is still strong without being approved for that patient group, it will just be even stronger if they can gain approval there as well." As for asthma, he forecast that the drug "will be the highest grossing IL biologic therapy."

That confidence is based on the data from LIBERTY ASTHMA QUEST where Dupixent demonstrated efficacy in difficult-to-treat patients, such as those with a high body mass index and low eosinophil levels. Mulligan said these data provide the drug with a competitive edge over the marketed IL-5 inhibitors – since at first glance the data also suggest it might be better than its major rivals, the anti-IL-5 inhibitors – **GlaxoSmithKline PLC**'s *Nucala* (mepolizumab), **AstraZeneca PLC**'s *Fasenra* (benralizumab) and **Teva Pharmaceutical Industries Ltd.**'s *Cinqair* (reslizumab).

The dosing regime of the Sanofi/Regeneron drug regime could be seen as a weakness, as Dupixent is administered every two weeks, Fasenra is given every eight weeks, and the GSK and Teva offerings are every four weeks. However those three are indicated solely for the treatment of severe patients with elevated blood eosinophil levels, and Dupixent has data suggesting greater comparative improvements in lung function and exacerbation reduction versus the IL-5 inhibitors, Mulligan noted. He added that key opinion leaders he has spoken to on both sides of the Atlantic believe Dupixent "has the potential to satisfy a key unmet need in the treatment of problematic patient groups" and Datamonitor Healthcare forecast Dupixent to erode up to 15% of patient share from Nucala and Cinqair.

There is an ongoing Phase III trial of Dupixent in pediatric asthma patients – VOYAGE – which is due to complete October 2020 and it is also being investigated for nasal polyps (Phase III) and eosinophilic esophagitis (Phase II). The therapy is seen as particularly important to Sanofi's fortunes going forward, as the French drugs major looks to offset the impact of generic competition and price pressures on its diabetes franchise.

Sanofi has hit the acquisition trail since the beginning of the year to expand its rare diseases business, agreeing to buy **Bioverativ Inc.** for €9.4bn and **Ablynx NV** for €3.9bn. Its 2018 guidance was lower than anticipated but the company will be hoping that these deals and strong growth for Dupixent will drive its business transformation strategy begun in 2015 and due to be completed in 2020.

Published online 3 March 2018

Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.

Click here for the entire pipeline with added commentary: http://bit.ly/2mx4jY3

Selected clinical trial developments for the week 23 February–1 March 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
AbbVie Inc.	veliparib	breast cancer, triple negative	BRIGHTNESS; *The Lancet Oncology* online, Feb. 28, 2018.
AstraZeneca PLC	*Synagis* (palivizumab)	RSV infection in infants	MAKI; *The Lancet Respiratory Medicine* online, Feb. 27, 2018.
Melinta Therapeutics Inc.	*Vabomere* (meropenem and vaborbactam)	urinary and reproductive tract infections	TANGO-1; *JAMA*.
Eli Lilly & Co.	*Trulicity* (dulaglutide)	diabetes, type 2	*The Lancet Diabetes & Endocrinology* online, Feb. 23, 2018.
Phase III Top-line Results			
ObsEva SA	nolasiban	infertility	IMPLANT2; positive results.
Phase III Initiated			
Idera Pharmaceuticals Inc.	IMO-2125 plus ipilimumab	melanoma, anti-PD-1 refractory	ILLUMINATE 301; by intratumoral injection.
Vertex Pharmaceuticals Inc.	VX-659, tezacaftor, ivacaftor	cystic fibrosis	F508del/F508del; the most common genetic form.
Leo Pharma AS	tralokinumab	atopic dermatitis	ECZTRA 3; the third Phase III study.
Basilea Pharmaceutica Ltd.	*Zeftera* (ceftobiprole)	skin and skin structure infections	First of two planned Phase III studies.
Phase III Announced			
Endocyte Inc.	177Lu-PSMA-617	prostate cancer	VISION; in PSMA-positive patients.
Vertex Pharmaceuticals Inc.	VX-659	cystic fibrosis	A long-term safety and efficacy study.
Updated Phase II Results			
Vertex Pharmaceuticals Inc.	VX-659	cystic fibrosis	Improved FEV1 in triple combo, well tolerated.
Asterias Biotherapeutics Inc.	AST-OPC1, oligo-dendrocyte progenitor cells from human embryonic stem cells	cervical spinal cord injury	SCiStar; signs of improved motor function.
Heat Biologics Inc.	viagenpumatucel-L (HS-110) plus nivolumab	non-small cell lung cancer, advanced	DURGA; durable responses.
DBV Technologies SA	*Viaskin Milk*	food allergies	MILES; positive results.
Summit Therapeutics PLC	ezutromid	Duchenne muscular dystrophy	PhaseOut DMD; decrease in muscle inflammation.
Magenta Therapeutics Inc.	MGTA-456	bone marrow transplant	Accelerated hemat-opoietic recovery.
Phase II Interim/Top-line Results			
Biohaven Pharmaceuticals Holding Co. Ltd.	remegepant, *Zydis* oral dissolving tablet	migraine, acute treatment	Positive results for bioequivalence.
Novavax Inc.	*NanoFlu* vaccine with Matrix-M adjuvant	influenza, seasonal	Well tolerated, immune responses.
Intensity Therapeutics Inc.	INT230-6	various cancers	Well tolerated, initial efficacy signs.
ARCA biopharma Inc.	*Gencaro* (bucindolol)	atrial fibrillation in heart failure	GENETIC-AF, trend for superior benefit versus metoprolol.

