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What Does 2018 Hold For The Pharma Industry?

ELEANOR MALONE eleanor.malone@informa.com

Prescription drug pricing, technology, business model innovation, M&A, gene therapies and immuno-oncology will be key issues of concern in 2018, according to a survey of industry stakeholders and experts. While oncology – and immuno-oncology in particular – is certain to continue as the therapeutic area of most activity and progress, other therapeutic categories were also singled out as offering particular interest in 2018. These included migraine, HIV, NASH and obesity.

IO'S ONWARD MARCH

After another year of significant progress in immuno-oncology, with checkpoint inhibitors from a handful of companies racking up the approval indications and countless trials of combination therapies under way, 2018 will bring many more advances, and maybe the odd setback.

Boehringer Ingelheim GMBH's head of discovery research, *Clive Wood*, anticipates "more clinical results that guide us to where and how we should use immunotherapy in cancer, in particular how to select combinations with checkpoint inhibitors." He is also prepared for "surprises about how different combinations work with different tumor types."

Datamonitor Healthcare oncology lead analyst *Hardik Patel* will be watching for top-line data from trials of PD-1/PD-L1 inhibitors and CTLA-4 inhibitors in combination in indications beyond melanoma – including **AstraZeneca PLC**'s study of *Imfinzi* (durvalumab) with tremelimub in non-small cell lung cancer, and **Bristol-Myers Squibb Co.**'s study of *Opdivo* (nivolumab) with *Yervoy* (ipilimumab), also in NSCLC. Patel is also keeping an eye on combinations involving PD-1/PD-L1 inhibitors and IDO inhibitors, including the Phase III ECHO 301 trial of **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) in combination with epacadostat, which is expected to be reported in the first half of the year.

Beyond the hotly anticipated IO+IO combinations there will be other areas of progress in combination treatment of cancer: Wood highlights immune cell-targeted and tumor-cell targeted therapies as a promising pairing. "I expect particularly effective results when the tumor cell-targeted therapy can stimulate immunogenic cell death and enhance tumor antigen priming. The SMAC mimetics are good case in point," he commented. Boehringer Ingelheim is developing a SMAC mimetic, including in combination with PD-1 inhibition.

Roche UK's medical director *Rav Seeruthun* has no fear that there are too many players developing investigational cancer immunotherapy treatments, despite the ongoing proliferation of trials. "My view is that it's going to lead to more personalized therapies, and all the drugs and combinations will find a place in different treatment pathways," he told *Scrip*.

As for CAR-T therapies, DMHC's Patel expects to see recently approved *Yescarta* (axicabtagene ciloleucel) and *Kymriah* (tisagenlecleucel) expand their markets both geographically and in terms of therapeutic indication. *(Also see "Gilead/Kite Pricing For*

CONTINUED ON PAGE 6

from the editor

eleanor.malone@informa.com

Welcome to our bumper New Year issue. It's packed with insights on what to expect for 2018, as well as round-ups of drugs approved and trials that went right – and wrong – in 2017. On top of that, some hardy pharma souls continued doing business in the dying moments of last year; if you missed the final flurry of M&A, approvals and trial read-outs, then look no further.

We were pretty busy ourselves at *Scrip* last month, launching our famed annual Scrip 100 Review. The print version will be out next week, but you can access all the content online right now, at www.scrip100.com. The review includes financial data on more than 650 companies, from the big 20 that generated the vast majority of the industry's total 2016 profit of $137bn and employed half of its workforce of 2.3 million, to the many loss-making minnows that nonetheless keep the industry's lifeblood of innovation circulating.

On the Scrip 100 site, our subscribers can access interactive charts offering a range of metrics for the companies in our Scrip 100 universe, and also download Excel versions of the charts. Beyond the data tables, you will find feature articles diving into topics as diverse as gene editing, international reference pricing, and how to future-proof talent. There are interviews aplenty with a range of industry executives, and insights into therapeutic areas from depression to cancer.

Last year's haul of new drug approvals (see p10) reflected the great advances that our industry has made in recent years. With immuno-oncology, gene therapy and artificial intelligence offering so much promise, expect another action-packed year.

Scrip

LEADERSHIP
Phil Jarvis, Mike Ward

SUBSCRIPTIONS
Daniel Frere

ADVERTISING
Christopher Keeling

DESIGN SUPERVISOR
Gayle Rembold Furbert

DESIGN
Paul Wilkinson

EDITORIAL OFFICE
Christchurch Court
10-15 Newgate Street
London, EC1A 7AZ

CUSTOMER SERVICES
Tel: +44 (0)20 7017 5540
or (US) Toll Free: 1 800 997 3892
Email: clientservices@pharma.informa.com

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TO ADVERTISE, CONTACT
christopher.keeling@informa.com

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Mitsubishi Seeks To Revoke Kolon Gene Therapy Deal But Damage Limited?
http://bit.ly/2lK6sNc

Mitsubishi Tanabe has sought to cancel the license agreement for Kolon Life Science's Invossa, clouding the South Korean firm's global ambitions for the allogeneic cell mediated gene therapy. However, analysts don't anticipate a big hit for Kolon even if the deal falls through given that the cancellation demand is not linked to Invossa's efficacy.

Genexine Seals I-O Licensing Deal With I-Mab, Builds Momentum
http://bit.ly/2CJMnhB

Genexine has reached a critical point in developing its immuno-oncology pipeline, firming up a $548m-plus licensing out pact for an asset with the Shanghai-based I-Mab Biopharma. The South Korean firm expects the deal to serve as a yardstick of 'value determination' in its future global transactions.

Interview: Orchard's Gene Therapies Bear Fruit With $110m Financing
http://bit.ly/2kPsNYr

The UK firm has attracted more top-tier investors who are clearly impressed with its gene therapy for bubble baby syndrome and a high-quality pipeline in other very rare diseases.

Charting The Slow-Growing Psoriatic Arthritis Market
http://bit.ly/2lJlfrx

Despite the availability of anti-TNF biosimilars, the global market for drugs for psoriatic arthritis will grow to $4.1bn in 2025 due to the entry of new branded drugs at high prices in the US, according to a new Datamonitor Healthcare forecast report.

Deal Watch: Boehringer's Busy End Of Year Includes Deals With Roche, Autifony
http://bit.ly/2EGu0KJ

The German pharma options potassium channel modulator technology from Autifony and partners with Roche on immunological approaches to irritable bowel syndrome. Roche unveils discovery pacts with Confo and DiCE.

Finance Watch: Happy Holidays For Flagship With A New $618m Fund
http://bit.ly/2EDJBe5

Private Company Edition: Flagship ends 2017 with its biggest life science fund yet totaling $618m. Also, December sees a year-end surge in VC deals, including a $100m Series B round for Allakos.

inside:

Roche Ramps Up Cancer Portfolio With $1.7bn Ignyta Buy

KEVIN GROGAN kevin.grogan@informa.com

The holiday season was a very happy one for **Ignyta Inc.** following the news that **Roche** is paying $1.7bn to acquire the San Diego-based rare cancer specialist.

Under the terms of the deal, which has been agreed unanimously by the boards at both companies, the Swiss major is paying $27 per share which represents a premium of 74% on Ignyta's closing price on Dec. 21 and 89% over its average stock price over the past 90 days. In return, Roche is getting its hands on entrectinib, which Ignyta has claimed could be a best-in-class therapy for non-small cell lung cancer (NSCLC) patients.

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Entrectinib is a tyrosine kinase inhibitor being developed for tumors that harbor NTRK or ROS1 fusions – the latter occur in about 2% of all NSCLC cases. In October, interim data presented at the World Conference on Lung Cancer in Yokohama from the Phase II STARTRK-2 trial in patients with ROS1 fusion-positive advanced NSCLC revealed that entrectinib demonstrated a 78% (25 out of 32) and 69% (22 out of 32) confirmed objective response rate (ORR).

The drug also showed a median duration of response of 28.6 months and median progression free survival (PFS) of 29.6 months in this population, with 53% of patients remaining on the study. Importantly, in terms of activity in the central nervous system, entrectinib showed 83% (five out of six) confirmed intracranial ORR in patients with measurable brain metastases.

With over 200 patients treated at the recommended Phase II dose, most adverse events were Grade 1-2 and reversible, and only 3% of patients discontinued from the study due to treatment-related side effects. With its duration of response, PFS data times and its ability to cross the blood-brain barrier, Ignyta believes entrectinib, which has PRIME designation from the EMA and breakthrough therapy designation from the US FDA, has the potential to be used as a first-line targeted therapy for patients with ROS1-positive NSCLC.

If approved, and Ignyta is hoping for a tissue-agnostic label, entrectinib would compete with **Pfizer Inc.**'s *Xalkori* (crizotinib), which is approved for ROS1+ NSCLC but has poor CNS penetration. Another product, Pfizer's lorlatinib, which is an ALK and ROS1 inhibitor with CNS activity, is in Phase II.

Another potential rival that will have watched the link-up with Roche with great interest will be another company looking at tissue-agnostic cancer therapies, **Loxo Oncology Inc.** Last month, the firm signed an agreement with **Bayer AG**, including a hefty $400m upfront fee, to develop and commercialize its NTRK inhibitor larotrectinib – this week (Dec. 20), Loxo initiated a rolling submission of its NDA for the latter to the US FDA for the treatment of TRK fusion cancers. *(Also see "Loxo's Larotrectinib Requires Paradigm-Change In Clinical Practice" - Scrip, 5 Jun, 2017.)*

Ignyta, which raised $160m after issuing 10m shares in a public offering in October, says it has an 'Rx/Dx approach' to development, combining precision therapeutics and in-house molecular diagnostics. Its pipeline includes taladegib, a small-molecule hedgehog pathway inhibitor which is in Phase Ib trials for ovarian cancer, RXDX-105, a RET inhibitor also in Phase Ib in patients with advanced lung cancer and other solid tumors, and RXDX-106, a pseudo-irreversible inhibitor of the TAM (TYRO3, AXL, and MER) family of receptor tyrosine kinases which is currently in late-stage preclinical development.

As for Roche, its pharmaceuticals chief Dan O'Day said in a statement that "cancer is a highly complex disease and many patients suffer from mutations which are difficult to detect and treat." He added that the Ignyta acquisition "builds on Roche's strategy of fitting treatments to patients" and will allow the company "to broaden and strengthen its oncology portfolio globally."

The deal comes at a time when Roche is preparing for a battering from biosimilar competition to some of its big-selling cancer therapies. *MabThera/Rituxan* (rituximab) is already suffering market share erosion in Europe and rivals to *Herceptin* (trastuzumab) and *Avastin* (bevacizumab) are lining up. *(Also see "New Drugs Shine But Biosimilars Blunt Roche Revenue Rise" - Scrip, 19 Oct, 2017.)*

Datamonitor Healthcare analyst Ali Al-Bazergan told *Scrip* that with the deal, Roche continues to focus on its bolt-on strategy to complement its oncology portfolio. He added that entrectinib "brings in an extremely promising multi-targeted NTRK/ROS1/ALK inhibitor" which is on track for dual NDA submissions in both the NTRK tissue-agnostic and the ROS1-positive NSCLC indications in 2018.

Al-Bazergan added that Bayer's partnership with Loxo for laratrenctinib "strengthens the market opportunity for entrectinib" and also "paves the way towards a best-in-class profile owing to strong results in the Phase II STARTRK-2 study with potential long-term differentiation coming from PFS and CNS activity."

Another company full of Christmas cheer following the Roche deal is **Nerviano Medical Sciences SRL** which licensed entrectinib to Ignyta in 2013. The Italian firm is eligible for royalties on the drug.

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Mallinckrodt Reduces Acthar Reliance With $1.2bn Sucampo Buy

ELEANOR MALONE eleanor.malone@informa.com

Mallinckrodt PLC has agreed to acquire **Sucampo Pharmaceuticals Inc.** for $1.2bn, including the assumption of the latter's debt. The deal most notably brings one significant marketed asset, and two late-stage candidates for rare diseases which are projected to generate up to $450m in peak sales between them, if approved.

The deal helps US-listed, UK-headquartered Mallinckrodt reduce its revenue reliance on controversial specialty medicine *H.P.Acthar gel* (repository corticotropin injection), which is used in a range of autoimmune, inflammatory and other conditions including lupus, multiple sclerosis and infantile spasms.

Acthar has attracted negative attention from investors, regulators and politicians because of its high price. Mallinckrodt acquired the product from Questcor in 2014, but it was originally approved in 1952; its price has increased from $1,650 to $34,034 a vial since 2001, with much of the increase arising before Mallinckrodt took ownership.

In January 2017 Mallinckrodt paid a fine under a settlement with the US Federal Trade Commission in a case in which Questcor was alleged to have acquired a competing product to keep it off the market. *(Also see "Mallinckrodt's FTC Settlement Seems A Blip For Acthar Blockbuster" - Scrip, 19 Jan, 2017.)* There have also been allegations of price fixing against Mallinckrodt and United BioSource, a subsidiary of US pharmacy benefit management group Express Scripts that describes itself as providing pharmaceutical and patient support services. Express Scripts announced in November 2017 that it was selling United BioSource to private equity firm Avista Capital Partners.

Acthar accounted for 34% of Mallinckrodt's net sales in 2016, but the product's sales fell by 5.6% in the third quarter of 2017, bringing the whole company's sales and earnings down. The company noted that increasing numbers of prescriptions were going unfilled, possibly because insurers were putting up more hurdles to reimbursement. Mallinckrodt warned that a further decline was foreseen in the fourth quarter.

Meanwhile, Mallinckrodt is also suffering from the broader challenges affecting specialty medicines and generics firms, particularly in the US.

Investor reaction to the Sucampo deal announcement was marginally positive: Mallinckrodt's shares closed up 0.7% at $23.48 following the announcement on Dec. 26, 2017. The small boost is nonetheless dwarfed by the 55% decline the stock has suffered since the start of 2017. Mallinckrodt's market capitalization stands at $2.2bn, down from $5.0bn at the beginning of the year.

While analysts at Morgan Stanley in a Dec. 26 note described the deal as "a marginal positive because it diversifies [Mallinckrodt] away from Acthar," Moody's ratings agency warned that it was considering downgrading Mallinckrodt's ratings because of added debt the company plans to take on to fund the acquisition. Moody's noted that the transaction would increase Mallinckrodt's gross debt/EBITDA (earnings before interest, tax, depreciation and amortization) ratio on a pro forma basis from 4.4 to 4.9, reducing its financial flexibility.

"Mallinckrodt also faces earnings pressure in its specialty generics segment and sales growth headwinds in 2018 on its largest drug, Acthar," it stated. "That said, the acquisition of Sucampo provides incremental earnings diversification for a few years and improves its pipeline of late-stage drugs."

AMITIZA REVENUE STREAM

Sucampo's main commercial product is *Amitiza* (lubiprostone), a treatment for various constipation indications, which is also awaiting a US approval decision (expected in January 2018) to treat pediatric functional constipation in children aged six to 17. The product is partnered with **Takeda** in the US, UK and Switzerland and with **Mylan** in Japan, and brought in total net sales of $456m in 2016, although more than half of that goes to Sucampo's commercial partners. Sucampo itself booked revenues of $201m in combined product sales and royalty payments, up 45% on the prior year.

Sucampo has settled with **Par** for the launch of an authorized generic version of the drug in the US in 2021.

Sucampo's other marketed product is the ocular pressure-lowering drug *Rescula* (unoprostone), which is sold in Japan and generates less than 5% of the company's revenues.

Sucampo has projected it will book total 2017 revenues of $250-255m and adjusted net income of $63-68m.

PIPELINE BOOST

The acquired company will flesh out Mallinckrodt's later stage pipeline with VTS-270 for the rare and fatal neurodegenerative disease Niemann-Pick type C and CPP-1X/sulindac for familial adenomatous polyposis (FAP), both in Phase III trials.

VTS-270, which has the potential to treat a large majority of all Niemann-Pick patients, is slated for FDA submission in 2018, with an approval decision expected in 2019.

Mallinckrodt will have global rights to the product, and expects to receive a priority review voucher should it be approved. It projects total peak sales of $150m.

Sucampo acquired the product through the purchase of **Vtesse Inc.** earlier in 2017. *(Also see "Sucampo Looks To Add Heft With Vtesse Acquisition" - Scrip, 3 Apr, 2017.)*

CPP-1X/sulindac is expected to complete Phase III at the end of 2018. Sucampo is developing it in partnership with **Cancer Prevention Pharmaceuticals** (CPP), from which Mallinckrodt says it would anticipate acquiring North American rights to the product for a nominal fee, should the trial succeed.

The drug is expected to be filed and potentially approved in 2019. Peak US sales of more than $300m are anticipated by Mallinckrodt, which would share some of the profits with CPP.

The Sucampo acquisition is just the latest in a string of transactions by Mallinckrodt, which is looking to divest under-performing businesses while purchasing more promising activities in bolt-on deals. *(Also see "Mallinckrodt's InfaCare Buy Leaves Room For Further Diversifying M&A" - Scrip, 7 Aug, 2017.)*

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CONTINUED FROM COVER

Yescarta Undercuts Novartis's CAR-T Kymriah" - Scrip, 18 Oct, 2017.)

Brian Atwood, MD of Versant Ventures and co-founder and CEO of **Cell Design Labs Inc.**, believes that ASCO 2018 "could be a very important meeting after a quiet 2017."

ADVANCED THERAPIES

The approval of **Spark Therapeutics Inc.**' vision loss gene therapy *Luxturna* (voretigene neparvovec-rzyl) in December was highlighted by Boehringer's Wood as one of the "flashes of success" achieved by gene therapies in 2017. "These are still heading to their coming of age," he said. "Further progress in a positive direction is likely in 2018."

Eduardo Bravo, CEO of allogeneic stem cell therapy developer **Tigenix**, concurred. "There has been a number of developments in regulatory processes around the world aimed at speeding up market access of these treatments," he said. "And with more products either close to or gaining approval, advanced therapies are closer than ever to delivering on their potential."

On the regulatory front, Informa Pharma News principal analyst *Amanda Micklus* expects the FDA "to continue in 2018 to fulfill provisions laid out in the 21st Century Cures Act to develop a regulatory framework around regenerative medicines. FDA commissioner Scott Gottlieb has already announced a series of regulatory guidances, including two final and two draft documents, and I believe there are more in the pipeline, including disease-specific guidances on gene therapy (the first of which is to be in hemophilia)."

Micklus believes the appointment of Scott Gottlieb was a "big win" for the cell and gene therapy industry in 2017: "He has been a champion for this market and understands that the FDA needs to modernize its processes when it comes to evaluating cell and gene therapies, including the use of adaptive clinical trial design and early and frequent communications with sponsors."

She expects the momentum generated around cell and gene therapies in 2017 with the approval of CAR-T therapies, positive clinical data read-outs, **Gilead Sciences Inc.**'s acquisition of **Kite Pharma Inc.** and other developments will continue into 2018, with "possibly accelerated filings for hemophilia gene therapy candidates from

Rita Balice-Gordon

bluebird bio Inc. or Spark" and lots of deal making both in terms of partnerships and "maybe more full-company acquisitions than we've seen in past years."

NEUROSCIENCE AND MORE

Others highlighted therapeutic advances in CNS, metabolic disorders and infectious diseases.

Roche's Seeruthun expects breakthroughs in neurodegenerative disease R&D, and highlighted Roche's ongoing Phase III Alzheimer's programs with amyloid-targeting crenezumab and gantenerumab as well as the Swiss group's recently licensed candidate for Huntington's disease, IONIS-HTTRx: Roche and partner **Ionis** will present data on the latter drug at medical conferences in 2018. *(Also see "Roche's Neuroscience Franchise Gets Lift From Huntington's Breakthrough" - Scrip, 12 Dec, 2017.)* "We are hoping to move in both diseases beyond slowing progression to modifying the disease," he said. Nonetheless, Datamonitor Healthcare lead analyst *Dan Chancellor*, who specializes in CNS, said "2018 should actually be a relatively quiet year for pivotal trial read-outs" in Alzheimer's.

