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▶ By Eleanor Malone, 29 December 2017

FROM ONGOING PROGRESS in IO to revolutions in AI, and from pricing headaches to new therapies for migraine: Scrip has gleaned from experts and industry executives their expectations and predictions for 2018's hot topics. Here is our digest.

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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.

Immuno-Oncology'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 tremelimumab 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 most hotly anticipated IO+IO combinations there will be other areas of progress in combination treatment of cancer: "When you think about it, beyond PD-1, CTLA4 and IDO, there's not a whole lot that we've learned yet but I think studies are going to start reading out with regard to modulators of the tumor microenvironment," commented *Scott Brun*, VP scientific affairs at AbbVie Inc. and head of AbbVie Ventures.

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

"We've seen the first iterations of CAR-T in specific hematologic malignancies. We're going to continue to learn about next-generation approaches to these cellular therapeutics that can enhance their specificity as well as their safety profiles," said AbbVie's Brun.

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.'s 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."

"I think we're going to learn more and more about how gene therapies can be applied to areas like ophthalmic disease, to hematologic conditions, to certain homogeneic conditions related to metabolics of the musculoskeletal system. From this first generation, there are still a lot of questions to be answered about variability of responses, about persistence, so I think 2018 is going to teach us a lot about that," said Brun.

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 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. "I think you're going to see more venture investment in neuroscience in neuroscience and inflammatory disease, particularly on taking learnings that have come out of immuno-oncology and applying them to modulation of the immune system as it applies to those types of diseases," predicted Brun.

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 be paid 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.

> **In 2018, companies will significantly scale their use of artificial intelligence for a wider range of commercial applications –**
> ***Arno Sosna, Veeva***

"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."

Amazon could use its scale to become the single largest buyer and distributor of generic medicines – *Salil Kallianpur*

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, 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 Healthcare partner *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."

Expect share buybacks to rate higher than M&A in C-suites – *Andy Smith*

But Andy Smith was not so sure. "Typically biotech stocks jump when investors think of repatriated cash as they seem to assume that it 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.