Source: Biomedtracker

Late-Stage CNS Drugs Key For Alkermes, But Early-Stage IL-2 Agonist Fascinates

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The excitement surrounding the multi-billion-dollar tie up earlier this month between **Bristol-Myers Squibb Co.** and **Nektar Therapeutics** on a potential new immune-oncology drug, an interleukin-2 agonist, has had a knock-on effect on Ireland/US specialty company, **Alkermes PLC**, which has just such an agonist in early-stage clinical studies.

Alkermes is currently focused on developing CNS/psychiatry drugs, an area in which it believes it has potential blockbusters in late development. However, companies are always on the lookout for the next breakthrough, and the potential of Alkermes's early-stage IL-2 targeted immuno-oncology (IO) compound, ALKS 4230, was spotlighted during its 2017 earnings call on Feb. 14, the same day that BMS and Nektar announced their collaboration.

The announcements coincided with a sharp 22% increase in Alkermes' share price on the same day to $67.18, although that had settled back down to around $57 a share by Feb. 27, as the markets absorbed the early nature of the company's research. "Alkermes is still working through early testing to assess the efficacy/safety profile and to optimize the frequent dosing of the drug," reported analysts at Morgan Stanley in a Feb. 14 note.

The results of Phase I dose escalation and dose expansion studies with ALKS 4230 are expected in the second half of 2018, the analysts said, and a subcutaneous formulation is in pre-IND development. The intravenous dosing regimen is currently a 30-minute infusion every day for five days, followed by nine days off treatment, a more onerous regimen than that currently used for Nektar's NKTR-214.

ALKS 4230 is a fusion protein comprising IL-2 linked to the alpha subunit of the IL-2 receptor, that is designed to bind more to intermediate-affinity IL-2 receptors found on CD8+ T-cells than to high-affinity IL-2 receptors found on other immune cells. This is expected to enhance antitumor immune responses through the selective expansion of natural killer and CD8+ T cells, without expanding regulatory T cells. Preclinical studies have found ALKS 4230 significantly delayed tumor growth in a melanoma xenograft model.

In contrast, BMS/Nektar's NKTR-214 consists of IL-2 conjugated to six chains of polyethylene glycol to produce an extended release molecule, and it acts as a CD-122 agonist – it binds to and activates CD-122, one of three components of the IL-2 receptor.

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APPOINTMENTS

Bristol-Myers Squibb has appointed ***José Baselga*** to its board of directors, effective from March 1, 2018. Baselga, who has joined BMS as a member of its science and technology committee, is currently the physician-in-chief at Memorial Sloan Kettering Cancer Center. He is responsible for the management of patient care and plays an active role in efforts to enhance and expand programs in clinical and translational research. Baselga is also involved in the American Association for Cancer Research, where he was previously president.

Wendy Sussman has joined **EMD Serono**, the biopharmaceutical business of Merck KGaA, as vice president of US healthcare government and public affairs. In this role, Sussman will lead the company's government policy strategy and advocacy at the federal and state level. Before joining EMD Serono, Sussman was VP of public affairs at Sandoz Inc., a Novartis Division.

Servier has appointed ***Lode Dewulf*** to the newly created role of chief patient officer. Dewulf was the first to hold the position of chief patient officer in the pharmaceutical industry, back in 2012, at UCB. His main objective is to develop Servier's 'Patient In' strategy in collaboration with patients and advocacy groups. He will report to Olivier Laureau, president of Servier.

Unum Therapeutics, a clinical-stage biopharma developing novel immuno-oncology drugs, has named ***Christiana Stamoulis*** president of the company. Stamoulis has been Unum's chief financial officer and head of corporate development since January 2015. Prior to joining Unum, she was senior vice president of corporate strategy and business development at Vertex Pharmaceuticals Inc.

Kala Pharmaceuticals Inc., a biopharmaceutical company developing product candidates using its proprietary mucus-penetrating particle (MPP) technology, has named ***Gregory Perry*** a member of its board of directors and chair of the audit committee. Perry has served as audit committee chair at Merus N.V. since 2016. He was previously chief financial and administrative officer at Aegerion Pharmaceuticals Inc. from 2015 until the company's merger with Novelion Therapeutics Inc., after which he was chief financial and administrative officer at Novelion until 2017.

Metrion Biosciences, a specialist ion channel contract research and drug discovery company, has appointed ***Barry Kenny*** and ***Andrew Southan*** to its board of directors. The appointments are intended to strengthen the company's commercial and business development capabilities. Kenny is currently chief business officer of Heptares Therapeutics Ltd, now part of Sosei Group. Southan joined Metrion as head of commercial operations in October 2016, and was promoted to chief operating officer in April 2017.

Forendo Pharma, a company developing novel oral treatments for endometriosis, has named ***David Colpman*** a non-executive director of its board of directors. Colpman's previous roles include head of global business development at Shire, as well as business development and commercial positions at Glaxo Wellcome and Novo Nordisk. He also serves on the boards of Orexo AB and HRA Pharma Ltd.

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