Instead, he is "looking towards the first approvals of the exciting anti-CGRP antibody class for migraine prevention." Added *Dan Digaudio*, drug analyst with Informa Pharma Intelligence's Pharmaprojects, "Will **Eli Lilly & Co.**'s galcanezumab, **Novartis AG**' erenumab or **Teva Pharmaceutical Industries Ltd.**'s fremanezumab be the first approved? The winner will have a clear advantage by being the first to deliver a breakthrough therapy to patients imprisoned by severe and chronic migraine attacks." Nonetheless, Chancellor warned that the devil will be in the details, with close attention expected to how the product labels are differentiated, and how that affects pricing and reimbursement. "Success in clinical trials for drugs for new classes has not always recently translated into immediate commercial success, so this additional hurdle should not be taken for granted," he cautioned.

Addressing earlier candidates in the R&D pipeline, **Sanofi**'s head of neuroscience research, *Rita Balice-Gordon*, expects 2018 to bring "new breakthroughs in how toxic proteins aggregate to cause neural dysfunction, plus links between brain function and diabetes/obesity."

Boehringer's Wood meanwhile believes that metabolic disease research "will see a new emphasis on clinical testing of combinations of drug candidates in obesity." He thinks the combinations will "take advantage of synergistic/additive efficacy at more favourable exposure levels" and expects a similar trend in non-alcoholic steatohepatitis (NASH).

For *Michael Haydock*, Datamonitor Healthcare lead analyst for cardiovascular and metabolic and infectious diseases, the biggest event in the infectious disease landscape in 2018 will be the expected US approval of Gilead Sciences' HIV combination bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in February, followed by EU approval in the third quarter. "It will be Gilead's flagship single-tablet regimen to replace *Genvoya*, which is already a blockbuster," he said. "**ViiV Healthcare**'s dolutegravir-based products have been stealing market share away from Gilead in recent years, so B/F/TAF is expected to reverse the tide and recoup some of Gilead's market share." DMHC predicts the product will reach peak sales of $5.7bn in 2022, helping to drive growth for Gilead as its HCV franchise continues to hemorrhage sales in the face of pricing competition and falling patient numbers.

PERSONALIZED MEDICINE

For *Robert Tansley*, investment director at Cambridge Innovation Capital, 2018 will see significant advances in personalized medicine, with ongoing improvements in cost-effectiveness and sensitivity of genomic analysis meaning "a wide range of tests are beginning to emerge." He believes

the personalization of medicine "will grow substantially in 2018 and beyond, improving response rates dramatically and making treatments much more effective and efficient than those seen in the past."

"We'll truly see personalized treatments coming into play in 2018," agreed Roche's Seeruthun, who added "we're coming to see genomic profiling become a standard of care. The challenge is how to use genomic profiling and aggregate datasets and use algorithms to personalize treatments, both in drug development and patient care."

DATA, DIGITAL TECHNOLOGY AND ARTIFICIAL INTELLIGENCE

Many of those *Scrip* spoke to highlighted digital technology in one form or another as an area of likely progress in 2018.

"It is clear that companies that have strong data driven cultures are the big winners in driving value. It is no longer about big, thick, small and other adjectives to describe data but it's about using the best approaches to drive better decision making," declared *Milind Kamkolkar*, chief data officer at Sanofi, which is embarking on an enterprise information management (EIM) capability "that will lead our business into an evolved way of building value."

Kamkolkar believes that "AI will reach critical mass as an enterprise capability with its first major win in Natural Language Intelligence." This will enable the extraction and analysis of data currently held captive in studies, publications and documents and the like to "create new insights we never had access to and better address unmet needs of our customers." He also highlighted blockchain as "a new way of managing and engaging with data in a secure and permission based way" that is worth watching in pharma in 2018: for example, Sanofi will be running some pilots to use it to give customers better access to their data in trials.

Cloud computing firm Veeva is focused on pharma and life science industry applications. Its general manager CRM, *Arno Sosna*, agrees about the rise of AI. "In 2018, companies will significantly scale their use of artificial intelligence for a wider range of commercial applications. With greater scale, applications such as predictive customer engagement will become more ubiquitous," he said. His colleague *Kilian Weiss*, general manager KOL solutions, notes that the huge and growing oncology market "will drive a shift in how pharma engages with stakeholders. Technology will play a key role in driving personalized customer experiences to meet the unique needs of the oncology space," he predicted.

Meanwhile, Veeva's vice president Vault EDC, *Richard Young*, thinks "risk-based monitoring (RBM) will be replaced this year by risk-based everything (RBX), a new approach where each data point can be analyzed to help companies make better decisions." Modern data systems will help manage the increasing volume and diversity of data sources, he added.

Medidata Solutions Inc. is another firm using a cloud-based platform to provide solutions to the pharma industry. *Glen de Vries*, president and co-founder, thinks "2018 will be a year that we look back on as the inflection point around collaboration that results in sustainable improved outcomes, both for patients and for the business of life sciences. Without restrictive categorizations like "pre-competitive," and with broader impact than the handful of platform trials run to date, we will see a proliferation of adaptive designs, comparator arms based on shared patient data pools and real-world data, and consistent acceleration of evidence generation -- all leading to access to the best possible therapies for patients in need."

One downside of the increasingly digitized world is the rising threat of cybercrime. *Viktors Engelbrehts*, director of threat intelligence at cybersecurity firm eSentire, warned that 2017 saw an increasing number of attacks carried out against biotechnology and other healthcare industry targets. With a 90% increase in alerts sent on hostile traffic, biotechnology is mostly targeted for its intellectual property. "To cybercriminals, biotech organizations are in a mix of being a source of information or IP theft, and also are a potentially easy target for traditional, financially motivated cybercrime," said Engelbrehts. Biopharma companies in 2018 should step up their defenses as these attacks are not going away.

Another threat for pharma comes from non-traditional firms entering the fray, and digital experts like Amazon should be closely watched in 2018. Although Amazon has yet to throw its hat in the ring, it is a "master" at getting products from manufacturers to consumers and this mastery is desperately needed in "a very inefficient" pharma supply chain, said *Salil Kallianpur*, former executive of GlaxoSmithKline India and co-founder and partner of The Digital Transformation Lab. He speculated that Amazon could "use its scale to become the single largest buyer and distributor of generic medicines and use its vast global shipping network to get medicines from 'factory to formulary' in a matter of hours," with cost savings passed on to patients.

Mehta Partners' *Viren Mehta*, a regular *Scrip* columnist, agrees that disruptors from outside the industry will leave big pharma in particular facing the challenge of defining "what is their critical value proposition" in 2018.

Data technology is undoubtedly a key component across the healthcare and biopharma universe, and looks set to revolutionize it in many ways, with cost pressures acting as a major impetus for change.

"Worldwide cost pressures will lead to continued disruption in healthcare. To achieve greater efficiency, innovation throughout the entire system, from new healthcare delivery models to novel R&D strategies will be key to progress in 2018," commented *Elias Zerhouni*, executive vice-president, global R&D at Sanofi, summing up the thoughts expressed by many others.

PRICING

Mehta points out that people today live longer "only to face more maladies of aging." He believes that whereas "the debate about the cost of medicine to date has been focused on each episode [of illness], soon a global or lifetime budget will anchor such discussions, within which each individual treatment will need to find its own rightful place." He believes the debate will tighten in 2018, with a shift from the concept of quality adjusted life years (QALY) per treatment to an overall quality adjusted life (QAL) valuation of medicine throughout a person's lifetime.

More immediately accessible to action, Kallianpur expects lifting barriers to generic drug competition will be a priority of the US government and FDA, with more focus in 2018 on speeding up approval of complex generics and biosimilars "to bring much needed choice and competition" to reduce the prices in categories that account for the most expensive medicines. Meanwhile, as regards high-priced branded medicines,

CONTINUED ON PAGE 8

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Edison director-analyst *Andy Smith* thinks "commercial payers will continue to flex their muscles in 2018."

DMHC's Chancellor wondered whether the promises that some pharma companies made in 2017 to limit annual drug price increases were isolated events. He pointed out that "two high-profile drug launches – *Ocrevus* and *Dupixent* – notably undercut the list prices of the competition" in 2018.

His colleague at Datamonitor Healthcare, *Tijana Ignjatovic*, noted that in the US eyes will be on the work of the Institute for Clinical and Economic Review (ICER), which "has been increasingly active and is now timing the release of its reports so they could be referenced by payers when making their coverage decisions… Its partnership with the VA (Department of Veterans Affairs) indicates that the direction of travel is heading towards greater influence, with the next step potentially working with the CMS." However, an impact on publicly funded Medicare coverage is unlikely in 2018, she believes, since it would require a legal change.

Ignjatovic will also be watching for "any new pricing or reimbursement mechanisms specifically for oncology combinations" since a burgeoning number of such treatments are coming through the pipeline and promise significant improvements in outcomes for patients – which poses a challenge for payers, especially where the elements of a combination are manufactured by different companies. "We expect that in multiple countries there are efforts to develop new policies to allow payers to negotiate a reduced price for such combinations." Such proposals are being considered in Germany although political factors may stymie legal reform.

Meanwhile, she notes that the UK will likely experience tough negotiations as the current Pharmaceutical Price Regulation Scheme expires at the end of 2018 while the NHS struggles with serious financial pressures.

M&A

There were mixed views among those consulted on merger and acquisition trends for the coming year. *Ali Al-Bazergan*, Datamonitor Healthcare lead analyst, is "anticipating bolstered M&A traction in 2018 on the back of the clarification of some uncertainties including pricing legislation and tax reform. The ability to repatriate ex-US cash at a one-time tax rate of 10% and clarification of corporate tax will allow biopharma to allocate capital towards higher-risk deal making. That said, companies will continue to use disciplined M&A as a vehicle to sharpen strategic focus into therapeutic areas that have critical mass, paving the way for a few larger deals."

Results Healthcarepartner *Kevin Bottomley* agreed: "Assuming that the latest corporate tax reforms are enacted in the US, this will unlock large pharma M&A, which has been quiet for the last 15 months. Expect large pharma companies to be targets and for example, **Pfizer Inc.**, to be active. All large pharma are seeking scale economies and pipeline."

So did *Leo Gribben*, UK TAS Life Sciences Leader at EY: "Overall, the prospects for the transaction market look good. If recent press commentary is anything to go by, with upcoming sales in OTC, consumer health and generics expected during the course of the next financial year, there could be a lot of assets coming to the market with no shortage of willing buyers.

"The question that everyone is posing is whether private capital could play a bigger part in these asset auctions than we have previously seen, both for those that will come with infrastructure and for those who have built the platforms to acquire brands with no infrastructure. Equally, throw into the mix some of the bigger players, who have the ability to be creative and swap assets, and it could help unlock some of the transactions.

"The US tax reform could also allow some the US majors to release their trapped offshore firepower. Some estimate that this could release funds worth over $150bn."

But Andy Smith was not so sure. "Typically biotech stocks jump when investors think of repatriated cash as they seem to assume that if will fuel M&A. I don't think that this will be the case and irrespective of where cash in the last few years has been derived – retained earnings, debt or repatriation – it more often gets spent on share buy-backs. Expect that to rate higher than M&A in C-suites," he predicted.

He also thinks that there is still a disconnect in price expectations between buyers and sellers. "In the US at least, small to mid-cap biotech have market caps that start at at least $1bn. Either price expectations have to rise at the acquiring companies, or more likely, prices will come down. I was told by an investor the other week that generalist investors are still overweight healthcare and continue to sell those holdings down (hence the fairly ugly 2017 tax loss selling season for biotech). This may continue in 2018 until prices get cheap enough to catalyze a new wave of M&A."

BREXIT

Last, but by no means least, Brexit was flagged as an important topic for 2018.

"UK pharma companies will continue to hedge against a 'hard' Brexit by investing in operations in the EU. Inward investment in UK pharma research will be strong; recruiting and retaining EU talent will be an ongoing challenge," said Bottomley.

Roche's Seeruthun acknowledged that "there are a lot of unknowns" but pointed out "the current UK government's interest is to maintain regulatory alignment." He sees Brexit as offering an opportunity for the UK medicines regulator MHRA to work alongside the European Medicines Agency and to take a leadership role and help ensure UK patients get earlier access to medicines. "But we need to maintain a very close relationship with the EMA." Seeruthun also said the industry needed "clarity relatively quickly" on the rules governing medicines entering the UK from the EU, both for clinical trials and prescribing.

Clive Wood expressed concern about the prospects for the wider European research effort. "Much has been said about the important topic of harmonization of drug regulation post-Brexit. I hope that as clarity emerges in the coming year, we can also focus on preserving the strength and integrity of scientific research cooperation across Europe," he said. "Europe is a critical link in the global engine of innovation for patients. To allow it to slip in any way, would be at our peril."

"The uncertain fallout of Brexit will continue to present a challenge for us all in 2018 and beyond. This means the final deal must have pragmatic solutions so that patients can have secure access to the medicines they need once the UK is out of the EU," said *Lars Bruening*, CEO of Bayer UK & Ireland.

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Roche Digs In To Early Breast Cancer With Perjeta

EMILY HAYES emily.hayes@informa.com

Genentech Inc./Roche has strengthened its foothold in early breast cancer with a new supplementary US FDA approval for the rising HER2 franchise star *Perjeta* covering use in the adjuvant (after surgery) setting and full approval in the neoadjuvant (before surgery) line of therapy.

FDA approved Perjeta (pertuzumab) on Dec. 20 for use with Genentech's HER2 franchise grandfather *Herceptin* (trastuzumab) and chemotherapy for adjuvant use in HER2-positive early breast cancer at high risk of recurrence. Per the label, the regimen should be given for one year – up to 18 cycles.

The filing had priority review, based on the Phase III APHINITY results, and approval came more than a month earlier than the user fee date of Jan. 28. The APHINITY study included 4,805 patients and with a median of 45.4 months of follow-up the combination of Perjeta with Herceptin and chemotherapy reduced the risk of breast cancer recurrence or death by 18% versus Herceptin and chemotherapy alone (p=0.047).

"High risk" wasn't precisely defined in labeling and may be subjective, depending on the patient. The company will be helping physicians understand what they think it means, Edith Perez, vice president and head of Genentech's US BioOncology Medical Unit, told *Scrip*.

The definition of "high risk" was broader than expected, "giving oncologists the freedom to treat any patients for whom they are particularly concerned about the possibility of recurrence, either based on their clinical features or their personal circumstances," Jefferies analyst Jeffrey Holford observed in a Dec. 21 note.

The agency has now also granted full approval of the Perjeta/Herceptin/chemotherapy combination in the neoadjuvant setting for HER2-positive, locally advanced inflammatory or early-stage breast cancer. The Dosage and Administration section of revised labeling for this indication now says that treatment should continue for one year, up to 18 cycles, whereas it had not previously been specified.

The accelerated approval in neoadjuvant breast cancer, granted in September 2013, was supported by the Phase II NeoSphere study, which used the emerging surrogate endpoint of pathological complete response (pCR). In that trial, 40% of those in the Perjeta/Herceptin/chemo arm had a pCR versus 21.5% for Herceptin with chemo. Approval marked the first and still only use of the FDA's accelerated pathway for neoadjuvant breast cancer drugs.

"After speaking with Roche, we estimate that the updated label for neoadjuvant use, which now specifies patients should receive up to 18 cycles [per] year of post-operative dosing, could add over $1bn of additional sales potential in this setting on top of current estimates. In terms of the adjuvant indication, we see the definition of 'high risk' as being broader than expected," Holford said.

Perjeta initially was approved in mid-2012 for first-line metastatic HER2-positive breast cancer.

The drug has become an important contributor to Roche group sales, bringing in CHF1.6bn ($1.6bn) in the first nine months of 2017, up by 17% from the year-ago period. The company declined to break out sales by indication.

Execs have emphasized the importance of APHINITY in earnings calls, noting that Perjeta sales already are above CHF2bn on an annualized basis.

Perjeta was just approved for adjuvant use, but guidelines from the National Comprehensive Cancer Network (NCCN) already recommended use for high-risk HER2-positive patients in the adjuvant setting who did not receive the drug prior to surgery.

Genentech's Perez explained that there has been debate in the breast cancer community, with some feeling that patients deserved access to Perjeta in the adjuvant setting as well as neoadjuvant use, but the company has not been promoting it in this line of therapy as that would have been an off-label indication before now.

With the launch of Perjeta in 2012 and the antibody drug conjugate *Kadcyla* (ado-trastuzumab) in 2013, "Roche is in a strong position to continue expanding its breast cancer franchise beyond Herceptin, regardless of biosimilars (which we expect in late 2017 in Europe and 2019 in the US)," Morningstar analyst Karen Anderson said in a Dec. 20 note.

"Patents on newly approved drugs Perjeta and Kadcyla run to 2025 and 2023, extending the profitability of the firm's Herceptin-based breast cancer franchise," Anderson noted.

APHINITY UNDERWHELMED

The new approvals represent an important step in staking a claim in the treatment of early cancer, a goal for many oncologic therapies across tumor types, even though results of the study underwhelmed investors at the time of release at the American Society of Clinical Oncology meeting in June.

Overall, the absolute difference between the two study arms (Perjeta/Herceptin/chemo versus Herceptin/chemo) was only 0.9% (94.1 vs. 93.2%).

Results were better in certain subgroups and analysts speculated that use would be confined to those at highest risk.

At the time, Jefferies analysts said that the data were at the bottom end of expectations and that they expected use would be prioritized in the 34% of patients in the highest-risk subgroup, who got the greatest benefit (a 23% improvement in disease-free survival).

But with the better-than-expected labeling and approval timing, along with input from physicians, Jefferies revised its expectations.

A recent proprietary survey of US breast oncologists suggests physicians already have extensive experience using Perjeta in metastatic and neoadjuvant breast cancer patients already, Holford said in his post-approval note Dec. 21. US oncologists expect to use Perjeta in about 44% of adjuvant patients who are now treated with Herceptin and Jefferies believes this equates to a CHF4.3bn revenue opportunity.

"Across all indications, we currently forecast risk-adjusted sales by 2021 of CHF6bn vs. consensus of just CHF4bn," Holford said.

Meanwhile, Roche also is positioning Kadcyla and other drugs for a role in early breast cancer.

The Phase III KATHERINE study tests Kadcyla in HER-2 positive early breast cancer and residual invasive disease following neoadjuvant therapy. Results are expected in 2018. The Phase III KAITLIN adjuvant study tests Kadcyla with anthracyclines, followed by taxanes combined with Herceptin plus Perjeta, versus treatment with anthracyclines followed by Kadcyla plus Perjeta. Results are expected in 2019.

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A Year To Remember For US Drug Launches

JESSICA MERRILL jessica.merrill@informa.com

The year 2017 was bountiful for US drug launches, and several new entrants represent significant medical advances in cancer and other therapeutic areas of high unmet medical need. The launch of the first CAR-T therapies, **Novartis AG**'s *Kymriah* and **Gilead Sciences Inc.**'s *Yescarta* – potential cures for some cancer patients – are notable enough to call 2017 a groundbreaking year for new drugs.

Commercial success is the real test for new drugs, at least for investors. The winners and losers on that front will be sorted out over the course of 2018, but several drugs are already poised to become blockbusters, including **Roche**'s *Ocrevus* (ocrelizumab) for multiple sclerosis, **Sanofi/Regeneron Pharmaceuticals Inc.**'s *Dupixent* (dupilumab) for atopic dermatitis and **GlaxoSmithKline PLC**'s shingles vaccine *Shingrix*.

"It's almost like there has been a slow retooling of the entire pharma sector and we are starting to see the results of that happening now," Bain & Co. partner Michael Retterath told *Scrip*. "What we saw is pharma retooling and moving into new technologies like gene therapy and CAR-Ts."

ZS Associates Managing Principal Maria Whitman agreed. "2017 has been a story on the innovation side," she said. "One of them is the CAR-T story, and we can add into it the gene therapy story. What this tells us is we are at the tip of an era of therapies that present new opportunities and also new challenges on the system."

A YEAR OF FIRSTS

FDA approved a record 46 novel new drugs in 2017, including four just in the week leading up to Christmas, breaking the previous record of 45 approvals in 2015.

The year far outpaced 2016 when it comes to the number of new launches, and it appears poised to exceed 2016 on the metric of commercial successes too. Only 22 new molecular entities were approved in 2016, and last year's early winners were new combination pills in hepatitis C, the quick but short-lived blockbusters *Epclusa* from Gilead and *Zepatier* from **Merck & Co. Inc.** The 2016 class included several drugs that were the second or third to market like Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab) for bladder cancer and **Eli Lilly & Co.**'s *Talz* (ixekizumab) for psoriasis.

The record-breaking number of approvals in 2017 returns the industry to a level of productivity more consistent with recent prior years. The 22 novel approvals coming out of CDER last year was the lowest annual total for the center since 2010.

NOVELTY

Among some of the most novel new drugs approved in 2017 were the CAR-T therapies Kymriah and Yescarta and **Spark Therapeutics Inc.**'s *Luxturna* (voretigene neparvovec-rzyl). Luxturna is viewed by many as the first true gene therapy approved in the US, though the CAR-T treatments have also been designated as gene therapies. Kymriah was approved in August for pediatric acute lymphocytic leukemia (ALL), while Yescarta was approved in October for a larger indication in adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. Luxturna was one of the last approvals of 2017, the first treatment for an inherited blindness that affects only a few thousand patients in the US.

Despite enthusiasm for the pioneering therapeutics, the commercial potential of the drugs remains uncertain; they target niche patient populations and are ultra high-priced, which could lead to reimbursement challenges that are expected to slow the launch trajectory.

Whether or not these innovative technologies turn into big revenue generators will be a key test for industry.

Drugs like Roche's Ocrevus and Sanofi/Regeneron's Dupixent, which debuted in the first half of 2017 and target larger patient populations, already appear on their way to achieving the industry's coveted blockbuster status. Ocrevus is one early standout when it comes to revenues. Ocrevus generated CHF497m ($503.6m) after launching in April, driven by strong efficacy data and a monopoly in a challenging patient population. Ocrevus is the first and only disease modifying therapy for primary progressive multiple sclerosis (PPMS), one of the most disabling forms of MS, and is also approved for relapsing forms of the disease.

Dupixent, meanwhile, also launched in April as the first systemic therapy for the treatment of atopic dermatitis, a painful skin condition. *(Also see "Sanofi/Regeneron Choose Access Over Price With Dupixent Launch" - Scrip, 28 Mar, 2017.)* It generated $118m through the third quarter, suggesting it is on a blockbuster trajectory.

Achieving $200m in first-year sales is generally viewed within the industry as an indicator that a new drug is headed toward blockbuster status, though launch timelines have lengthened across the industry in recent years as reimbursement and market access have become more challenging.

Another notable launch was **Biogen Inc.**'s *Spinraza* (nusinersen), yet another groundbreaking technology and the first medicine approved for the rare neurodegenerative disease spinal muscular atrophy (SMA); it is an antisense oligonucleotide drug that manipulates the RNA to produce proteins needed for proper muscle function.

Spinraza was approved by FDA in late December 2016 but is included here because the launch occurred primarily in 2017. Biogen priced the drug higher than expected, $750,000 for the first year of treatment and $375,000 in subsequent years due to the lower dosing schedule, and initial sales exceeded expectations. Spinraza generated $521m in the first nine months of 2017, though sales appeared to be plateauing in the third quarter. Analysts still expect Spinraza to become a blockbuster, despite some unsteadiness as some patients begin switching to the lower maintenance dosing.

MANY FAST FOLLOWERS

While the level of innovation was notable in 2017 in some instances, many of the NMEs that launched were fast followers, the second- or third-to-market drugs, or even the fourth or fifth.

"The negative trend was in first-in-class medicine approvals," Whitman said. In oncology, she pointed out that only 42% of the NMEs approved represented novel mechanisms of action.

The fast followers were particularly evident in the PD-1/L1 category, where **Merck KGAA/Pfizer Inc.**'s *Bavencio* (avelumab) and **AstraZeneca PLC**'s *Imfinzi* (durvalum-

ab) were the fourth and fifth PD-1/L1 inhibitors to market, respectively, following Merck's *Keytruda* (pembrolizumab), **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) and Roche's *Tecentriq* (atezolizumab).

How the PD-1/L1 market will shake out over the long-term is still the big question; the market is expected to become even more oversaturated as additional drugs are approved. The early entrants – Keytruda and Opdivo – are dominating the market, while cancer leader Roche's Tecentriq has turned in a solid early performance in bladder cancer and lung cancer.

Pfizer did not break out sales of Bavencio in 2017, generally a sign the revenues are not material to the company's financials. Bavencio was approved by FDA in March for Merkel cell carcinoma, a rare skin cancer, and gained a bladder cancer indication in May. Imfinizi was approved by FDA in May for bladder cancer and had not yet generated material sales as of AstraZeneca's third quarter financial results.

A similar dynamic unfolded in breast cancer, where Novartis and Lilly are fast followers behind Pfizer's first-to-market CDK4/6 inhibitor *Ibrance* (palbociclib), which launched in 2015 and has become a pillar of Pfizer's oncology portfolio. Ibrance generated $2.41bn in the first nine months of 2017 and Novartis and Lilly are hoping to capture a piece of the action with **Kisqali** and **Verzenio**, respectively. Kisqali was approved by FDA in March, though Novartis said the full US launch began in earnest in August. Verzenio was approved in October. It's too early still to say whether the new entries are impacting sales of Ibrance (Kisqali only generated $26m in the third quarter, according to Novartis), but competition could put more pressure on price in the category.

Followers weren't just in oncology, however. Sanofi/Regeneron's *Kevzara* (sarilumab) was approved in May as the second IL-6 inhibitor for rheumatoid arthritis, which will compete against Roche's entrenched *Actemra* (tocilizumab). **Johnson & Johnson**'s *Tremfya* (guselkumab) is a first-in-class IL-23 blocker approved in July for psoriasis but it will compete in a crowded category for psoriasis drugs, which includes J&J's own IL-12/IL-23 blocker *Stelara* (ustekinumab). **Valeant Pharmaceuticals International Inc.** launched a third-to-market IL-17 blocker *Siliq* (brodalumab) for psoriasis. Fast followers in pharma are becoming far more commonplace, putting more pressure on drug companies to execute quickly on their launch, even as new drugs often face more market access challenges that lengthen the launch trajectory.

"The first mover advantage is more difficult to play than it used to be, particularly in oncology," Whitman said.

"There is an increased focus of companies pursuing the same disease areas. We see it over and over again," said Bain's Retterath. "When a company launches, the follow up product that is launching behind is often six months out, and the one after that is another six to 12 months. You have a very small window while the competitive dynamic is changing in the market."

The competitive and commercial dynamics remain as difficult as ever.

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A Snapshot Of The Drugs That Launched In 2017

MANUFACTURER & DRUG	INDICATION	US APPROVAL (THROUGH OCTOBER)
Biogen Spinraza	Spinal muscular atrophy	December 2016
Synergy Trulance	Chronic idiopathic constipation	January
Valeant Siliq	Psoriasis	February
Novartis Kisqali	HR+/HER2- metastatic or advanced breast cancer	March
Pfizer/Merck KGAA Bavencio	Merkel cell carcinoma	March
Tesaro Zejula	Recurrent ovarian cancer	March
Roche Ocrevus	Primary progressive and relapsing multiple sclerosis	March
Sanofi/Regeneron Dupixent	Atopic dermatitis	March
Neurocrine Ingrezza	Tardive dyskinesia	April
Novartis Rydapt	Acute myeloid leukemia, systemic mastocytosis and mast cell leukemia	April
Teva Austedo	Chorea associated with Huntington's disease	April
AstraZeneca Imfinzi	Urothelial cancer	May
Sanofi/Regeneron Kevzara	Rheumatoid arthritis	May
Portola Bevyxxa	Anticoagulant for VTE	June
J&J Tremfya	Plaque psoriasis	July
Puma Nerlynx	Early-stage HER2 over-expressed breast cancer	July
Gilead Vosevi	Fixed-dosed combination for hepatitis C	July
Celgene Idhifa	AML with an IDH2 mutation	August
AbbVie Mavyret	Fixed-dose combination for hepatitis C	August
Pfizer Besponsa	Relapsed/refractory B-cell precursor acute lymphoblastic leukemia	August
The Medicines Company Vabomere	Antibiotic for complicated urinary tract infection	August
Novartis Kymriah	Pediatric acute lymphoblastic leukemia	August
Eli Lilly & Co Verzenio	HR+/HER2- breast cancer	September
Bayer Aliqopa	Relapsed/refractory follicular lymphoma	September
AstraZeneca Calquence	Relapsed/refractory mantle cell lymphoma	October
Gilead/Kite Yescarta	Certain types of B-cell lymphoma	October
GlaxoSmithKline Shingrix	Shingles vaccine	October

Source: Pink Sheet Performance Tracker (not inclusive of every FDA approval)

ICER Views Kymriah, Yescarta As Cost Effective

MANDY JACKSON mandy.jackson@informausa.com

The Institute for Clinical and Economic Review (ICER) said in a draft report issued on Dec. 21 that the recently approved chimeric antigen receptor T cell (CAR-T) therapies from **Novartis AG** and the **Gilead Sciences Inc.** subsidiary **Kite Pharma Inc.** are cost effective at current prices.

This is the first formal critique of the list prices for Novartis's Kymriah (tisagenlecleucel) and Gilead/Kite's Yescarta (axicabtagene ciloleucel), the first two treatments approved in the US in which T cells are removed from a patient and genetically reengineered to target a specific antigen on cancer cells – CD19 in the case of both products. Kymriah and Yescarta each appear to be generally cost effective in their approved indications at costs that in many cases won't break the health care system's bank.

Kymriah was approved on Aug. 30 for the treatment of pediatric and young adult patients (up to age 25) with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or has relapsed after at least two prior lines of therapy and Novartis set its price in that indication at $475,000 before discounts. The company also negotiated an outcomes-based contract with the Centers for Medicare and Medicaid Services (CMS) under which CMS will not pay for Kymriah if patients don't respond within the first month of treatment.

The wholesale acquisition cost (WAC) for Gilead/Kite's Yescarta, approved on Oct. 18 for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, is $373,000. However, the ICER report notes that the cost of leukapheresis to extract patients' T cells is included in the cost of Kymriah, but not in the price for Yescarta.

Cost effectiveness was outlined by ICER as $150,000 or less per quality-adjusted life year (QALY) gained and Kymriah came in below this threshold 99% of the time when compared to chemotherapy with clofarabine in the product's approved indication. By the same measure, Yescarta judged against chemotherapy was cost effective 68% of the time. The therapies were analyzed in multiple scenarios and models, including short- and long-term cost effectiveness, and societal versus health care costs.

However, the analysis of Kymriah took into account the outcomes-based agreement that Novartis has with CMS and potentially other payers, while Yescarta was evaluated by its announced WAC price alone, since Gilead has not disclosed any outcomes-based agreements. If such contracts were in place, ICER acknowledged that Yescarta's cost effectiveness would be more favorable under agreements that give discounts and provide for cost-forgiveness when patients don't respond to treatment.

The costs of the medicines also are not expected to be overly burdensome for the health care system. ICER estimates that the cost of any biopharmaceutical product would have to be renegotiated if its annual budget impact exceeds $915,000 per patient.

Looking at a five-year time horizon, Kymriah's annual budget impact was estimated at $198,000 if payers cover only patients that respond within the first month post-infusion. Yescarta's annual budget impact in terms of a five-year horizon was forecast to be $209,000 per patient.

Kymriah did not exceed the $915,000 annual budget line when its price, including ancillary costs at treatment centers and hospitals, didn't exceed the threshold of $50,000 per QALY, $100,000 per QALY or $150,000 per QALY. However, Yescarta's costs did exceed that line at $100,000 and $150,000 per QALY, but not at $50,000 per QALY.

ICER noted several limitations for its assessment, including the fact that both Kymriah and Yescarta have only been studied in small, single-arm clinical trials, while most standard-of-care therapies have been tested against comparators in large randomized trials. Also, approvals have been granted based on response rates rather than progression-free or overall survival endpoints.

And in terms of how the treatments will be paid for, there are still a lot of unknowns about contracts with payers and health care providers, including the handling of adverse events, such as severe cytokine release syndrome (CRS) and neurotoxicity. Both are common side effects for CAR-T therapies that can be severe in the immediate weeks following infusion with the reengineered cells, requiring hospitalization in some cases until symptoms subside.

The ICER report noted the impressive efficacy of CAR-T therapies to date, which have given patients and parents a lot of hope where there was none before for relapsed and refractory patients. However, the same patient groups also noted a fear of the unknown, including long-term safety and the duration of responses over years rather than months. Aside from the medicines' costs, there also was a concern about the costs of travel to certified treatment centers and time off from work while patients are monitored for side effects.

A B+ FOR HEALTH BENEFITS

With efficacy, safety and cost in mind, ICER gave Kymriah and Yescarta a B+ rating, meaning that there is high certainty of a small net health benefit.

ICER estimated that 68% of Kymriah-treated patients and 30% of clofaradine-treated patients would be alive and responding to treatment at one month. The numbers dropped to 43% and 11%, respectively, at one year and remained stable at 42% and 11% at five years.

CRS and neurological toxicities were the main safety concerns for Kymriah as well as hypogammaglobulinemia due to B-cell aplasia in some patients, requiring ongoing intravenous immunoglobulin (IVIG) treatment, and the unknown potential in the longer term for mutagenesis by the chimeric gene inserted into the patients'T cells.

As with Kymriah in pediatric ALL, Yescarta and Kymriah provided remission for greater percentages of patients than salvage chemotherapy in these adult patients with relapsed or refractory B cell lymphoma.

ICER said there was not enough data from the JULIET study of Kymriah in non-Hodgkin's lymphoma to forecast survival for Kymriah-treated patients, but the analysis of data from the ZUMA-1 study of Yescarta showed a big survival benefit. Novartis is seeking approvals in the US and EU for diffuse large B cell lymphoma (DLBCL), but ICER's cost-effectiveness analysis did not look at Kymriah in the future indication, only pediatric and young adult ALL.

ICER estimated at one month that 76% of Kymriah-treated patients and 26% of chemotherapy-treated patients would be alive and responding to treatment. CRS and neurological toxicities also were the major safety concerns for Yescarta as well as the unknown potential mutagenesis.

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The Year's Clinical Trials In Review: Big Hits In 2017

EMILY HAYES emily.hayes@informa.com

When it comes to pharmaceutical drug development the wins can be few and far between, but when a new drug performs well in a mid- to late-stage clinical trial, the rewards can be rich – for patients and investors. Here are some of the notable clinical trial successes in 2017.

CV OUTCOMES STUDIES GALORE

The long-awaited release of full results for **Amgen Inc.**'s FOURIER cardiovascular (CV) outcomes study of the cholesterol-lowering PCSK9 inhibitor *Repatha* (evolocumab) finally came in March 2017, at the American College of Cardiology meeting. The drug demonstrated a statistically significant reduction in the number of events included in the primary composite endpoint, though the magnitude of the benefit (15%) was lower than expected. Repatha now has a CV outcomes claim based on the data.

How this will translate into reimbursement access and sales remains to be seen, but the drug already started to outperform **Sanofi/Regeneron Pharmaceuticals Inc.**'s competing PCSK9 inhibitor *Praluent* (alirocumab) in the fourth quarter of 2016. Results from the ODYSSEY CV outcomes study of Praluent are due in early 2018.

Merck & Co. Inc. announced in June that its cholesterol-lowering anacetrapib significantly reduced major coronary events in the REVEAL CV outcomes study, a surprising outcome in light of failures of other drugs in the CETP inhibitor class. However, due to the commercial challenges of launching this kind of candidate, Merck opted not to pursue regulatory approval.

Other CV outcomes successes include positive results for **Johnson & Johnson**'s SGLT2 inhibitor/diabetes drug *Invokana* (canaglifozin) in the CANVAS outcomes study and **Novartis AG**'s IL-1β inhibitor antibody canakinumab (ACZ885) in the CANTOS atherosclerosis study.

These positive data contrasted with negative results for **AstraZeneca PLC**'s diabetes drug *Bydureon* (long-acting exenatide) in the Phase IIIb/IV EXSCEL outcomes study.

VIIV'S TWO-DRUG HIV COMBO

The possibility of a two-drug regimen for HIV maintenance therapy became a reality with the release of full data from the pivotal SWORD studies for **ViiV Healthcare**'s *Tivicay* (dolutegravir) and **Janssen Pharmaceuticals Inc.**'s *Edurant* (rilpivirine) in February. (Viiv is majority owned by **GlaxoSmithKline PLC**.) The US FDA approved the regimen in November for patients with HIV type 1 whose virus has been suppressed for at least six months, after a speedy review thanks to a priority review voucher, and the fixed combination pill is now branded as *Juluca*. Analysts say the introduction of a two-drug regimen is groundbreaking for the HIV market, though it may take time to introduce such a big change.

A GOOD YEAR IN HEMOPHILIA

The year closed out with gene therapy coming into its own, with the approval of **Spark Therapeutics Inc.**'s *Luxturna* and hemophilia gene therapies drawing attention at the American Society of Hematology (ASH) annual meeting in December. Early data for Spark's hemophilia B candidate SPK-9001, partnered with **Pfizer Inc.**, and **BioMarin Pharmaceutical Inc.**'s valoctocogene roxaparvovec in hemophilia A both received glowing reviews in the *New England Journal of Medicine* – editorials suggested that a cure for the devastating disease is now in sight.

The hemophilia treatment space has also recently undergone a big change with the approval of **Roche**'s *Hemlibra* (emicizumab), a bispecific monoclonal antibody that binds to both Factor IXa and X, for hemophilia A with inhibitors.

The company also announced positive results from the HAVEN 3 study of patients with hemophilia and no inhibitors, data that could see the drug used in a much bigger population, and HAVEN 4, which tested a more convenient monthly dosing schedule. Updated data from older studies presented at the ASH meeting support the drug's safety profile and durable efficacy.

AZ'S IMFINZI & ROCHE'S TECENTRIQ GAIN GROUND

Positive data for **AstraZeneca PLC**'s PD-L1 inhibitor *Imfinzi* (durvalumab) in the PACIFIC study set the drug up for an interesting market opportunity in treating stage III non-small cell lung cancer, with a head start over competing PD-1/L1 inhibitors for this indication. Success in this line of therapy took some of the edge off of the failure of the company's Imfinzi/tremelimumab combination to demonstrate a significant improvement in progression-free survival in the MYSTIC study of first-line metastatic lung cancer.

AstraZeneca announced in October that FDA has accepted a filing to cover earlier use, based on PACIFIC data. Imfinzi was approved in May for treatment of second-line bladder cancer, a space crowded with others in the same class. AstraZeneca reported sales of only $1m in the third quarter of 2017 and said that it was more focused on launching in lung cancer.

Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab) looks well positioned following the release of positive results in December for the drug in combination with the company's VEGF inhibitor *Avastin* (bevacizumab) and chemotherapy in the IMpower150 study in first-line NSCLC. The same month, the company reported that the combination worked well in first-line kidney cancer in the IMmotion151 study. The drug had faced a setback, however, earlier in the year with the failure of Tecentriq to demonstrate a significant benefit for progression-free survival in a Phase III confirmatory study in bladder cancer, the drug's first approved indication.

ROAD PAVED FOR CANNABINOIDS

Publication of full Phase III results for **GW Pharmaceuticals PLC**'s *Epidiolex* (cannabidiol) for Dravet syndrome, a severe type of pediatric epilepsy, in the *New England Journal of Medicine* in May marked an important step for advancing pharmaceutical-grade cannabinoids as a therapeutic option. The drug is one of over 50 cannabinoids in any stage of development, in a field that is heavily focused on neurological conditions. GW filed the drug for approval in the US at the end of October and has been raising funds in order to prepare for commercial launch. On Dec. 28, the company announced that the FDA accepted the filing and granted it priority review status; the user fee date is June 27, 2018.

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The Year's Clinical Trials In Review: Big Misses In 2017

LUCIE ELLIS lucie.ellis@informa.com

In the high-risk, high-reward field of pharmaceuticals, the clinical trial disappointments come as frequently as the misses. The year 2017 included some exceptional advances and some big flops as well.

Topping the list of clinical trial disappointments would have to be **Axovant Sciences'** intepirdine for Alzheimer's disease. Sure, intepirdine is in a therapeutic category filled with landmines and investors have all but come to expect failure in Alzheimer's disease, but somehow Axovant's parent company **Roivant Sciences GMBH** and its CEO Vivek Ramaswamy had investors hoping for a win. Axovant debuted on the public markets in 2015 with the biggest IPO ever for a biotech – a sign of the enthusiasm.

But the excitement was tamped down in September when the selective 5-HT6 receptor antagonist failed to show a benefit in mild-to-moderate Alzheimer's patients in the Phase III MINDSET clinical trial. In the end, the bigger surprise was that Axovant managed to convince investors a drug **GlaxoSmithKline PLC** sold for $5m had such big potential. The company's stock fell 74% on the news while investors wait to see if intepirdine performs better in patients with dementia with Lewy bodies, where a Phase IIb trial is underway. Hopefully, better news is in store for Axovant in 2018.

Just months after Axovant's Alzheimer's dreams crashed and burned, **Celgene Corp.** had to watch its own dream to lead in Crohn's disease go up in smoke. The company announced in October that it was terminating two Phase III clinical trials testing mongersen after a data safety and monitoring committee overseeing the REVOLVE trial determined the study was futile. The disappointment was palpable, given that mongersen was one of Celgene's highest profile late-stage development programs, and the setback shook investors. The company's stock fell 8.4% on the news, with investors questioning the company's ambitions to expand in inflammation & immunology.

Celgene also paid handsomely to acquire mongersen, an oligonucleotide that decreases a protein called Smad7. The firm paid $710m to buy privately held **Nogra Pharma Ltd.** to get its hands on the asset in 2014.

MYSTIC'S MISS

While programmed cell death protein 1 (PD-1) and program death-ligand 1 (PD-L1) inhibitors are the apple of the immuno-oncology sector's eye, representing huge breakthroughs in the use of the immune system to battle cancer, the development space is not all success stories.

AstraZeneca PLC took a frontal blow in July when its PD-L1 drug *Imfinzi* (durvalumab) failed to meet primary progression free survival (PFS) endpoints in the Phase III MYSTIC trial in non-small cell lung cancer (NSCLC).

Top-line data showed that Imfinzi in combination with the CTLA-4 inhibitor tremelimumab failed to significantly improve PFS compared to platinum-based standard of care chemotherapy in previously untreated patients with metastatic NSCLC, a potentially lucrative indication.

Merck's *Keytruda* (pembrolizumab) is the only PD-1 inhibitor approved for first-line NSCLC, with indications for use as a monotherapy and in combination with chemotherapy. A successful trial in combination with tremelimumab in first-line metastatic NSCLC was how AstraZeneca hoped to jump ahead of rivals in the highly competitive immuno-oncology space. The company also concluded that Imfinzi alone, although not formally tested, would not have met a pre-specified threshold of PFS benefit over standard of care in the NSCLC trial.

The news was a hit for AstraZeneca, which responded by partnering its PARP inhibitor *Lynparza* (olaparib) with **Merck & Co. Inc.** the same day in exchange for $1.6bn upfront. All hope is not lost for AstraZeneca. MYSTIC is ongoing, assessing overall survival (OS) endpoints for Imfinzi monotherapy and the Imfinzi plus tremelimumab combination, with data expected in the first half of 2018.

"MYSTIC technically still has a few more chances to succeed," Biomedtracker analysts said at the time. "However, even a successful OS outcome would likely have a minimal real-world impact with the availability of Keytruda which showed both a PFS and OS benefit," they noted.

And, Imfinizi did show a benefit in a different Phase III trial, PACIFIC, in patients with unresectable stage III NSCLC after standard chemo-radiation treatment. Data from PACIFC, which were presented at the European Society of Medical Oncology meeting in September 2017, showed that the drug improved progression-free survival by just over 11 months – 16.8 months in the Imfinzi arm compared to 5.6 months with placebo – with a hazard ratio of 0.52.

Research has been focused on later stages of lung cancer, particularly patients with metastatic stage IV disease. The latter setting makes up about 50% of lung cancer patients, but this still leaves the other 50% with stages I, II and III – which represents a sizeable market opportunity.

AstraZeneca believes it is ahead of competitors in this earlier NSCLC setting. Trials of other anti-PD-1/L1 agents, such as Merck's Keytruda and **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab), launched in 2017.

AstraZeneca filed a supplemental biologics license application (sBLA) for Imfinzi in stage III NSCLC to the US FDA in Oct.

IMVIGOR211 SURPRISE

Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab) stumbled in May this year when the company's confirmatory Phase III IMvigor211 study in bladder cancer did not meet its primary endpoint. The drug failed to show a survival benefit in patients with previously-treated metastatic urothelial cancer when compared with chemotherapy. The result was a surprise as the drug had been granted accelerated approval by the FDA in 2016 for bladder cancer patients who had or were being treated with platinum-based chemotherapy, based on data from the IMvigor210 trial.

IMvigor211 is the first randomized Phase III study of Tecentriq compared with chemotherapy in people with advanced bladder cancer who were previously treated with a platinum-based chemotherapy. The study evaluated the efficacy and safety of Tecentriq compared with chemotherapy (vinflunine, paclitaxel or docetaxel) administered every three weeks in 931 people with previously-treated metastatic urothelial cancer who progressed during or following a platinum-based regimen.

Roche said at the time of the IMvigor211 failure that "while these results are not what we had expected, we believe that Tecentriq will continue to play an important role in the treatment of people with advanced bladder cancer."

Tecentriq has a second confirmatory study, IMvigor130, ongoing to complete conditional approval of the drug for first-line bladder cancer patients who are ineligible for cisplatin chemotherapy. Topline results from the IMvogor130 trial are expected in 2019.

The drug won approval in Europe in 2017 for locally advanced or metastatic bladder cancer after prior platinum-containing chemotherapy or for patients who are considered cisplatin ineligible. But the bladder cancer market is more competitive now than ever before and Tecentriq's limited effect in the IMvigor211 trial will set it back compared to other approved PD-1/PD-L1 therapies.

Bavencio, **Merck KGAA/Pfizer Inc.'s** PD-L1 inhibitor, was granted US accelerated approval in second-line advanced or metastatic urothelial cancer on May 9, 2017, shortly after AstraZeneca's Imfinzi gained its first approval, for the same indication on May 1, again in the US. Keytruda was approved on May 18 in the US for first-line patients who are ineligible for cisplatin-containing therapy, and (with a breakthrough designation) patients with disease progression on or after platinum-containing chemotherapy. Keytruda also won expanded approval for the same indications in Europe this year.

KEYTRUDA STUMBLE

Furthermore, in July this year, Merck's Keytruda suffered a setback when it failed to show a survival benefit in the KEYNOTE-040 study of head and neck cancer. This trial was meant to produce confirmatory data for Keytruda, which had already received accelerated approval in the US as a second-line treatment for patients with head and neck cancer.

Despite the endpoint miss in KEYNOTE-040, Merck does not expect a label change for Keytruda in the US because median overall survival (OS) for the anti-PD-1 drug in the study of recurrent or metastatic head and neck cancer was still better than investigator's choice of chemotherapy.

However, similar to Roche's predicament in bladder cancer, Keytruda is competing against BMS's *Opdivo* in head and neck cancer, which already has full FDA approval in the same second-line patient population.

END OF ROAD FOR TWO HCV COMBOS

This year also saw **Johnson & Johnson** and Merck discontinue their interferon-free regimens for chronic hepatitis C (AL-335/odalasvir/simeprevir and uprifosbuvir/ruzasvir/grazoprevir, respectively) because of a lack of clinical differentiation from currently available options and rapid contraction of the HCV market.

Dropping these treatment regimens stung for both pharmas as they previously invested in multi-billion-dollar deals to acquire viable combinations.

J&J company **Janssen** suspended development of its triple combination therapy, known as JNJ-4178, in Sept., also ending its development partnership with **Achillion Pharmaceuticals Inc.** for the combination treatment.

The companies said at the time that ongoing Phase II studies with JNJ-4178 would be completed as planned, but there would be no additional developments thereafter. As a result of the termination of the Janssen agreement, Achillion will not receive any future milestone-based or royalty payments and Janssen will not bear the future costs of developing and commercializing the HCV portfolio. Achillion currently has no plans to advance the HCV program on its own.

The combination had previously reported promising Phase II data indicating potential for a six-week duration of treatment. But Janssen is moving away from HCV drug development due to the efficacy of what's already available to patients – particularly **Gilead Sciences'** sofosbuvir-driven portfolio. Gilead is effectively the only HCV company with a nucleoside polymerase inhibitor in its portfolio now that J&J and Merck have stepped back from the space; its sofosbuvir product is marketed as *Sovaldi* as a monotherapy and is the backbone of the combination treatments *Harvoni*, *Epclusa* and *Vosevi*.

Janssen and Achillion joined up in May 2015 to develop JNJ-4178 as part of a worldwide license and collaboration arrangement. Under the original deal, Achillion received $225m equity investment from J&J's venture arm, **Johnson & Johnson Innovation - JJDC Inc.** Achillion was also eligible for up to $900m in milestones and double-digit royalties.

Meanwhile, Merck announced in Sept. that it was ending development efforts for its HCV pipeline, which was driven by nucleoside polymerase inhibitor MK-3682 (uprifosbuvir); the centerpiece of the New Jersey pharma's $3.9bn buyout of **Idenix Pharmaceuticals Inc.** in 2014.

Eliav Barr, Merck senior VP for global clinical development for infectious diseases and vaccines, said at the time that the number of treatment options available for HCV, along with a review of clinical data for Merck's two-drug and three-drug next-generation combinations, resulted in the pharma determining it would not continue investing in development of further regimens.

This decision ended work on the two-drug MK-3682B regimen, which included uprifosbuvir and ruzasvir (a follow-on to Merck's NS5A inhibitor elbasvir), as well as a three-drug regimen including those two compounds and Merck's protease inhibitor grazoprevir.

A ROUGH YEAR FOR CANCER VACCINES

The year of 2017 was not kind to cancer vaccines, a very tough development space. Studies of **Argos Therapeutics Inc.**'s pivotal trial of the dendritic vaccine rocapuldencel-T in metastatic kidney cancer and **Agenus Inc.**'s Prophage G-200 in a National Cancer Institute-funded Phase II study of glioblastoma were both recommended for early termination in February, due to the unlikelihood of improving overall survival. Argos, however, decided to press on with its study, called ADAPT. September brought news that **Bavarian Nordic AS**' e Phase III PROSPECT study of the prostate cancer vaccine *Prostvac* (rilimogene galvacirepvec) in metastatic castration-resistant prostate cancer, was recommended for early termination due to futility, sending the firm's share price down more than 48%.

QUESTIONING REGENERON

Regeneron Pharmaceuticals Inc.'s announced in November that it was scrapping its ophthalmic combination of nesvacumab and *Eylea* (aflibercept) after data showed no improvement over Eylea alone in two Phase II studies, one in diabetic macular edema and the other in wet age-related macular degeneration. The news caused investor to question the company's long-term growth potential beyond Eylea.

The next key catalyst is the release of results from the Phase III PANORAMA study of Eylea in diabetic retinopathy, which are due in the first half of 2018.

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Tackling RWE Challenges To Demonstrate Healthcare Value

Real world evidence (RWE) is expected to have a significant impact on how healthcare technologies will be developed and consumed and on biopharmaceuticals, in particular. The major challenge to RWE becoming truly embedded in the healthcare continuum is that there is still not common ground about what counts as relevant data.

Much of the debate across the healthcare continuum continues to focus on value and value frameworks in the US and health technology assessments in a regulatory context and reimbursement content, ex-US. Different stakeholders – whether producers, payers or patients – may pick and choose which real world data points they wish to emphasise and then convert into RWE. Fortunately, there is a growing body of evidence highlighting how companies are overcoming these challenges and embracing RWE.

Real world data (RWD), the underlying data supporting the generation of RWE, encompasses all information generated in routine medical practice such as electronic health and medical records (EHR), claims data, pharmacy data, and clinical outcomes assessments. It also includes epidemiological data, registry data, health survey data, plus a host of new forms of information such as social media data, wearables-derived data, sensor and behavioural data.

Large scale computational power to apply against RWD is becoming increasingly affordable and accessible to all stakeholders. As such, this creates greater opportunities for real world insights into patient behaviours, treatment costs and drug performance.

The US Food and Drug Administration defines RWE as evidence generated from real world data in a highly pragmatic way. One of the main arguments in favour of using real world data is that clinical trials are often too narrow, excluding too many people and are not pragmatic enough. Consequently, trials have been conducted that do not represent how the drug might perform in a real world setting.

The Salford Lung Study is a much cited example of a real world effectiveness trial in that it demonstrated a higher magnitude of effect in the real world than had been seen in a randomized controlled trial. Conducted in 75 general practices in and around Manchester in the UK, and sponsored by UK pharma GSK, the study com-

pared the effectiveness of fluticasone fluorate/vilanterol to maintenance therapy in treating patients with chronic obstructive pulmonary disease (COPD). Published in the New England Journal of Medicine in September 2016, the study found that the rate of moderate or severe COPD exacerbations was significantly lower by 8.4% with the therapy than with standard care.

Large scale computational power to apply against RWD is becoming increasingly affordable and accessible to all stakeholders.

Other trials that have an RWE component are already in the works. Sanofi, the French pharma major, is sponsoring ACHIEVE CONTROL, an observational study enrolling 3,324 patients and due for completion in July 2018. The study is designed to assess the clinical and health outcomes of Toujeo (insulin glargine) compared to commercially available basal insulins for initiation of therapy in insulin-naïve patients with uncontrolled Type 2 diabetes. The key metric will be the proportion of patients with individualized HbA1x target attainment at six months without documented hypoglycemia.

Novartis, the Swiss pharma, is sponsoring PANGEA 2.0 an observational study involving 1,500 patients that is due to complete in March 2020. The study has been designed to examine the long term benefit of switching multiple sclerosis patients with disease activity, following treatment with currently available drugs, to Gilenya (fingolimod). Therapeutic efficacy of the switch will be evaluated by modified Rio score, NEDA-4 and 2D focussed disability score. PANGEA 2.0 will also assess new forms of data acquisition and the predictive power of proposed treatment using the MSDS 3D patient management system.

RWE is being used in different forms by regulatory authorities. Pharmacovigilance is a mandatory requirement from several regulatory authorities and that, in most cases, is based on real world data. Regulators are increasingly asking for commitments from drug developers for post-marketing safety studies as a condition to product registration and approval. Indeed, the FDA has made progress on using RWE within rare disease drug development and post-market safety surveillance. It has been used, for example, to support the approval of New Drug Application (NDA) submissions for rare diseases or in small population settings.

A study published in the Journal of the American Medical Association (JAMA) 9 May 2017, highlights the importance of post-approval surveillance of safety issues. The study examined 222 novel drugs and biologics approved by the FDA between 2001 and 2010 and noted that there were 123 post-marketing safety events – 59 safety communications, 61 boxed warnings and three outright product withdrawals – impacting 71 new therapeutics.

Regulators and policymakers are starting to look at how to incorporate RWE in product assessments. The US 21st Century Cures Act requires the FDA to develop guidance for using RWE to support approvals of new indications for existing drugs and post-approval study requirements. In the US, the FDA published final guidance on the use of RWE for regulatory decision making for medical devices in August 2017 and has announced plans to publish draft guidance on the use of RWE for the assessment of safety and effectiveness in regulatory submissions before the end of 2021.

Similarly, the European Medicines Agency (EMA) adaptive pathways program, in principle, embraces greater use of RWE to support conditional approval and/or expansion of indications once a product is initially approved in a narrower population.

Indeed, in a bid to provide patients access to innovative but often expensive medicines – usually cancer drugs – a number of European countries have introduced managed entry agreements. These can take many different forms although finance-based schemes are more prevalent than performance-based ones. Finance-based MEAs range from simple discounts to more nuanced price and volume caps. Performance-related MEAs, most frequently used by Italy, are designed to determine refunds for non-responders and involve patient registries managed by the Italian Medicines Agency (AIFA) to allow sharing other clinical information and safety data between regulators, clinicians and pharmacists.

Real World Examples

Several drugs have been approved with real world data. Amgen used RWE to supplement a clinical trial of Blincyto (blinatumomab), its drug which received accelerated approval from the FDA in December 2014 for treatment of acute lymphoblastic leukemia. Amgen submitted a single study as well as a historical comparator arm of patients who received standard of care as the control arm. The company reported a significant treatment response in the Phase II single arm study and two years later, when publishing its Phase III randomized, open-label TOWER study, obtained the same median overall survival of 7.7 months for Blincyto versus 4 months for standard of care.

Similarly, Alexion Pharmaceuticals Inc managed to secure an extension to the label from the European authorities when investigators used a disease registry to obtain a comparator group to measure the efficacy of Soliris (eculizumab) as a treatment of paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis. Initially, the drug's use had been restricted to patients with a certain disease severity.

Novo Nordisk is investing significant effort in generating RWE to support its diabetes franchise. RWE from a post-marketing study conducted by but requested by the French authorities for the GLP-1 agonist Victoza helped broaden the product's label to an additional patient subgroup in Quebec. Moreover, the Danish pharma believes two RWE-generating studies around the long acting insulin Tresiba, launched in Europe in 2013 and in 2016 in the US, both highly competitive and price-sensitive markets, will strengthen the company's positon in pricing negotiations, beef up its marketing communications and enhance its value dossier in markets where the product has yet to launch.

While much of the focus is on using RWE to get regulatory approval of drug applications, it can also be used for clinical practice guidelines to decide how to best manage patients, for payers deciding whether to pay for a drug, and for comparative effectiveness.

Highlighting The Value Proposition

Eli Lilly & Co used real world data to size the single-use vials for its recently launched IV cancer drug Lartruvo (olaratumab) in an effort to reduce potential waste and cost of treatment. An analysis of population-based weight and body surface data, from more than 240,000 oncology patients, informed the decision to develop a 190mg vial alongside the original 500mg Lartruvo vial. The company reckons the trade-off is a cost reduction of $1,132 per patient per administration.

Japan's Takeda says RWE has confirmed the benefits of its best-selling inflammatory bowel disease therapy Entyvio (vedolizumab) in US medical practice. RWE collected in the US conformed the efficacy of the drug, first launched in the US in 2014, as a treatment of ulcerative colitis (UC) and Crohn's disease. The company believes the Entyvio RWE will help the IBD community decide on the drug's role in their medical practices.

Indeed, the VICTORY (vedolizumab for health outcomes in inflammatory bowel diseases) consortium of ten IBD medical centers reported on a cohort of 180 patients with moderate to severe active UC, who were treated for 12 months in routine practice, and followed through electronic medical record searches, review of clinical records or by questions addressed to the centers. Some 77% of patients achieved mucosal healing, defined as having a Mayo endoscopic subscore of zero or one, while 51% of patients had a clinical remission and 41% had a steroid-free remission.

Defending Optimal Pricing

While RWE does not guarantee access, it is clearly having an impact on the thinking of payers. Indeed, RWE originating from, for example, patient registries, EHRs, claims data or cohort studies, is likely to become an increasingly important means of supporting innovative pricing and outcomes-based contracting strategies, proving the value of medicines to payers, potentially improving the probability of winning reimbursement.

Following a health technology assessment (HTA), NICE, the National Institute for Health and Care Excellence, who is responsible for assessing that the National Health Service of England and Wales is getting value for its money, changed its mind and decided to recommend Johnson & Johnson's Zytiga (albiraterone acetate) for chemotherapy-naïve metastatic castration-resistant prostate cancer patients after the company presented RWE from US insurance claims data.

Many managed entry agreements or risk sharing deals in Europe rely on gathering real world data. France agreed to reimburse Celgene Corp.'s Pomylast (pomalidomide) for multiple myeloma under a risk-sharing scheme. The company will have to repay the cost of the drug if a patient does not respond to the treatment. Risk-sharing schemes are also in place elsewhere in Europe, while a recent evaluation of NICE submissions has revealed that RWE drives HTA approval in 86% of submissions.

Regulators are increasingly using RWE to monitor any post-approval safety concerns. This has been particularly useful when looking at novel anticoagulants especially when compared with industry mainstay warfarin. In recent years, more than 100 observational studies have been published on real world use of anticoagulants. In the US, these have typically used claims databases from Medicare and Medicaid, while the European studies have relied upon national databases. Importantly, it appears that the anticoagulants behave in the real world as they did in clinical trials.

One huge potential source of data is the FDA's Sentinel program which houses electronic health care data for more than 223 million individuals – about half the US population -- from health plans, health care systems and academic medical centers. Moreover, the number of individuals in the network will increase in the coming years with the addition of data from the Centers for Medicare and Medicaid Services. Indeed, the large and growing number of patients covered by the US FDA's Sentinel electronic data network offers drug sponsors looking to satisfy post-market safety requirements using real world data an extensive data set. Having participated in a pilot program, Pfizer also noted the potential to look beyond post-approval safety signals. The company noted that Sentinel could also be used to conduct drug utilization studies to look at off-label uses as well as questions around appropriate use.

Not surprisingly, Boehringer Ingelheim has used real world data to build its case for its direct thrombin inhibitor Pradaxa (dabigatran), the first of the new gen-

eration of anticoagulants. The company has enrolled 34,500 patients in the GLORIA-AF study and plans to include a total of 56,000 in the registry. So far, the company has been running observational studies but is considering ways of doing prospective pragmatic trials in the future. Possibilities, as the field evolves, include running real world trials to support supplemental indication filings with the FDA.

Pfizer, the world's largest pharma company, is leading the use RWE at almost every stage of a medication's life cycle. The company conducts a significant amount of non-interventional research. For retrospective studies it uses de-identified secondary data sources such as insurance claims and EHRs to evaluate epidemiology, treatment patterns, clinical outcomes, healthcare resource use and costs associated with a treatment of disease. Moreover, patient data generated by wearables, apps or even tapping into social media will become an important source for understanding patient needs and behaviours.

Typically, the company will provide RWE on epidemiology and unmet needs through analysis of secondary data sources and collecting information from patients, physicians and payers. Real world data is also often included in economic models, while supplemental information, such as healthcare resource use, productivity loss and out of pocket expenses, is collected during the running of clinical trials. Following launch, companies may conduct comparative effectiveness research to either identify and understand sub-populations or provide value differentiating evidence.

While there is an expectation that all pharma companies will need to have RWE strategies in place, one of the biggest roadblocks in using RWE for regulatory purposes is the inadequate data in electronic healthcare records (EHR). This is because the traditional outcome measures that are used in conventional drug development are not generally found in EHRs. The challenge is that much of the needed clinical information is stuck in the doctor's notes as unstructured data. Advances in machine learning and natural language processing are expected to provide some resolution to this challenge and enable practitioners to mine the gold buried deep within unstructured clinical notes within EHR.

Moreover, as most sources of real world data are not actually collected for research purposes, data quality is an issue. EHRs, for example, are primarily intended for patient management, rather than for research, and there is a clamour for more alignment across all stakeholders to develop consistent data structure and gathering methods. Indeed, transitioning from an ad hoc to an industrial approach to curating RWE will require collaboration and investment from all stakeholders. Regulators, in collaboration with the pharma industry and payers, still need to formulate robust standards for RWD collection from a variety of sources.

Motivating this are are manufacturers, payers and third parties, who are looking beyond their own walls to establish the true value of medicines. Most value-based contracts to date have been bilateral and payer population-specific, where the manufacturer and the payer share data. An alternative option would be to include broader sets of relevant RWD – including data generated by third parties – into the parties' value-contract adjudication calculations. This would have stakeholders seeking out additional appropriate sources of data to analyse, not necessarily just a specific payer's population, but an even larger representative real world population set in order to reduce administration costs and potential conflicts.

While such data sharing for value-based contract administration purposes is not commonplace, industry has long been quite content to use third-party generated data to administer prescription market share-based contract. Indeed, reliable and independent third party data can be important in subsequent value-based contract negotiations.

RWE clearly has huge potential to inform healthcare stakeholders – whether manufacturers, regulators, clinicians, patients or payers. While there are still multiple challenges with RWE becoming a consistent mainstay of the healthcare regulatory oversight and commercial performance insight, it is clear that there is an appetite among all stakeholders to resolve them. Big data capabilities and linkage of data sources will drive an increased development and application of real world evidence.

Michael Pace, Senior Principal, Pricing and Market Access, Commercialisation and Outcomes, ICON plc.

Mike has over 20 years of executive experience with global biopharmaceutical firms and digital health start-up ventures, leading commercial strategy, payer and specialty pharmacy account management, market access contracting and operations, sales, sales training and leadership development functions. At EMD Serono, he instituted the outcomes-based contracting effort that led to the first outcomes-based agreement on a specialty medication with a health plan, followed by the first outcomes-based agreement with a pharmacy benefit manager in the United States.

Jim Carroll, Vice President, Real World Evidence, Commercialisation and Outcomes, ICON plc.

Jim Carroll leads ICON's Real World Evidence Strategy & Analytics group, which develops real world data (RWD) and technology based solutions to support sponsors who are seeking to expand labelling and market access, while staying ahead of the growing demand for evidentiary requirements. Jim has over 20 years' CRO and pharmaceutical experience. He joined ICON from inVentiv Health, where he led the formation of a new business unit focused on providing novel RWD-driven services.

The Return Of The US Pharma Sales Force

JESSICA MERRILL jessica.merrill@informa.com

The steady US sales force decline that began a decade ago is reversing, driven by growth in oncology, although the number of sales reps in the US remains well below the peak level of the primary care blockbuster era.

Data from the consulting firm ZS Associates and PharmaForce Deployment Analyzer show the number of pharma sales reps in the US grew significantly in 2016 year-over-year and held steady in the first part of 2017. There were more than 70,000 pharma sales reps in the US in 2016 for the first time since 2011, the year **Pfizer Inc.**'s crown jewel *Lipitor* (atorvastatin) went generic.

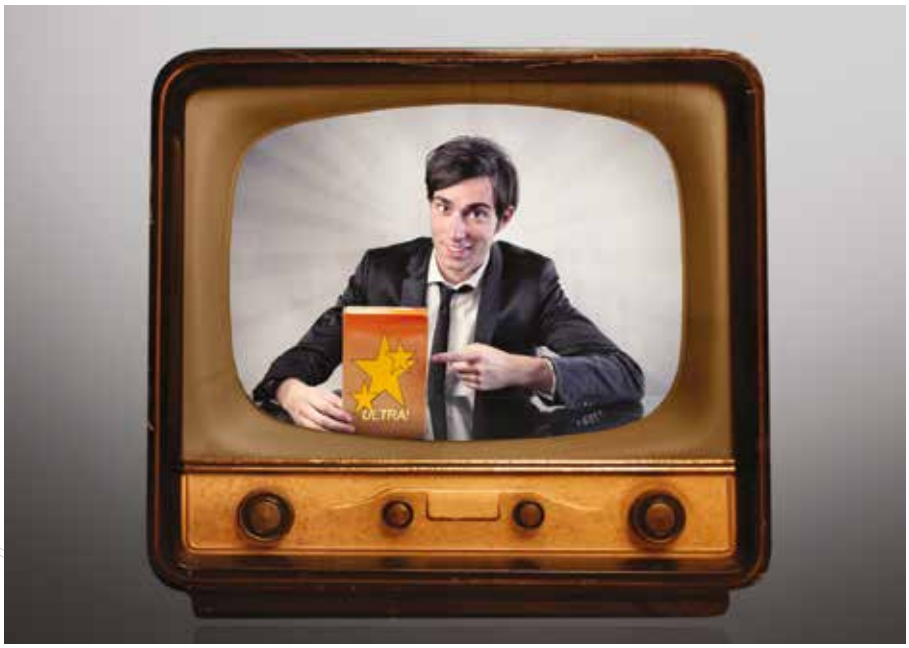
In the first half of 2011, there were more than 75,000 sales reps in the US, but the number declined to 65,000 by the end of that year; the decline continued until 2014, when there were around 55,000 pharma sales reps in the US, according to the ZS/PharmaForce data. Pharma companies began cutting their promotional spending, particularly the size of their commercial sales teams, in 2012 as the commercial mix of products changed and as companies turned more focus to programs like copay assistance and market access strategies.

By the end of 2014, the number of reps in the US had begun edging up again to about 61,000 reps, and the momentum continued.

"It almost sounds like back to the world of Lipitor and *Plavix*," joked ZS Managing Partner Pratap Khedkar in an interview. But of course, it's not the world of Lipitor and Plavix. It is the world of *Opdivo* and *Keytruda*. Thus, it's not too surprising that the number of sales reps in the US is still 31% lower than in the peak of 2005, when there were more than 100,000 US pharmaceutical sales reps.

The challenges for commercial teams are also different today, as the growth is coming largely from oncology, not primary care, and while access to physicians is generally challenging, it is particularly difficult to reach oncologists.

Access to physicians has declined considerably since 2009, according to ZS' AccessMonitor, which evaluates data from thousands of physicians. Only 46% of physicians are considered accessible to sales reps in 2017 compared to 51% in 2014 and 65% in 2012. The numbers are even more striking when it comes to oncology, where only 24% of physicians were considered accessible in 2017 compared to 80% in 2009.



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Only 46% of physicians are considered accessible to sales reps in 2017; the numbers are even more striking when it comes to oncology, where only 24% of physicians were considered accessible in 2017 compared to 80% in 2009

"Oncologist access is down to 25%, which means 75% of the time the rep can't get in when they want to," Khedhar said.

In oncology, drug makers tend to organize their sales force around a product, or in some cases even by indication. But as companies add new cancer drugs or as the products add new indications it could put more pressure on access, according to ZS.

"There are only 12,000 oncologists in the US," Khedhar said, "so all of those sales forces have to talk to the same doctors."

Consider that in the PD-1/L1 space alone there are currently five approved drugs and another 20 in development, and it is clear the promotional market is going to become saturated. "Oncologists are going to say no way," Khedkar said.

Data shows that oncologists are more willing to speak to sales reps when a new drug is approved. The steepest access declines in the last six years correspond with gaps in new launches.

Another age-tested pharma promotional vehicle is also on the rise – direct-to-consumer advertising. Spending by pharmaceutical companies on DTC advertising has rebounded to levels not seen since 2006.

But pharma companies are also exploring ways to reach consumers beyond their living room and at the point of care in physicians' offices. Pharma is investing about $800m in point-of care promotions in doctors' offices and hospitals, according to ZS.

"The point is if you are sitting on your couch watching TV, the odds are you aren't even going to see a doctor for months, but here it is actually hitting you when you are in that healthcare mode," Khedhar said.

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Millendo Gets European Foothold With Alizé Acquisition

KEVIN GROGAN kevin.grogan@informa.com

After pulling the plug on one investigational endocrine disorder therapy last month, **Millendo Therapeutics Inc.** of the US has got hold of another one – for unrelenting hunger – through its acquisition of France's **Alizé Pharma SAS**.

In the all-stock deal, Millendo has gained Alizé's livoletide, which demonstrated positive Phase II results last year in reducing hyperphagia, or insatiable hunger, in patients suffering from the rare genetic disease Prader-Willi Syndrome (PWS). Livoletide is an analog of unacylated ghrelin, commonly known as the 'hunger hormone' and the companies claim it has the potential to be a first-in-class treatment for PWS, the most common form of genetic obesity, which has an estimated prevalence of one to nine per 100,000.

Livoletide has been granted orphan drug designation in PWS, which is caused by the lack of expression of several genes on chromosome 15, by the FDA and has received a positive opinion from the European Medicines Agency for orphan drug status.

Livoletide will help fill the gap in Millendo's pipeline left by the recent decision, made with almost no fanfare, to cull MLE4901, a drug acquired from **AstraZeneca PLC** in January 2016 for polycystic ovary syndrome (PCOS). Earlier this year, Millendo presented positive Phase II data on the therapy for the treatment of menopausal hot flashes but the firm said last month that it had decided to discontinue development of MLE4901 "after assessment of the clinical risks and benefits of the program."

The axing of MLE4901 meant that Millendo just had one product in development, nevanimibe. A Phase IIb study of the drug is scheduled to begin next year for classic congenital adrenal hyperplasia and the treatment, a selective inhibitor of acyl-CoA:cholesterol acyltransferase 1 which is codenamed ATR-101, is also in Phase II for Cushing's syndrome and Phase I for adrenocortical carcinoma.

Now, with the acquisition of Alizé, Millendo has "two first-in-class, late-stage clinical assets and a presence in both the US and Europe," CEO Julia Owens told *Scrip*. She noted that the plan was to build a fully integrated company in endocrinology and she feels that "we can create significant value by ultimately marketing our products, at least in the US and potentially Europe. Our focus on endocrine diseases is appropriate for that as a modest-sized sales force can cover the necessary physician population effectively."

That said, Owens added that, "We will remain open to partnering as a core function for the company, though more likely for other territories when it comes to commercial rights to our programs. We also remain active in seeking new partnerships for programs that can be added to our pipeline."

She went on to say that based on the intent to be a fully integrated company, "having a European presence was a natural step and one we would have taken anyways in the next few years." Owens pointed out that "we have been conducting clinical trials in Europe for years and have worked closely with groups like the European Network for the Study of Adrenal Tumors. Extending that to having a R&D team in Europe will facilitate those activities and set us up for further expansion of our work in Europe."

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Summit Completes 2017 With Discuva Buy

JOHN DAVIS john.davis@informa.com

The Nasdaq and AIM-listed UK biotech **Summit Therapeutics PLC** announced the day before Christmas Eve that it was acquiring fellow UK company, **Discuva Ltd.**, and that company's antibiotics discovery platform for finding novel mechanisms of action.

Privately-held Discuva was bought for a mix of cash and shares, £5m ($6.7m) in cash and £5m in new ordinary shares of Summit, which is unlikely to unduly stretch Summit's finances. Following the acquisition, the University of Oxford spin-out says its cash runway remains at just over 12 months, with its cash and cash equivalents able to fund the company's activities through to Dec. 31, 2018.

Discuva has a proprietary bacterial genetics-based platform that facilitates the discovery and development of novel differentiated antibiotics, combining transposon technology with bioinformatics to create a platform for discovering new antibiotics. The company was targeting the ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* sp.) pathogens that represent the leading cause of multi-drug resistance and hospital-acquired infections.

The acquisition also brings with it Discuva's 2014 development agreement with the big pharma company, **Roche**. The Swiss multinational had an agreement with Discuva under which it would pay development, commercialization and sales milestone payments on any compound developed using the Discuva technology that is, or has been, optioned by Roche. The agreement involved the development of new antibiotics to treat life-threatening infections caused by multi-drug resistant Gram-negative bacteria using Discuva's proprietary Selective Antibiotic Target IdentificatioN (SATIN) technology.

The acquisition of Discuva underlines a renewed sense of confidence at Summit Therapeutics, which secured a US BARDA contract worth up to $62m in the third quarter of 2017 to support, in part, the Phase III development of one of its two lead products, the "precision antibiotic" candidate, ridinilazole. Summit also raised £14.9m ($20.1m) in a follow-on public offering of American Depositary Shares in September 2017, and announced it had licensed Latin American rights to ridinilazole to Brazil's **Eurofarma Laboratorios SA** on Dec. 21, 2017, for $2.5m up front and up to $25m in milestones.

The initiation of a Phase III clinical program for ridinilazole, involving two clinical studies, is expected in the first half of 2018.

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AstraZeneca's Pipeline Reaps Rewards Of Return To Science

ALEX SHIMMINGS alex.shimmings@informa.com

A year of "unprecedented" activity and a Phase III pipeline brimming over with products allowed **AstraZeneca PLC** to claim at an R&D day on Dec. 14 that its focus on science in the five years since CEO Pascal Soriot arrived has changed the culture of its business.

Sean Bohen, chief medical officer and EVP of global medicines development told analysts that the sheer number of positive results announced during 2017 "really outweighed the number of unfavorable outcomes", namely MYSTIC's PFS results for PD-L1 inhibitor *Imfinzi* (durvalumab), the complete response letter for hyperkalemia treatment ZS-1 and the Phase III failure of asthma product tralokinumab.

High points of the year were the FLAURA trial of *Tagrisso* (osimertinib), Imfinzi's PACIFIC study and the launch *of Fasenra* (benralizumab). Looking forward to 2018, the company is expecting data readouts for *Farxiga* (dapagliflozin; the DECLARE outcomes study), roxadustat (Phase III), PT010 (Phase III) and anifrolumab (Phase III), while it also continues to advance its oncology lifecycle programs for *Lynparza* (olaparib), Tagrisso, Imfinzi and *Calquence* (acalabrutinib). See table on page 24 for AstraZeneca's expected late-stage pipeline news flow next year and into 2019.

"Developing medicines for patients is high risk, high reward, and occasionally you will encounter disappointment. However, this year, we were rewarded with an extensive list of successes across all the main therapy areas following the science that's truly rewarded AstraZeneca this year, and we hope to continue our success in 2018 and beyond," Bohen told analysts. "This is a clear illustration of the improvement in AstraZeneca's R&D productivity and just how the culture of our business has focused on science in the last five years."

In support of his premise, Bohen pointed to the number of US FDA breakthrough therapy designations granted in 2016 and 2017 – five in total. "We rank well compared to the rest of the industry when we look at our three main therapy areas."

All this is resting on increased success rates in early stage development, he added, and this "underpins our confidence that the productive pipeline is sustainable for years to come." AZ has nearly tripled the number of its scientific publications since 2010 and "the number of high-impact publications continues to grow."

Indeed, the brisk pipeline pace set in 2017 is set to continue next year when the company is hoping to return to sales growth, mainly driven by its oncology portfolio. Further out, observers say, earnings are also set to gain momentum. "On a revenue basis, 2017 should be the trough, but EPS may not begin to grow until 2019," said Tim Anderson at Bernstein in a Dec. 14 research note, adding that in the longer term, EPS growth should be among the very best of the nine major EU/US pharmaceutical companies the analysts cover.

But this also means the firm should be wary. "If industry consolidation occurs, between AstraZeneca's full Phase III pipeline, its superior growth and its comparatively smaller size, it could be a take-out candidate," he added.

Natixis analysts also see 2018 as a transition year, owing to the impact of *Crestor* generics and the fact that new replacements Imfinzi and Tagrisso are "just ramping up". They also said in a Dec. 15 research note that they do not expect to see any real uptick in EPS until 2019, when they expect it to rise by 14%.

ONCOLOGY RICHES

Overall, oncology will remain the key focus of AstraZeneca's three major therapy areas, which also include cardiovascular/metabolic and respiratory, but Bohen also highlighted interesting candidates for Alzheimer's disease (lanabecestat) and lupus (anifrolumab). "Pipeline opportunities that often get overlooked."

Within oncology, the anti-PD-L1 immuno-oncology product Imfinzi will stay front and center. The company is sanguine, in public a least, about MYSTIC's ultimate prospects – slating a second-half filing in first-line lung cancer, following the overall survival results in H1 – although little further was said about it during the R&D day.

Some analysts believe this reticence told its own story. Analysts at Bernstein pointed out that the company's refusal to be drawn on whether a separation could be seen in the PFS curves even without a significant difference bodes ill. "**Bristol-Myers Squibb Co.** was willing to disclose PFS data on its '214, ahead of having OS data, so why not AstraZeneca? A logical inference would be that there was no curve separation," they said.

Natixis analysts were a little more optimistic. "We still think these results could be positive. That said, we may be more cautious on the addressable patient population," they said. "Indeed, based on recent developments in immuno-oncology (IO) we think that while IO+chemo combinations show efficacy in all patients (PD-L1 positive and negative), this is less sure for IO+IO combinations like Imfinzi + tremelimumab tested in MYSTIC."

This means, they added, that there is a possibility that these final results will show efficacy in patients with a PD-L1>25%, which would limit the number of target patients to 40% of the addressable population, i.e. close to 125,000 patients, or peak sales of around $2bn.

For PACIFIC however, AstraZeneca expects a regulatory decision in the US in the first half, followed by the EU and Japan in the second for Imfinzi in locally advanced or Stage 3 unresectable non-small cell lung cancer following standard chemoradiation therapy.

AstraZeneca says there are an estimated 105,000 patients in Stage 3 lung cancer, of which about 76,000 are unresectable. "This is a meaningful opportunity and one that matters a lot for patients and their caregivers," Bohen said. "We continue to see the PACIFIC trial two years to three years ahead of competition in the Stage 3 setting."

Further clinical readouts for Imfinzi in other indications, such as bladder, liver and head and neck cancers, but these markets

are much smaller than for lung cancer. The product is also being tested in combination with and IDO1 inhibitor epacadostat, and other lifecycle opportunities are being evaluated.

Following the success of FLAURA of the next-generation EGFR inhibitor Tagrisso in NSCLC the company is looking forward to regulatory decisions on the expansion of its indication to include the first-line EGFR-mutated NSCLC setting. Filings have recently been made in the EU and Japan, with the US expected soon. Overall survival data are still awaited from this study, however, but it is difficult to give guidance as events are slow to accrue and patient crossover is occurring, Bohen told analysts.

Tagrisso is currently on the market for use in second-line T790M-mutated NSCLC patients and performed strongly in the third quarter.

AstraZeneca's PARP inhibitor Lynparza features heavily in its pipeline plans. The company presented data from the Phase II basket trial MEDIOLA at the World Congress on Lung Cancer meeting in October.

The data from the small cell lung cancer population showed that the Lynparza plus Imfinzi combination was well-tolerated compared with historical data on topotecan, the current standard of care for the second-line setting. Furthermore, the duration of response and overall survival data exceeded those previously reported with topotecan. "All responses occurred prior to the addition of Imfinzi, suggesting that the initiation of these responses was driven by Lynparza. Interestingly, the median overall survival data suggest that Imfinzi, or the combination, may have long-term efficacy potential, even in patients who lack an objective response," Bohen said.

Further MEDIOLA data reported at the San Antonio Breast Cancer Symposium showed Lynparza and Imfinzi were well tolerated in the germline BRCA-mutated metastatic breast cancer population. "The objective response rate was 52% and a little lower than what we observed in the OlympiAD trial. But this may have been due to later line of therapy and smaller sample size," said Bohen.

AstraZeneca sees significant opportunity to expand Lynparza through its collaboration with **Merck & Co. Inc.** and the two companies have agreed development plans and more trials are expected to be announced in the first half of next year. In October, AstraZeneca gained a US approval of its BTK inhibitor Calquence, in a "reasonably small indication", namely previously-treated mantle cell lymphoma (MCL). The company estimated that around 3,000 patients are diagnosed with mantle cell lymphoma each year in the US. It has just presented the MCL data at the American Society of Hematology Meeting, "along with a couple of chronic lymphocytic leukemia trial updates in monotherapy and in combination with GA101, or obinutuzumab, where Calquence demonstrated early efficacy signals along with good tolerability". The major Phase III data for its use in the larger chronic lymphocytic leukemia indication study are not due until 2019.

'If industry consolidation occurs, between AstraZeneca's full Phase III pipeline, its superior growth and its comparatively smaller size, it could be a take-out candidate'

CARDIOVASCULAR

In the cardiovascular/metabolic arena, AstraZeneca says it is "taking a holistic approach". Foremost here are the plans for the SGLT2 inhibitor for diabetes Farxiga and its cardiovascular outcomes study DECLARE due in the second half of next year.

Added to which is the DPAP-HF study in heart failure due in 2019 (although the company wouldn't be drawn on whether an interim analysis would be forthcoming in 2018) and the DAPA-CKD in renal patients in 2020. "We want to stop disease and regenerate organs," Bohen said.

Glossing over the CRL in May for ZS-9 in hyperkalemia, Bohen said: "I want to take this opportunity to remind you of the potential for providing a best-in-class treatment for hyperkalemia, once approved."

It has already had the positive CHMP opinion in the EU and more news in the US will be reported in due course. "We have made significant progress in addressing the deficiencies identified during the FDA inspection of the dedicated facility for ZS-9 in Texas." For its potential first-in-class treatment for anemia and chronic kidney disease and end-stage renal disease roxadustat, AstraZeneca expects data from the Phase III OLYMPUS trial next year in chronic kidney disease patients who are not receiving dialysis. The primary endpoint is to demonstrate a superior hemoglobin increase with a non-inferior MACE incidence over placebo. This is one of a number of HIF prolyl hydroxylase inhibitors approaching the market.

A Chinese rolling regulatory submission is completed, and a US regulatory submission is due in 2H 18.

RESPIRATORY

The US approval of Fasenra in severe eosinophilic asthma was another high point in 2017. Based on the results of the WINDWARD program, the IL-5α receptor inhibitor is under regulatory review in the EU, Japan and several other countries with decisions anticipated in first half of next year.

Next steps are to develop an autoinjector in the GRECO trial for which a readout is expected in the second half of 2018. Then there is the Phase III VOYAGER program looking at Fasenra in patients with severe COPD. For those patients who have an exacerbation history, "it's pretty well established that there's an inflammatory component underlying those exacerbations. And we're looking at benralizumab as a potent agent to reduce that hyperreactivity and inflammation and reduce that risk of exacerbation," said Bohen.

Its other great hope in respiratory area is tezepelumab, particularly since the failure of tralokinumab. The anti-thymic stromal lymphopoietin biologic is the first epithelium-targeting medicine with potential differentiated efficacy in patients with moderate to severe asthma.

In September, along with partner **Amgen Inc.**, AstraZeneca presented the PATHWAY Phase IIb data for tezepelumab at the European Respiratory Society Congress in Milan, which indicated what AZ believes is potential best-in-disease efficacy. First Phase III trial NAVIGATOR has initiated with a patient enrolled. "We will need to see the final Phase III profile, but at this stage, tezepelumab has the potential to be one of the broadest and most promising biologic medicines for the treatment of respiratory diseases."

CONTINUED ON PAGE 24

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Progress should also come next year for AstraZeneca's third major respiratory product, the triple combo PT010 (budesonide/glycopyrronium/formoterol), which is being pursued for both COPD and asthma.

There is a significant unmet need in COPD patients that is well established, with around 40% to 50% of patients treated with inhaled corticosteroid and long-acting beta agonist, receiving an add-on medicine in the form of a long-acting muscarinic antagonist.

"The differentiating factor for PT010 will be the pressurized metered-dose inhaler plus the fast onset of action and the inclusion of budesonide," said Bohen. The data readout is expected to start in the first half of next year, followed by regulatory submissions.

BEST OF THE REST

Outside its core therapy areas, AstraZeneca sees much promise in its lupus therapy anifrolumab and its Alzheimer's disease therapy lanabecestat, a BACE inhibitor.

Based on promising Phase II data, the anifrolumab development program includes an additional precision medicine strategy to best identify which patients will respond better to anifrolumab based on an interferon gene signature test. The product differs from its competition in that it blocks the interferon receptor rather than targeting interferon itself, thereby providing more complete isoform blockade.

Both its Phase III trials, TULIP 1 and TULIP 2, are fully recruited with primary endpoints at 48 weeks, and readout expected in the second half of next year. Regulatory submissions are due in 2019. Looking forward, AstraZeneca has an ongoing Phase II trial with subcutaneous administration, plus an ongoing Phase II trial in lupus nephritis.

But the Natixis analysts said they thought "the group may be tempted to sell this product to a third party, as it does not fit fully with the therapeutic areas it wants to focus on". They estimate anifrolumab to bring in close to $500m in peak sales.

And with **Eli Lilly & Co.**, AstraZeneca is hoping to buck the trend in Alzheimer's with lanabecestat. While acting on BACE, it takes a different approach from other candidates in this field by depleting amyloid beta in cerebral spinal fluid. "We have seen several setbacks with other medicines in this disease," said Bohen. "This is a different mechanism of action than that of the anti-amyloid beta antibodies and is a mechanism underpinned by strong genetic evidence."

The Phase II/III AMARANTH trial for early Alzheimer's disease is now fully recruited. A second Phase III trial, DAYBREAK, for mild Alzheimer's disease, is still recruiting.

The product has a fast track designation and the first Phase III data are expected in 2019. *Published online 22 December 2017*

AZ's Late-Stage Pipeline News Flow In 2018 and 2019

H1 2018	H2 2018	2019
Regulatory decision		
Lynparza - ovarian cancer 2L (EU, JP)-breast cancer (US)	Lynparza - breast cancer (JP)	
Tagrisso - lung cancer (US)	Tagrisso - lung cancer (EU,JP)	
Imfinzi - lung cancer (PACIFIC) (US)	Imfinzi - lung cancer (PACIFIC) (EU, JP)	
	Bydureon BCise - type-2 diabetes (EU)	
Fasenra - severe, uncontrolled asthma (EU,JP)	Bevespi - COPD (EU)	
Regulatory submission		
Lynparza - breast cancer (EU)	Lynparza - ovarian cancer 1L	Lynparza - pancreatic cancer 1L - ovarian cancer 3L
	Imfinzi+ treme - lung cancer 1L (NEPTUNE)	
Imfinzi+/-treme - lung cancer 3L (ARCTIC)	Imfinzi+/-treme - lung cancer 1L (MYSTIC) - head & neck cancer 1L, 2L (KESTREL, EAGLE)	Imfinzi+/-treme - lung cancer 1L (POSEIDON) - bladder cancer 1L (DANUBE)
moxetumomab pasudotox - hairy cell leukaemia 3L	Selumetinib - thyroid cancer	
	Roxadustat - anaemia (US)	Brilinta - CAD2/type-2 diabetes CVOT
		Farxiga - type-2 diabetes CVOT (DECLARE)
	PT010 - COPD	Fasenra - COPD
		Anifrolumab - lupus
Key Phase III data readouts		
Lynparza - ovarian cancer 1L	Lynparza-pancreatic cancer 1L	Lynparza-ovarian cancer 3L
		Imfinzi-lung cancer (PACIFIC) (final OS)
Imfinzi+/-treme - lung cancer 3L (ARCTIC) - lung cancer 1L (MYSTIC) (final OS) - head & neck cancer 1L, 2L (KESTREL, EAGLE)	Imfinzi+treme - lung cancer 1L (NEPTUNE)	Imfinzi+/-treme - lung cancer 1L (POSEIDON) - bladder cancer 1L (DANUBE) - liver cancer 1L (HIMALAYA)
		Brilinta-CAD/type-2 diabetes CVOT
	Farxiga-type-2 diabetes CVOT1(DECLARE)	Farxiga-HF
PT010 - COPD	Fasenra - COPD	
	Anifrolumab - lupus	lanabecestat-Alzheimer's disease

Source: AstraZeneca Late-Stage Pipeline Webcast Dec. 14, 2017

AbbVie's Upadacitinib Aces Another Arthritis Trial, But Safety Concerns Linger

EMILY HAYES emily.hayes@informa.com

AbbVie Inc.'s JAK1 inhibitor upadacitinib succeeded in another Phase III rheumatoid arthritis study – this time as a monotherapy – but concerns persist about cardiovascular safety due to a small number of cases of pulmonary embolism, one fatal, as well as competitive positioning relative to other drugs in the same class.

AbbVie reported Dec. 20 that upadacitinib (ABT-494) met the co-primary endpoint in the Phase III SELECT-MONOTHERAPY study, which tested the candidate in patients with moderate-to-severe rheumatoid arthritis (RA) who did not adequately respond to treatment with methotrexate.

Two different once-daily doses were tested – 15 mg and 30 mg – against methotrexate. Both doses hit the mark on the co-primary endpoint measure at 14 weeks, which included the ACR20 score, meaning a 20% improvement on the American College of Rheumatology disease scale, reflecting improvements in tender and swollen joint counts, and low disease activity.

The two doses also demonstrated significant improvements on all secondary endpoints, including ACR50 and ACR70, meaning a 50% and 70% improvement, respectively.

Upadacitinib is an important drug for AbbVie in preparing for the future beyond its TNF blocker *Humira* (adalimumab). The company has touted upadacitinib and the IL-23 inhibitor risankizumab as highly differentiated, best-in-class agents across a range of immune-mediated conditions, marking AbbVie's progress from one drug to a portfolio of therapies for immune disorders.

The Phase III SELECT program for upadacitinib includes six studies evaluating the drug in more than 4,000 patients with moderate-to-severe rheumatoid arthritis in various treatment scenarios. In addition to SELECT-MONOTHERAPY, two other studies have been positive.

SELECT-BEYOND and SELECT-NEXT tested upadacitinib in moderate-to-severe rheumatoid arthritis patients who did not respond to or were intolerant of biological disease-modifying anti-rheumatic drugs. In addition to rheumatoid arthritis, upadacitinib also is in development for a range of other related conditions, including psoriatic arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis and atopic dermatitis.

On the safety front, AbbVie reported that results in the SELECT-MONOTHERAPY study were in line with previously reported studies and that no new safety signals were detected. The rate of serious adverse events was 5% for the 15 mg dose, 3% for the 30 mg dose and 3% for methotrexate.

However, in the test drug arms, the company also reported two concerning cases in patients with pre-existing cardiovascular risk factors. One patient on the 15 mg dose died after a hemorrhagic stroke caused by a ruptured aneurysm. Another on the 15 mg dose had a pulmonary embolism (PE).

"Across the SELECT rheumatoid arthritis program, including both the placebo-controlled and extension periods, the rate of deep vein thrombosis and PE remains consistent with the background rate for the RA patient population," AbbVie said in a statement about the data.

Pulmonary embolism also was a concern in the SELECT-BEYOND study – two cases were reported and one was fatal. Cardiovascular safety has been a factor holding back **Eli Lilly & Co./Incyte Corp.**'s competing JAK1/2 inhibitor baricitinib, which is due to be refiled with the US FDA in January, following a complete response letter in April that asked for additional safety data. *(Also see "AbbVie's New Generation JAK inhibitor Looks Good But CV Specter Looms" - Scrip, 12 Sep, 2017.)*

Pfizer Inc.'s *Xeljanz* (tofacitinib), a JAK1/2/3 inhibitor, is the first and only in the class approved for rheumatoid arthritis, available on the US market since 2012, and has not been associated with these kinds of cardiovascular events, though it does have a boxed warning for serious and life-threatening infections.

BMO Capital Markets analyst Alex Arfaei said in a Dec. 20 note that the monotherapy data for upadacitinib appear modestly better than baricitinib in the RA-BEGIN study in terms of efficacy and did not alleviate cardiovascular safety concerns.

"We believe these concerns should result in increased regulatory scrutiny, and tempered physician uptake. Moreover, we do not believe [upadactinitib] can significantly displace the well-entrenched Xeljanz, which does not have these safety concerns," Arfaei said.

Arfaei also noted the impact of anti-TNF biosimilars after 2018 in the EU and 2022 in the US and the patent expiry of Xeljanz in 2025 as competitive factors that will put pressure on new JAK inhibitors in rheumatoid arthritis.

The analyst is forecasting risk-adjusted sales for upadacitinib of about $2bn (20%-40% below consensus) by 2023.

Biomedtracker's David Dahan told *Scrip* that the death due to a hemorrhagic stroke and the pulmonary embolism event appear concerning, especially since two cases of PE were reported in SELECT-BEYOND.

"The company notes that the overall incidence of deep vein thrombosis and pulmonary embolism remains consistent with the background rate for the rheumatoid arthritis population suggesting that these cardiovascular events should not derail approval of upadacitinib. However, as results from additional Phase III trials are disclosed any additional cardiovascular adverse events will be monitored carefully," Dahan said.

Leerink Swann analyst Geoffrey Porges, however, found the latest safety results to be reassuring.

Porges views the single fatal hemorrhagic stroke as unlikely to have been drug-related and said that one case of PE "does not seem unusual given the size of the trial, the background rate in this population and AbbVie's disclosure that the patient had pre-existing cardiovascular risk factors."

"We continue to believe AbbVie's upadacitinib program, which is enrolling over 4,500 patients, is sufficiently large to report multiple pulmonary emboli without risking the approvability of the drug," Porges said.

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The Next Challenge: Improving And Predicting Responses As CAR-T Therapies Advance

MANDY JACKSON mandy.jackson@informausa.com

Now that investigators have shown promising efficacy for chimeric antigen receptor T cell (CAR-T) therapies in patients who've run out of options, researchers and biopharmaceutical companies are trying to understand why some patients stop responding while others don't respond at all.

CAR-T cell persistence, loss of the targeted antigen and emergence of treatment-resistant mechanisms are areas of interest. Combining CAR-T therapies with other drugs and developing bispecific CAR-T candidates are among the approaches that are being explored to increase response rates and extend survival. These were hot topics during the American Society of Hematology (ASH) meeting In December, where data for the first two CAR-T therapies approved in the US and several CAR-T hopefuls were presented between Dec. 9 and 12.

Surprising efficacy in relapsed and refractory leukemia and lymphoma patients who previously were treated with multiple lines of therapy led to US FDA approval in August for **Novartis AG**'s *Kymriah* (tisagenlecleucel) and in October for **Gilead Sciences Inc.**'s *Yescarta* (axicabtagene ciloleucel), developed by the recently acquired subsidiary **Kite Pharma Inc.**

Both CAR-T therapies involve the removal of patients' T cells, which are genetically reengineered to target CD19 on cancer cells before being infused back into the patients. But while Kymriah, Yescarta and other CAR-T therapies have shown unprecedented efficacy, there still are many patients whose cancer doesn't respond and some whose disease stops responding after a few months.

"Despite the impressive clinical results, approximately half the patients with refractory or relapsed large B-cell lymphomas will not have a durable response after anti-CD19 CAR-T-cell therapy. The reasons for this variation in response are not completely understood, but a number of strategies are being investigated to enhance the therapeutic efficacy of CAR-T cells against lymphoma," Eric Tran, Dan Longo and Walter Urba wrote in a Dec. 10 *New England Journal of Medicine* (*NEJM*) editorial published on the same day as articles about Kymriah and Yescarta studies.

Tran is an assistant member of the T Cell Response Laboratory, part of the Earle A. Chiles Research Institute within the Providence Cancer Center in Portland, Ore. Longo is an oncologist at **Dana-Farber Cancer Institute** in Boston and a professor at **Harvard Medical School**. Urba is an oncologist and director of research at the Providence Cancer Center.

JUNO HOPES FOR SAFETY, EFFICACY GAINS

Juno Therapeutics Inc. was neck-and-neck with Novartis and Kite in the race to bring a CD19-targeting CAR-T therapy to market, but safety issues for its first candidate JCAR015 put the company two years behind its main competitors.

Juno believes that its follow-on candidate JCAR017 (lisocabtagene maraleucel), which has a 4-1BB co-stimulatory domain rather than CD28, is not only a better product than JCAR015, but could be a best-in-class product based on emerging safety and efficacy data.

"Recent studies have shown intrinsic differences in CAR-T cells that use CD28 rather than other co-stimulatory molecules, such as 4-1BB, but it remains unclear whether either co-stimulatory domain will confer differences in activity or persistence in patients and whether such responses are dependent on the tumor type. Therefore, optimization of CAR constructs and manufacturing as well as combination strategies with immunomodulatory agents are being explored," University of Texas **MD Anderson Cancer Center** Professor Sattva Neelapu, a lead investigator for the ZUMA-1 clinical trial that supported approval for Gilead/Kite's Yescarta, and colleagues wrote in a Dec. 10 *NEJM* article about the study's latest results.

Juno developed JCAR017 with its defined composition platform under which it manufactures T cells in very specific amounts to produce a defined dose of engineered cells, so that patients are getting the promised dose – not too few or too many CAR-T cells. "We've done a lot of science and a lot of work to get that right," Juno's President of Research and Development Sunil Agarwal told *Scrip*.

Agarwal noted that investigators who have tested multiple CAR-T therapies in clinical trials see JCAR017 as a potentially effective, yet safer treatment option.

"One of the fundamental concepts that existed even just a year ago was that all CARs are the same and in order to get a benefit to the patients you have to have toxicity," Agarwal said. "People view JCAR017 as a second-generation CAR, and they say that you can have efficacy without toxicity. It's a fundamental shift from a year ago to today."

In the Phase I study TRANSCEND, which is enrolling patients with relapsed or refractory aggressive B cell non-Hodgkin lymphoma (NHL), the overall response rate (ORR) was 74% at three months among 19 diffuse large B cell lymphoma (DLBCL) patients treated with JCAR017 and the complete response (CR) rate was 68%.

By comparison, an analysis presented at ASH of 81 DLBCL patients enrolled in the pivotal Phase II JULIET study for Kymriah showed three-month ORR of 38% and CR of 32% stabilizing at six months with ORR of 37% and CR of 30%. In terms of safety, 58% of patients experienced cytokine release syndrome (CRS) – 15% Grade 3 and 8% Grade 4 – and 21% had neurotoxicity (12% Grade 3 or 4). Both side effects are common in patients treated with CAR-T therapies and frequently are severe.

For JCAR017, CRS and neurotoxicity – a deadly side effect for five patients treated with predecessor JCAR015 – were experienced by 36% and 21% of the 67 patients enrolled in TRANSCEND's core group. Only 1% experienced severe CRS while 15% had severe neurotoxicity.

Some DLBCL patients in both TRANSCEND and JULIET were treated on an outpatient basis, staying close to their treatment centers so they could return quickly if severe CRS or neurotoxicity were suspected.

Enrollment in TRANSCEND's pivotal cohort is ongoing and Juno expects that cohort to generate the necessary data to support a biologic license application (BLA) in time for a BLA submission to the FDA in the second half of 2018 with approval anticipated in the latter part of 2019. Juno's partner **Celgene Corp.**, which plans to start a global trial for JCAR017 in DLBCL in 2018, has rights to the CD19 program outside of North America and China.

Celgene and its other CAR-T partner **bluebird bio Inc.** could have the fourth CAR-T therapy on the US market with their candidate bb2121, which targets B cell maturation antigen (BCMA) for the treatment of multiple myeloma. The companies anticipate FDA approval in 2020.

SHORT-LIVED RESPONSES

But even with complete response rates that are far superior to standard-of-care chemotherapy, many patients in the clinical trials conducted to date are not responding or stop responding after the first few months of treatment.

MD Anderson's Neelapu said in an interview with *Scrip* that at least a third of patients who don't respond to CAR-T therapy or who eventually stop responding no longer express CD19, which is at least one mechanism for CAR-T resistance along with the emergence of immune checkpoints, such as PD-L1. He said the answer may be combination therapy with PD-L1 inhibitors or treatment with bispecific CAR-T therapies, which involve T cells reengineered to seek out two targets on cancer cells instead of one.

Juno presented findings during the ASH meeting from its assessments of JCAR017 infiltration into tumor tissue to explore potential mechanisms of treatment resistance and patient relapse. CAR-T cell infiltration was higher in patients who responded to treatment, but in most patients with disease progression CAR-T cells were rare or absent in tumor tissue even though CD19 was present and CAR-T cells were detected in peripheral blood.

The company noted that "there does not yet appear to be a singular resistance pathway upregulated in the tumor at the time of progression, but well-known pathways such as PD-L1 and IDO were upregulated in different patients. These data suggest that combinations with other immunotherapies may be beneficial to further improve outcomes with JCAR017 therapy."

COMBINATION THERAPY OPTIONS

Juno and Celgene are enrolling patients with DLBCL in a study that tests JCAR017 in combination with **AstraZeneca PLC**'s PD-L1 inhibitor *Imfinzi* (durvalumab). Another study will be initiated in 2018 to test JCAR017 in combination with a Bruton tyrosine kinase (BTK) inhibitor in chronic lymphocytic leukemia (CLL).

Agarwal noted that the CAR-T field still is trying to figure out the best staging of the cell therapies and targeted or immuno-oncology agents. He said Imfinzi will be administered three or four weeks after JCAR017 infusion, because there is some concern that with a checkpoint inhibitor in the bloodstream at the time of CAR-T administration the reengineered cells could expand too quickly, increasing the incidence of severe toxicities.

Safety is a crucial question in regard to combination therapy given the severe initial CRS and neurological side effects observed within the first few weeks or months of treatment.

The Tran, Longo and Urba NEJM editorial noted that "combining anti-CD19 CAR T-cell therapy with other agents, such as Bruton tyrosine kinase inhibitors and inhibitors of immune checkpoint pathways (e.g., programmed death 1 [PD-1] protein or its ligand [PD-L1]), may also increase therapeutic efficacy. However, because the mechanisms of the toxic effects associated with this therapy are not completely understood, strategies that enhance the potency of these products run the risk of inadvertently worsening the already daunting toxic effects."

Juno is not deterred by the safety question in its pursuit of agents that could be added to CAR-T treatment to improve the efficacy of the therapies. The company recently announced a license agreement with **Eli Lilly & Co.** for the gamma secretase inhibitor (GSI) LY3039478 to test in combination with its BCMA-targeting CAR-T therapy JCARH125 in 2018. *(Also see "Deal Watch: Vertex Selects First Candidate Under CRISPR Gene-Editing Collaboration" - Scrip, 13 Dec, 2017.)*

Juno said in Dec. 6 announcement about the deal that "gamma secretase is an enzyme that cleaves a set of transmembrane proteins, including BCMA. Multiple publications have shown that treatment with GSIs can increase surface expression of BCMA on tumors, particularly multiple myeloma. Increased cell surface BCMA may increase potency of a BCMA-directed CAR-T therapy."

Celgene Corporate Vice President-Translational Development, Kristen Hege said during the company's Dec. 10 investor event during ASH that one of the things Celgene is trying in order to boost CAR-T cell persistence is to test its partnered therapies – both BCMA-targeted bb2121 and JCAR017 against CD19 – in combination studies. Hege noted that product modifications are under consideration as well.

"We also have another program that we have partnered with bluebird which is skewing the product – the BCMA CAR-T product – toward a stem cell memory phenotype that at least in animals has been shown to be associated with more durable persistence," Hege said.

MORE PREDICTIVE DATA ARE NEEDED

However, she also noted that there is not enough data available yet from clinical trials "that really hone in on what the predictors of the deeper or less-deep responses are, even predictors of resistance," but research in that area is ongoing.

Bluebird President and CEO Nick Leschly also noted during his company's Dec. 9 ASH investor event that there have been no specific indicators to date to explain why patients didn't respond or stopped responding to treatment with bb2121.

"There were patients that did have a decrease in BCMA expression, some of them did not; patients that had ongoing T-cell expansion and some that had decreased, so it's still unclear what's causing the potential resistance or escape at this point," Leschly said.

What is clear is that a lot more research is needed not only to test new CAR-T candidates, but to improve responses to the therapies.

Novartis Senior Vice President David Lebwohl, Franchise Global Program Head for CAR-T therapies, said during the company's Nov. 11 investor event to discuss data presented at ASH that "we do not yet know how to predict which patients are going to respond. However, we do have a very extensive analytic program looking at immuno-phenotyping of cells as well as the patients' tumors, and we obviously will keep looking to try to find something that can predict response."

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Unlocking Market Access For Novel Drugs In China

BRIAN YANG brian.yang@informa.com

After an eight-year hiatus, China's public payer, the Ministry of Human Resources and Social Security (MHRSS) updated its national reimbursement drug list (NRDL) in 2017.

That translates into a novel drug waiting an average of six years to gain national reimbursement in China.

The lack of coverage has meant low uptake of innovative therapies upon market launch in China, according to a recent report by industry associations, led by R&D based Pharmaceutical Association Committee (RDPAC), and written by McKinsey.

Among six therapies launched on the market, **Merck & Co. Inc.**'s *Januvia* (sitagliptin), **Roche**'s *Avastin* (bevacizumab), **Bayer AG**'s *Xarelto* (rivaroxaban), **Pfizer Inc.**'s *Enbrel* (etanercept), **Novartis AG**'s *Lucentis* (ranibizumab) and Roche's *Tarceva* (erlotinib), sales in China are only 16% of their respective sales in Japan, despite China having a much larger population.

Apart from a higher GDP (Japan's $39,000 vs. $8,100 in China) and larger healthcare expenditure (10.2% vs. 6.2%), Japan's timely reimbursement (within 3 months of launch) also contributes to the large difference, noted the report.

A timelier reimbursement is thus vital to ensure market access for novel drugs in China.

To that end, policy makers should actively listen to input from the industry and align closely with each other, proposed the report, entitled *Improve Market Access to Novel Drugs and Ensure Healthier China*, released on Dec.13 in Beijing.

Unlike the National Health Service in UK and the US Ministry of Health, Labor and Welfare, China lacks a central agency to coordinate among state agencies, and between the central government and local authorities in making reimbursement policies.

A cross-agency leading payer is necessary to oversee the policy making process, noted the report.

Additionally, policy makers need to regularly listen to industry input, and seek comments from stakeholders. In the past, agencies in China generally released drafts and asked the industry to comment within two weeks, which left insufficient time to have the comments reflected in the final regulations.

Other stakeholders, including physicians, patient groups should also be included in the comments gathering process, the report recommended.

China needs to employ transparent and evidence-based standards when it considers what drugs to be included for reimbursement, it proposed.

Although China has started its national drug negotiation mechanism, mainly relying on expert comments, there is a need for a reimbursement framework based on a drug's clinical evidence.

Recent reports exposed so-called "magic drugs (*Shenyao*)", such as *Shapuaisi* (bendazac lysine) eye drops, sales of which reach CNY750m ($115m) a year, despite a lack of clear clinical benefits.

"The clinical evidence should be evaluated by an independent third-party committee," said McKinsey's partner, Zhou Gaobo, who presented the report.

Timely updating of the NRDL is another measure to encourage drug innovation in China. Several countries require clinical evaluation and drug price negotiations to be completed within three months to six months evaluation, while in China there is no such requirement, although the MHRSS has talked about updating the list on a rolling basis.

In China, when a novel drug from certain makers is not selected for national drug negotiation or the maker chooses not to participate, the best way forward is to negotiate with local authorities, recommended the report.

"A drug maker should consider the flexibility to negotiate solely with provincial government, in a bid to get their drugs reimbursed, rather through the national negotiations," said the report.

Makers should set their product's ex-factory prices to reflect China's market conditions, no matter whether the product is included in the list or not because of a price monitoring system, emphasized the report.

Because several provincial governments endeavor to cover individual drugs ahead of the national coverage, drug makers should actively seek local coverage. One example is Eastern Zhejiang province, which recently extended coverage to 36 drugs, mainly anticancers, treatment for severe mental disorders, hemophilia, diabetes and cardiovascular conditions.

SEPARATE FUNDING

As increasing numbers of innovative drugs are heading to the market, China should consider setting up a separate fund to provide coverage for such drugs, said the report.

Such funding would allow hospitals to start using them, and patients could access upon their market launches.

The low market share of commercial insurance also deters market access for such treatment. Private health insurance accounts for 10% of the total health insurance market, owing to a lack of electronic health records (EHR) and little influence over hospital prescription decisions, as well as low public awareness.

China's single pay-for-service method doesn't help either. Other countries such as Australia, UK and France use more sophisticated methods combining several treatment-based methods.

To cure the market access condition, China should take a combination of measures, suggested the report. One is that MHRSS should take a leadership role, supported by the National Health and Family Planning Commission (NHFPC). Others include:

- Allow makers to submit reimbursement applications and conduct regular negotiations;
- Local authorities shouldn't further adjust the reimbursement level once it has been set by the central government;
- Hospitals shouldn't further negotiate drug prices after the NRDL listing;
- Link quantity with pricing;
- Exclude innovative new drugs from limitations of "one drug, two products" allowed in each hospital;
- Improve Pharmaceutical Affairs Committee inside hospitals.

The lack of reimbursement poses the biggest challenge to drug makers, now that the national medicines agency China FDA has made major improvements to the new drug approval process, said Jean-Christophe Pointeau, **Sanofi** China GM and deputy chairman of RDPAC, who presented at the launch event.. *Published online 29 December 2017*

Pharma-BAT Digital Health Tango In China: Will It Pay Off?

BRIAN YANG brian.yang@informa.com

2017 has been marked by active deal-making between drug makers and internet giants in China. From **GlaxoSmithKline PLC** to **Sanofi**, pharma companies eagerly embraced a new environment in which patients turn to their smartphones for health solutions.

From disease management to commercial model innovation, digital tools have become more important in a country with the world's largest mobile phone and internet users.

China has surpassed the US as the largest mobile pay market, and among Chinese physicians, 71% of them prefer internet and mobile devices to get medical information and mobile phones and internet are two most used tools, noted a survey conducted in 2014 by the international public relations firm Ruder Finn.

An integrated approach that combines traditional face-to-face interaction with mobile and digital information provision is thus vital to win the battle for attention of the physician and patient.

ONLINE TO OFFLINE

So far, the biggest role for digital health apparently is medical information offering and disease management. Many drug makers look at smartphone apps and code-based technology centered on chronic diseases and vaccines as a fast and cost-effective way to reach tens of millions of users in China.

GSK, for one, inked a deal with Alibaba to reach out to millions of healthy Chinese adults who browse online regularly but haven't thought about getting shots to protect them from illness. The innovative service platform uses Alibaba's online commerce site Taobao to feature information on GSK vaccines, starting with *Cervarix*. Users can get vaccination consultation and book an appointment, all done via a smartphone or website.

The tie-up with Alibaba came days after GSK nixed its neurosciences research unit in Shanghai, as a part of an R&D restructuring after new CEO Emma Walmsley took over.

Similarly, French drug maker Sanofi has signed a deal with Alibaba to provide medical information and diseases management. Based on Alibaba's code-based product traceability tool, it will be integrated with information on chronic ailments such as cardiovascular disease and diabetes.

Sanofi also rolled out its *MC2* project, a multi-channel platform providing physicians with information and customized feedback through online tools ranging from telephone, email, Chinese social network WeChat and web conference.

ONCOLOGY AND AI

Digital health's latest battlefield is artificial intelligence, driven by China's policy push to become a world power in AI and led by companies both large and small.

On Dec.14, the government released a national Three-Year Plan in artificial intelligence. The plan calls for several priorities including medical imaging assistance platform, video and imaging identification systems and service robotic devices.

Alibaba has already invested $227m in the Hong Kong-based startup **SenseTime** that focuses on artificial intelligence research and has multiple advanced technologies for facial recognition, machine learning and smart city systems.

Meanwhile, the Hangzhou-based Alibaba is developing machine-learning to get automated diagnosis of sarcoidosis, an inflammatory condition forming on organs including the lungs.

Additionally, Alibaba is partnering with Intel and the Beijing-based oncology diagnosis and big data firm **LinkDoc** to conduct a competition to help scout for talent, find appropriate algorithms, and analyze computer tomography lung images to precisely diagnose sarcoidosis.

But the real leader in AI could be the Shenzhen-based **Tencent**, which is building a national platform for an AI-based medical imaging diagnosis system. In August, Tencent launched *Miying* (Seek Imaging), the first AI-based esophageal cancer diagnosis system. Esophageal cancer is among the most prevalent cancer types in China, especially among rural residents. The Tencent system can screen for the cancer with 90% accuracy, and 95% for sarcoidosis on lungs. The plan is to work with medical institutions and expand to more cancer types.

MEDICAL INSURANCE PLUS

Facing challenges of limited or no coverage for innovative new drugs, companies are looking for new ways to expand the access. And technology could aid these efforts.

One such tech startup is **CareVoice**, which developed a 'Yelp' review app for healthcare services in China in which users can get personalized health care options, based on reviews and recommendations.

Initially targeting mid-to-high income consumers in Shanghai, CareVoice has partnered with health insurers AXA and pharmacy operators 1Yaowang to provide expats and Chinese users with health management and medical need.

The partnership will allow the insurer know more about their customers and provide more customized services.

CareVoice founder Sébastien Gaudin previously worked at Sanofi. Some of the startup's recent partnerships include one with **Johnson&Johnson** to expand education on contact lenses in China, and the Saas (software as a service) InsurTech platform to improve health and insurance experiences.

"Pharma companies have market access challenges to get innovative drugs covered by social insurance and are seeking new ways to reduce pay-out for patients and/or generate new sources of revenues beyond drugs," Gaudin told *Scrip* in a written response.

Increasing the awareness for commercial insurance products is vital in China, said the entrepreneur.

He also underscored the importance of leveraging resources from insurance and pharma companies so that beneficiaries can be diagnosed earlier and benefit from easier access to relevant medical providers and treatment, while lowering cost for all stakeholders.

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China API Juggernaut Rolls On But Can India Recoup?

ANJU GHANGURDE anju.ghangurde@informa.com

India could be staring at a national health crisis in the backdrop of its continuing massive reliance on Chinese active pharmaceutical ingredients (APIs), including those used in drugs for high-burden diseases such as diabetes and cardiovascular ailments, according to a report by the professional services firm KPMG and the Confederation of Indian Industry (CII).

India accounts for 20% of the global disease burden and in addition to communicable diseases such as malaria and tuberculosis, the growing numbers for non-communicable diseases (NCDs) pose additional health care challenges. NCDs account for about 60% of all deaths in India.

The KPMG-CII report, released Dec. 20, notes India's heavy reliance in 2016 on Chinese imports for both APIs as well as key intermediates such as 6APA (100%), penicillin (98.5%) and ciprofloxacin (99%) in the antibiotics segment. Dependency on Chinese API imports was also as high as 98% and 100% for drugs such as digoxin and losartan, respectively, in the cardiovascular segment with similar high reliance for metformin and glimepiride (diabetes) and isoniazid and streptomycin (tuberculosis). India had an estimated 64m cases of cardiovascular disease and around 69m cases of diabetes in 2015.

Public health emergencies may require large quantities of specific drugs to be made available in a short timeframe and the report cautions that a foreign supplier of APIs "may not be as responsive" to immediate public health demands as local producers. "The inability to procure certain medicines could lead to a national health crisis," it notes.

India imported nearly 272m kg of bulk drugs and intermediates valued at nearly $2.8bn in 2016. China alone is said to account for around 70% of such imports by value. Cut-price imports from China have led to a gradual erosion of India's bulk drug manufacturing capacity, with several sites closing.

Ravind Mithe, partner, strategy and operations, management consulting, KPMG in India, called for "urgent interventions" from the government as well as industry given the strategic nature of India's dependence on its Asian neighbor. "Such high dependency means that any disruption in the supply of APIs can potentially result in significant shortages of essential drugs in India," he said.

The KPMG-CII report identifies a string of measures as part of a structured approach to help India achieve self-sufficiency in the API segment. Short-term recommendations include using existing capacities, focusing on quality, identifying critical APIs and securing the supply chain. Mid-term efforts need to be geared toward, among other things, nurturing entrepreneurship in the bulk-drug industry and establishing a conducive ecosystem of policies, regulations and financial incentives.

Industry experts, however, lamented that although there has been long-running discussion around the dire situation in the Indian API segment, not much real on-ground impetus has been provided by the government.

India's 2017 draft pharmaceutical policy outlines measures to encourage end-to-end indigenous drug manufacturing, including that of APIs and their precursor intermediates, though some experts told *Scrip* that quite a few of these measures are "not really workable."

In 2015, an Indian expert committee headed by V. M. Katoch, a former director general of the Indian Council of Medical Research and secretary, department of health research, had recommended a raft of measures to revive and promote the production of APIs in the country, including the "judicious and liberal" use of anti-dumping duties and safeguards.

However, India's Department of Pharmaceuticals (DOP) viewed the implementation of the Katoch committee recommendations in a fixed timeframe as untenable, according to local media reports in June. The government at that time indicated that it was looking into the issue of duty structure, assistance to bulk-drug parks and interest-rate support to the industry, and trying to obtain necessary approvals for providing funds. An umbrella scheme was being prepared, within which assistance to the bulk-drug industry for common facilitation would be a sub-scheme, the DOP is reported to have said.

The Chinese industry, on the other hand, is known to be backed by strong policy support and other incentives from the government to set up mega API clusters that create economies of scale. While China's labor cost has increased over the years, productivity also has improved, aided by factors such as superior quality infrastructure and production techniques. China's labor productivity is estimated to be nearly 1.5-times higher than that of India.

CHINA REFORMS

Meanwhile, some industry experts mentioned how ongoing reform in China could work in India's favor in the API segment, if only the industry and government could operate in tandem to seize the opportunity.

Dilip Shah, secretary general of the Indian Pharmaceutical Alliance (IPA), told *Scrip* that with the China Food and Drug Administration (CFDA) joining the International Council for Harmonization (ICH) as a new regulatory member, and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) as a new observer, it will mean greater enforcement and compliance requirements in China. This, in turn, will add to costs for some players and force others to shut down.

Shah said that this could "disturb" the traditional Chinese advantage, providing opportunities for Indian manufacturers to make APIs from the basic stage and look at alternative sources. "It may be a blessing in disguise," Shah said, but emphasized that the Indian government should look into the issue of APIs on "mission mode" and also ensure the commercial viability of any plans. India had earlier joined ICH as an observer.

China's joining ICH was in the spotlight earlier this year. Theresa Mullin, director of US FDA's Office of Strategic Programs in the Center for Drug Evaluation and Research, noted in an August blog post that discussions with the CFDA revealed that it faces many of the same challenges that other ICH partners and the FDA do. China needs to ensure that patients have access to innovative products, and that pharmaceuticals are safe and held to a consistent quality standard, she added.

The blog post also pointed out that new ICH members are required to, among other criteria, implement a basic set of regulatory requirements for the manufacture of pharmaceuticals, for the conduct of clinical trials and for stability testing of pharmaceutical products.

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Bumpy Ride Awaits Indian Firms In 2018 (And Then There's Amazon)

ANJU GHANGURDE anju.ghangurde@informa.com

Potential turbulence on home turf and an uptick in the intensity of competition on the US market could make 2018 quite a tough year for Indian firms to navigate – at least that's the general forecast of key industry experts.

Compounding the challenge is the Amazon factor that could mean widespread disruption in the US market, a key contributor to revenues for several frontline Indian firms, although the online retail giant has not publicly confirmed its intent to enter the US prescription drug arena yet.

Dilip Shah, secretary general of the Indian Pharmaceutical Alliance (IPA), which represents leading domestic firms, said that the "single minded pursuit" of "access at affordable prices" by the Indian government and "complete disregard" for promotion, development and growth of the industry could have "major adverse impact" on the growth and sustainability of the Indian pharmaceutical industry in 2018.

"These pursuits include generic prescribing, drug substitution, the pricing regulator's activism and amendments to India's Drug Prices Control Order (DPCO), 2013," Shah told *Scrip*.

There has been significant debate in 2017 around the government's plans to consider a potential legal frame under which physicians in India will have to prescribe medicines by their generic names only. *(Also see "India Premier Pushes For Generic Prescriptions But Hurdles Loom" - Pink Sheet, 4 May, 2017.)* Dr Ajit Dangi, president and CEO of Danssen Consulting, noted that the generics-only diktat is a "worrisome development" for companies that have successfully built strong brands in spite of intense competition in a market "cluttered with hundreds of me-too brands."

Besides, a poll-bound India could mean that "political expediency will dictate populist measures," IPA's Shah said. India heads into general elections in 2019.

A top executive of a leading multinational concurred that health is part of the political agenda, but maintained that was also "good," since health will be accorded the much-needed importance it deserves. He noted that while patient-centric policies and announcements are welcome, there are several research studies, including the IMS Study in 2013 on Healthcare Access in India, that shows that the real barrier to access is the inability to pay out-of-pocket and the lack of insurance cover.

PRICE CAPS, CONTRACT MANUFACTURING

Unsurprisingly, pricing is expected to stay a prominent theme in 2018, though it remains to be seen if things could be as acrimonious as in 2017. *(Also see "India's Pricing Tussle Escalates After Regulator Names "Overcharging" Firms" - Pink Sheet, 12 Apr, 2017.)*

Sanjiv Kaul, partner at the private equity firm, ChrysCapital, told *Scrip* that while price-capping is "here to stay" as it is the "only effective policy" that the government can implement in the short term, such fixing of prices will only be for drugs and devices that are deemed essential, such as in the oncology, nephrology and cardiovascular segments.

Kaul believes that the impact of price-capping will be more on healthcare services companies rather than pharmaceutical firms. However, even the services firms, he says, will "adjust" prices by charging more for the service versus the product (most hospitals have already tweaked their pricing, he points out) so that a ceiling price on a device does not hamper their profitability.

2017 witnessed the contentious capping of prices of stents and then knee implants in India, which set off a chain of events including the US medical device lobby group AdvaMed seeking the intervention of the US Trade Representative.

Kaul also predicts the rise in AYUSH [ayurveda, yoga and naturopathy, unani, siddha and homoeopathy], nutraceuticals and cosmeceuticals in the Indian market. "While the pharma market stabilizes post GST [Goods and Service Tax] trade disruptions, the biggest growth will come from ayurvedic, nutraceutical and cosmeceutical products thanks to the rising middle class and increasing GDP per capita." GST was implemented with effect from July 2017 and has been dubbed as the biggest tax reform since India's independence. GST replaces most indirect taxes currently in place and eliminates a multiplicity of taxes and their cascading effect in the country.

Danssen Consulting's Dangi, a former president and executive director of Johnson and Johnson India, also said that India's draft pharma policy 2017, which proposes to rein in contract manufacturing, if implemented, would be a "major blow" to both Indian as well as multinational companies.

"There is substantial spare manufacturing capacity in the industry and if this recommendation goes through, it will significantly increase manufacturing cost and also affect SMEs [small and medium-sized enterprises] which form the bulk of contract manufacturers," Dangi maintained. *(Also see "OPPI Chief Vaidheesh On Burning Industry Issues In India" - Scrip, 4 Dec, 2017.)*

US REFORM, FDA ACTION

But it's probably the US market – in the backdrop of reform propelled by the FDA – that could potentially tip the growth scales one way or the other for Indian firms.

IPA's Shah says that US protectionist policy, as manifested in tax reforms and 'Make in America' efforts, could have a powerful impact on industry.

In addition, FDA reforms, he indicates, could be a mixed bag. "They would on one hand benefit the generic industry by more action in area like REMS [Risk Evaluation and Mitigation Strategy], but also hurt on the other by quicker approval of ANDAs bringing in intense competition," Shah maintained. The FDA has been keen to deal with REMS abuses that block generic entry.

Kaul too anticipates an increase in competition in the US through quicker ANDA approvals; smaller players will not stop filing ANDAs as they have already invested in manufacturing plants and R&D, he says. The FDA has been working to prune the

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number of review cycles necessary for an ANDA approval. He also sees a shift in focus from revenues to EBITDA [earnings before interest, taxes, depreciation and amortization] for larger generics players.

"Teva has already announced major cuts in expenses and in the tail-end products. Expect other large generics [firms], including Indian peers, to follow suit," Kaul declared.

AMAZON EFFECT

Significantly, all the experts *Scrip* reached out to recognize the disruption that a potential entry of Amazon in the US prescription drugs space could bring.

Shah suggests that an Amazon entry may appear beneficial in the short term, but could turn "painful" as the online retail giant acquires "muscle power" to negotiate bulk purchases.

Dangi underscores that major disruption and competition in the pharmaceutical industry is not going to come from other drug firms but from the "Googles and Amazons of the world."

"These companies will depend more and more on technology and digitization to disrupt the market not only affecting the logistics and supply chain but also diagnosis and cure by bringing healthcare to one's doorstep," he said.

Kaul believes that Amazon, and perhaps more importantly, CVS-Aetna, will re-define the pharma supply chain in the US. This, he notes, will have a larger impact on branded/patented products as innovators will not be able to command the market and distributors will push for more and faster genericization (already 75% by volume, he estimates). *(Also see "CVS/Aetna To Merge In Defensive Play To Reshape Health-Care Delivery" - Medtech Insight, 4 Dec, 2017.)*

"It would be really interesting if Amazon also vertically integrates to acquire (or partner with) a manufacturer – that would change the entire ball game," Kaul said.

The MNC executive quoted previously, however, offers a word of caution. He specifies that while no sector seems "safe" as Amazon explores unchartered territory, those expecting Amazon to rush into healthcare may need to press a pause button as the online retail giant will have to watch out for regulatory risks so that it does not "taint its reputation" in any way.

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Profile: Novartis' Gildea On Stable Girl Grit And Drones

ANJU GHANGURDE anju.ghangurde@informa.com

Deborah Gildea

Deborah Gildea's early days as a stable girl probably provided some useful grounding on compassion and the significance of money. Some of that exposure also perhaps helps her navigate the tightrope between social and commercial metrics as head (APAC) of **Novartis**' Social Business.

In an interview with *Scrip*, Gildea commends **GlaxoSmithKline PLC** 's former chief executive Andrew Witty for his role in changing the access to medicines paradigm in the pharmaceutical industry. She supported the development of GSK's access to medicines strategy in 2010 and moved to Asia to lead its implementation across emerging markets. The soft-spoken but firm Gildea was GSK's general manager, developing countries Asia (Cambodia, Laos, Myanmar and Papua New Guinea) prior to joining Novartis in 2017.

Gildea, who was in India recently as Novartis' for-profit social business initiative, Arogya Parivar, completed a decade of operation, also discussed how digital platforms and drones could help improve access to healthcare.

ANJU GHANGURDE: *What are the key things that shaped you when growing up?*

DEBORAH GILDEA: I worked as a stable girl from when I was 12 until I went to university. On Sundays, I would be in sole charge of the horses and I needed to cycle several miles to get there come rain, snow or wind. This gave me a strong sense of responsibility and the pocket money I earned provided increased independence.

AG: *Who was your biggest influence, and why?*

DG: The woman I worked for [as a youngster at the stable] was super organized and I guess this rubbed off. She also taught me that in life you always have a choice in any situation. Always recognizing the choice, no matter how unpalatable, puts you in the driving seat no matter what the twists and turns of life may bring you.

AG: *Who do you admire in the industry, and why?*

DG: The person I most admire in the industry is Sir Andrew Witty. The drive and commitment that he has given to access to medicines has changed and challenged everyone in the industry to think differently, focusing attention on the 5 billion who still struggle to access good healthcare.

AG: *The more challenging role of the two: being APAC head of Novartis' social business or mother?*

DG: Both roles have their moments! However, becoming a mother has been the best personal development investment that I have ever made. It has made me more self-confident, patient and unruffled when things don't go smoothly. Parenthood is also a wonderful bridge to connect with the many people that I get to meet in the course of my work. When you sit and talk together, you soon come to realize that every parent wants the same things for their children - for them to be safe, healthy and able to access education. I feel very fortunate to have been born in a country where it is easier to provide these for my child.

AG: *One on-ground learning in markets like Cambodia, Laos, Myanmar, Papua New Guinea, India and across your numerous career roles that has always stayed with you?*

DG: The barriers to accessing medicines are consistent across all the markets that I have worked in. The questions that you need to ask are: Do patients understand that they have a disease than can be treated (if it is acute) or managed (if it is a chronic condition)? Do the medicines that the patient needs fit within the patient's lifestyle, beliefs and the healthcare system that is available? Are the medicines available in the community where the patient lives? Is the medicine affordable for the patient? And is the patient able and willing to take the medicine for as long he/she needs? The relative importance of each barrier can vary from market to market but you need to address them all if you want to improve access to medicines for patients.

AG: *How do you step back and get perspective?*

DG: This is very humbling work. Each time I go and sit with some patients I am reminded how fortunate I am and how much more there is to do. As a team, we focus on making small sustainable differences rather than pretending that there is a magic bullet solution.

AG: *If you weren't a pharma executive, what would you be?*

DG: I would follow my parents' example and run a small business of my own, although my business idea keeps changing!

AG: *What has your proudest moment been in corporate life?*

DG: Having two of my team selected for a prestigious 18-month global development program [in GSK]. There were only 10 places available across the whole of Africa and Asia. I would love to make a similar impact on my team's development in Novartis.

AG: *One change you effected in your company (in GSK or Novartis) that you believe is important/invaluable?*

DG: I was fortunate enough to be part of the three-person team that developed the Access to Medicines strategy for GSK soon after Andrew Witty became CEO. I then got the opportunity to implement the strategy at a regional level and to set up a country from scratch.

AG: *The term social business, some may say, is a bit of an oxymoron. What are three key essentials you believe are sacrosanct to ensure a balance between doing good for community and for the company?*

DG: We always start by providing health education first. As we learn about community's needs we then look to find ways to make our activities self-sustaining.

Separating health education from our commercial activities ensures that our health educators and the doctors who volunteer at our health camps are free to focus on the needs of patients. At a country head/area level we focus on a mixture of social and commercial metrics. To be successful, both sets of metrics need to be achieved.

AG: *Where and how do you see Novartis' social business in five years…a bigger canvas, more players or more challenges?*

DG: I would like to see the social business become a sizable part of Novartis in all low- and middle-income countries. My ambition is also to create a talent pipeline for the wider business. This is an extremely complex and challenging area to work in which provides rapid development opportunities for people with the right mind set and energy.

As we become even more successful I would expect other players to enter this space. This is very healthy for us and it will stop us from becoming complacent.

AG: *Non-traditional players like Google, Apple and Amazon could potentially reshape various aspects in the phama sector including areas like social business. Do you expect to harness some of this potential?*

DG: I believe that social media has tremendous potential to provide patients with essential information and to link them to qualified HCPs. We are already experimenting with a new approach in the Philippines that has a digital platform as its backbone. The data that has been gathered so far is providing new insights into patients' needs at a community level. This helps us to provide very targeted health education. The next phase will be to find novel ways to make medicines available to communities who traditionally have little/no supply. We are looking at numerous options including e-prescriptions and the use of drones.

AG: *One myth about the pharma industry and top women executives in the corporate world that you'd like to set straight?*

DG: The belief that price is the only barrier to patients being able to access medicines. We need to address the full ecosystem if patients are to be able to access healthcare no matter where they live in the world.

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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 two weeks 15–28 December 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Motif Bio PLC	iclaprim (iv)	skin and skin structure infections	REVIVE-1; *Clinical Infectious Diseases*, Dec. 21, 2017.
Gilead Sciences Inc.	momelotinib	myelofibrosis	Simplify 2; *The Lancet Haematology*, Dec. 20, 2017.
Roche	*Tecentriq* (atezolizumab)	bladder cancer	IMvigor211; *The Lancet*, Dec. 18, 2017.
Allergan PLC	*Avycaz* (ceftazidime plus avibactam)	hospital acquired pneumonia	REPROVE; *The Lancet*, Dec. 15, 2017.
AstraZeneca PLC	AZD8931	colorectal cancer	FOCUS4-D; *The Lancet Gastroenterology & Hepatology*, Dec. 15, 2017.
Phase III Interim/Top-line Results			
Celgene Corp.	*Revlimid* (lenalidomide) plus rituximab	indolent non-Hodgkin's lymphoma	RELEVANCE; not superior to chemotherapy regimen.
AbbVie Inc.	upadacitinib, an oral JAK1 selective inhibitor	rheumatoid arthritis	SELECT-MONOTHERAPY; met all endpoints.
Gedeon Richter PLC/Allergan PLC	*Vraylar* (cariprazine)	bipolar I depression	RGH-MD-54; positive results.
Merck & Co. Inc.	*Keytruda* (pembrolizumab)	gastric cancer as second-line therapy	KEYNOTE-061; missed primary endpoint.
Shire PLC	SHP609 (idursulfase) by intrathecal administration	Hunter syndrome and cognitive impairment in children	Missed endpoints; no impact on iv use in current Hunter syndrome indications.
Phase III Initiated			
Odonate Therapeutics LLC	tesetaxel	breast cancer	CONTESSA; an oral taxane for locally advanced or metastatic disease.
Bayer AG	molidustat, oral	anemia due to chronic renal failure	MIYABI ND-C and ND-M; non-dialysis patients.
Poxel SA/Sumitomo Dainippon Pharma Co. Ltd.	imeglimin	diabetes, type 2	TIMES 1; in Japan.
Diffusion Pharmaceuticals Inc.	trans sodium crocetinate	glioblastoma	INTACT; in newly diagnosed inoperable disease.
VBL Therapeutics	ofranergene obadenovec (VB-111), anticancer gene therapy	ovarian cancer	OVAL; in platinum- resistant disease.
BioLineRx Ltd.	BL-8040	mobilizing stem cells in multiple myeloma	GENESIS; in addition to G-CSF in transplant patients.
Biohaven Pharmaceuticals Holding Co. Ltd.	trigriluzole	obsessive-compulsive disorder	At 35 sites in the US.
Minerva Neurosciences Inc.	MIN-101	schizophrenia	For negative symptoms.
Incyte Corp.	epacadostat	renal cell cancer	KEYNOTE-679/ECHO-302; as first line therapy.
Novo Nordisk AS	*Tresiba* (insulin degludec)	type 1 diabetes	EXPECT; in pregnant women.

VBI Vaccines Inc.	Sci-B-Vac vaccine	hepatitis B	PROTECT, CONSTANT; a third-generation product.
Phase III Announced			
Verrica Pharmaceuticals Inc.	VP-102	molluscum contagiosum	A double-blind study.
Apellis Pharmaceuticals Inc.	APL-2	geographic atrophy	Associated with age-related macular degeneration.
Eyenovia Inc.	phenylephrine plus tropicamide	mydriasis	MicroStat; to dilate pupils.
Eyenovia Inc.	*MicroProst* (Gla203)	glaucoma	a micro-formulation of a prostaglandin.
Updated Phase II Results			
Abivax	ABX464	HIV/AIDS	ABX464-005; HIV reservoir reduction observed.
Ascend Biopharmaceuticals Ltd.	ASN-002, interferon-gamma gene therapy	nodular basal cell carcinoma	Clinical responses seen.
Phase II Completed			
RXi Pharmaceuticals Corp.	RXI-109, a self-delivering RNAi	wound healing	Improved scar appearance, well tolerated.
Phase II Interim/Top-line Results			
Innovation Pharmaceuticals Inc.	*Kevetrin* (thioreido-butyroanitrile)	ovarian cancer	Modulates p53 protein, anticancer effects seen.
UCB SA	bimekizumab	psoriatic arthritis	BE ACTIVE; skin and joint symptoms improved.
Galera Therapeutics Inc.	GC4419, a dismutase mimetic	severe oral mucositis in head and neck cancer	Reduced symptoms.

Source: Biomedtracker

APPOINTMENTS

Neurotrope Inc. has appointed ***Charles Ryan*** CEO, effective Feb. 15, 2018, following the resignation of ***Susanne Wilke***. Ryan served as senior vice president and chief intellectual property counsel at Forest Laboratories for more than 10 years, and is currently president and CEO of Orthobond Corp. Neurotrope is evaluating bryostatin-1 in a Phase II study for advanced Alzheimer's disease, and is conducting preclinical studies of bryostatin for Fragile X syndrome, Niemann-Pick type C disease, and Rett syndrome.

Concert Pharmaceuticals Inc., the US biopharma company creating a pipeline of deuterated new medicines, has appointed ***Marc Becker*** as CFO, effective Jan. 4, 2018. Before joining Concert, Becker was senior vice president and CFO at CRISPR Therapeutics, and before that was CFO and senior vice president of r4EVO Biologics.

Timothy Crew has been named CEO of the Philadelphia-headquartered generics firm, ***Lannett Co. Inc.***, effective Jan. 2, 2018, succeeding Arthur Bedrosian. Crew was most recently CEO of Cipla North America, and before that he was senior vice president and commercial operating officer at the North American generics division of Teva Pharmaceuticals.

Tustin, California-based **Peregrine Pharmaceuticals Inc.**, which is transitioning from an R&D-focused business to a pure-play contract development and manufacturing organization (CDMO), has appointed ***Roger Lias*** as president and CEO; Lias is currently a board director of Peregrine, and since Sept. 2017 has been president of its wholly-owned CDMO subsidiary, Avid Bioservices. Before that, Liais was executive director, head of global biologics business development at Allergan PLC. Lias succeeds ***Steven King***, who has resigned as president and CEO to pursue other professional interests.

Allergan PLC has promoted ***Wayne Swanton*** to executive vice president, global operations following notification that ***Rob Stewart***, executive vice president and COO, was leaving. Swanton will join Allergan's leadership team and will maintain responsibility for global manufacturing, quality, supply chain, procurement, pharmaceutical technology, operational excellence, engineering, environmental health and safety, and security.

Following his departure from Allergan, ***Rob Stewart*** is joining the US generics company, **Amneal Pharmaceuticals LLC**, as president, and will become President and CEO of Amneal Pharmaceuticals Inc. when the merger of Amneal and Impax Laboratories Inc. is completed. ***Paul Bisaro***, the president and CEO of Impax, will become executive chairman. Amneal's co-CEOs and co-founders, ***Chirag*** and ***Chintu Patel***, will serve as co-chairmen of the combined company's board of directors.

Acticor Biotech, the 2013 spin-off from France's governmental research institute, Inserm, which is developing a monoclonal antibody fragment for the acute treatment of ischemic stroke, has named ***Yannick Plétan*** chief medical officer. Plétan was formerly head of the medical division at Roche in France.

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